

Evidenztabelle

zur S3-Leitlinie Diagnostik, Therapie
und Nachsorge des Melanoms

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1. Informationen zum Dokument

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2. AG Diagnostik

2.1. Frage I.2. und I.3. Apparative Verfahren zur klinischen Diagnostik des malignen Melanoms - Adaptation

Frage I.2. Welche diagnostischen Verfahren sind geeignet, die klinische Diagnose des MM zu verbessern?

Frage I.3. Welche Hilfsmittel oder apparativen Verfahren können die klinische Diagnostik des MM ggf. weiter verbessern?

2.1.1. Synopse Quelleitlinien (kurz)

Thema/Fragestellung	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)	LL Kanada Cancer Care Ontario 2007
2. Welche diagnostischen Verfahren/Hilfsmittel können helfen, die klinische Diagnose des MM zu sichern?	Klinische Untersuchung, Anamnese mit Konzentration auf Veränderungen von Hautläsionen; Dermatoskopie wird empfohlen (A); Beobachtungsperiode möglich; Einsatz von „Sequential digital dermoscopy imaging“ und/oder „Total body photography“ kann in Zweifelsfällen in Erwägung gezogen werden (B)	Klinische Untersuchung, Dermatoskopie	Klinische Untersuchung, Dermatoskopie	(nur relevant für medikamentöse Therapien)
3. Erhöht der Einsatz der Dermatoskopie (mit/ohne Schulung der anwendenden Ärzte) die diagnostische Genauigkeit?	Training in Dermatoskopie wird empfohlen für Ärzte, die regelmäßig pigmentierte HV untersuchen (A)	Empfohlen	Keine Erwähnung	

2.1.2. Empfehlung, Hintergrundtext und Literatur Australische Quell-Leitlinie

(mit Seitenangaben der Quellleitlinie)

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
Schlüsselempfehlungen	<p>S. 31</p> <p>1. Training and utilisation of dermoscopy is recommended for clinicians routinely examining pigmented skin lesions Grade of Recommendation: A</p> <p>2. Consider the use of sequential digital dermoscopy imaging to detect melanomas that lack dermoscopic features of melanoma Grade of Recommendation: B</p> <p>3. Consider the use of baseline total body photography as a tool for the early detection of melanoma in patients who are at high risk for developing primary melanoma Grade of Recommendation: C</p>	<p>S. 84</p> <p>A. Recommendations</p> <p>Investigation and diagnosis</p> <p>GPs should receive training as recommended in the NICE <i>Referral guidelines for suspected cancer</i> [44] on the diagnosis of precancerous and cancerous lesions, and should receive feedback through audit on their diagnostic accuracy.</p> <p>GPs should refer certain groups of skin lesions as described in Box 1 and Figure 14 directly to an LSMDT without biopsy. This practice should be subject to audit.</p> <p>All excised skin specimens should be sent for histopathological examination as recommended in the NICE <i>Referral guidelines for suspected cancer</i>. [45]</p> <p>Dermoscopy should be available in all MDTs, but its use requires training.</p>	<p>Die französische LL gibt keine Empfehlungen zur klinischen Erstdiagnose eines Melanoms; die Dermatoskopie wird jedoch im Abschnitt über Untersuchung und Nachsorge von R0-resezierten Patienten (N0, M0) kurz besprochen sowie auf Gutachten der Haute Autorité de Santé (HAS) und der Agency for Healthcare Research and Quality (AHRQ) verwiesen:</p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
		<p>There should be equity of access so that all tissue samples are reviewed in high-quality histopathology services. Accurate diagnosis in dermatopathology depends on clinicopathological correlation, involving input from both clinician and pathologist. Although this can be achieved in difficult cases by interspecialist discussion or seeing the patient records, in some instances (such as cutaneous lymphoma) it may be essential for the patient to be seen jointly. Accordingly, for good clinical governance, it is recommended that the histopathology reporting of any specimens likely to be considered by a skin cancer MDT should be undertaken in a laboratory having easy access to relevant clinicians, patient records and the attending patient.</p>	
Hintergrundtexte	<p>S. 29 - 30</p> <p>5.6 Evidence-based assessment of aids to the clinical diagnosis of melanoma</p> <p>5.6.1 Dermoscopy Dermoscopy (surface microscopy, oil</p>	<p>S. 90</p> <p>E. Evidence</p> <p>Dermoscopy One RCT found that, following a brief training intervention for GPs in the use of dermoscopy, there was a significant</p>	<p>S. 44</p> <p>EXAMEN CLINIQUE, DERMOSCOPIE Les performances diagnostiques de l'examen clinique et de la dermoscopie dans le diagnostic des tumeurs cutanées font</p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	<p>epiluminescence microscopy, dermatoscopy) is a technique that uses a hand-held magnifying device combined with either the application of a liquid between the transparent plate of the device and the skin, or the use of cross-polarised light. This technique allows the visualisation of diagnostic features of pigmented skin lesions that are not seen with the naked eye. [15-18]</p> <p>Meta-analyses performed on studies in a variety of clinical and experimental settings have shown that using dermoscopy improves diagnostic accuracy for melanoma.[19,20]</p> <p>From a meta-analysis of nine level II diagnostic studies subject to varying degrees of verification bias performed prospectively in a clinical setting [21-31] the diagnostic accuracy for melanoma, as expressed by the relative diagnostic odds ratio, was 15.6 (95% CI 2.9-83.7) times higher for dermoscopy compared with naked eye examination. Importantly the meta-analysis was restricted to studies that directly compared the two methods within each study. Sensitivity of dermoscopy was</p>	<p>improvement in the accuracy of clinical diagnosis of melanoma and in the diagnosis of melanoma using dermatoscopy. The improvement was significantly greater for the use of dermatoscopy than for clinical diagnosis.</p> <p>Three systematic reviews and one case series provide evidence that hand-held dermatoscopy improves diagnostic accuracy as compared with unaided examination. There is evidence from one systematic review that the diagnostic accuracy of dermatoscopy depends on the degree of experience of the examiner.</p> <p>Teledermatology</p> <p>One RCT compared teledermatology with face-to-face consultation as a method of examining patients with skin lesions at a dermatology department. All patients received a further, independent face-to-face skin examination with a consultant dermatologist. For each randomised group, concordance between the two consultations for each patient was</p>	<p>actuellement l'objet d'une expertise par la Haute Autorité de Santé (HAS) et ne seront donc ici qu'évoquées. Ces performances ont surtout été étudiées pour le diagnostic initial du mélanome, et non dans la situation spécifique du patient ayant déjà eu un mélanome. Pour ces derniers, la probabilité de survenue d'un autre mélanome est beaucoup plus élevée que dans la population générale. Une revue systématique publiée par l'<i>Agency for healthcare research and quality</i> (AHRQ) a récemment revu les performances de l'examen clinique pour établir une éventuelle stratégie de dépistage systématique des cancers de la peau et a montré que les performances diagnostiques (en termes de sensibilité et de spécificité) des dermatologues étaient supérieures à celles des non-dermatologues [17]. À noter cependant que cette revue systématique a été faite avant</p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	<p>18% (95% CI 9%–27%; P=0.002) higher than for eye examination, but there was no evidence of an effect on specificity [31] (see Appendix 4). Specificity can also be examined by its effect on excision rates of benign lesions, which was not addressed in the meta-analysis. Two such studies suggest reduced rates of excision of benign lesions using dermoscopy (reduced benign to malignant ratio of excised lesions and reduction of patients referred to biopsy) and provide indirect evidence for improved specificity in a specialist setting. [22,23]</p> <p>While there are fewer studies on dermoscopy in general practice, all three that were undertaken in this context (one study with both general practitioners and inexperienced specialists or trainees) [32] show a consistently improved sensitivity for the diagnosis of melanoma or the identification of suspicious lesions requiring biopsy. [21,32,33] It should be noted that all the studies cited were undertaken by clinicians with some training in dermoscopy (restricted to lectures or reading material in some</p>	<p>measured, primarily for management plan and secondarily for diagnosis. There was significantly greater concordance between consultations for management plan and for diagnosis in patients randomised to face-to-face skin examination than in those randomised to teledermatology. No difference was detected between randomised groups for patient satisfaction.</p> <p>One RCT compared two types of teledermatology (by live videoconference and by sending still photographic images) with traditional outpatient consultation, as methods for GPs to refer patients to dermatologists. The dermatologist requested a subsequent hospital appointment for 69% of patients examined by the still image method, compared to 46% of patients examined by videoconferencing and 45% of patients examined in person.</p> <p>One RCT compared teledermatology with standard referral and found that patients in the teledermatology group received definitive treatment</p>	<p>que la dermoscopie, une technique initialement mise au point en Europe et en Australie, soit largement diffusée aux États-Unis.</p> <p>Deux méta-analyses récentes ont montré que pour les dermatologues expérimentés, la dermoscopie améliorerait les performances diagnostiques [160, 161]. Dans l'étude de Bafounta <i>et al.</i>, le rapport de vraisemblance positif estimé de la dermoscopie et de l'examen clinique ont été respectivement de 9,0 [IC95 : 5,9-19,0] et 3,7 [IC95 : 2,8-5,3] [160]. La méta-analyse de Kittler <i>et al.</i> a confirmé ces données, montrant clairement que seuls les opérateurs expérimentés amélioreraient leurs performances diagnostiques [161].</p> <p><i>KLINISCHE UNTERSUCHUNG, DERMATOSKOPIE</i> <i>Die diagnostische Leistungsfähigkeit der klinischen Untersuchung und der</i></p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	<p>studies). For this reason, and based on other evidence [34], some formal training in dermoscopy is required to achieve improvement in diagnostic accuracy.</p> <p>5.6.2 Sequential digital imaging Sequential digital dermoscopy imaging (SDDI) involves the capture and assessment of successive dermoscopic images, separated by an interval of time, of one or many melanocytic lesions to detect suspicious change. This is performed in two settings: short-term digital monitoring (over a period of 1.5–4.5 months) for suspicious melanocytic lesions, and long-term monitoring for surveillance (usually at intervals of 6–12 months). [35] Four level II studies that were conducted in a specialist setting show consistently that SDDI allows the detection of melanoma that lack dermoscopic evidence of malignancy. [35–38] In one prospective study of melanomas diagnosed by a variety of clinical means, 34% were detected using the changes detected by SDDI exclusively and were without dermoscopic features of</p>	<p>significantly more quickly than patients in the standard referral group. Teledermatology patients were significantly more likely to avoid the need for a further clinic visit compared with control patients.</p> <p>One RCT compared teledermatology consultation using a videolink with outpatient consultation and found no difference between the groups in the reported clinical diagnoses.</p> <p>One RCT of teledermatology compared to traditional consultation found no significant difference between groups for patient satisfaction with either their care or the management of their skin problems, and 85% of the telemedicine patients reported that they would use the system again.</p> <p>Two systematic reviews suggest that there is no consensus from primary studies on whether teledermatology is more cost-effective than traditional management of dermatology patients.</p>	<p><i>Dermatoskopie in der Diagnostik von Hauttumoren ist zur Zeit Gegenstand eines Gutachtens der Haute Autorité de Santé (HAS) und wird hier daher nur erwähnt. Die Wirksamkeit dieser Verfahren ist vor allem für die Primärdiagnostik des Melanoms untersucht worden, nicht für die spezielle Situation der Patienten, die bereits ein Melanom gehabt haben. Für letztere ist die Wahrscheinlichkeit, ein weiteres Melanom zu überleben, sehr viel höher als in der Allgemeinbevölkerung. Ein systematisches Review der Agency for Healthcare Research and Quality (AHRQ) hat unlängst die Wirksamkeit der klinischen Untersuchung untersucht, um möglicherweise eine Strategie zum systematischen Screening von Hauttumoren zu etablieren und um zu zeigen, dass die diagnostische Wirksamkeit der klinischen Untersuchung (Sensitivität und Spezifität) bei Dermatologen der von Nicht-</i></p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	<p>melanoma. [36] Long-term digital monitoring is generally used in the surveillance of high-risk patients, usually with multiple dysplastic naevi. In contrast, short-term digital monitoring of individual suspicious naevi can be used in any patient setting. At this time diagnostic accuracy of the technique was not able to be assessed.</p> <p>5.6.3 Automated instruments for the diagnosis of primary melanoma An automated diagnostic instrument is defined as one that requires minimal or no input from the clinician to achieve a diagnosis. Each automated instrument offers different technology with differing diagnostic ability. Guidelines for assessing such instruments have been published. [39] To date, only three instruments have had their diagnostic accuracy compared with a human diagnosis in the clinical field with a sample size that could allow some assessment of their application to the wider clinical arena. [25,40,41] The instruments showed a significantly inferior [25,41] or equivalent [40] specificity for the</p>	<p>Audit data from the UK indicates that GPs report quicker referral of dermatology patients through teledermatology.</p> <p>S. 99</p> <p>E. Resource implications</p> <p>Investigation and diagnosis The main resource implication of the recommendations concerning the investigation and diagnosis concerns the additional role for histopathologists. The increased workload has been calculated taking account of LSMDT and SSMDT working, implementation of the minimum dataset, doubling the reporting of severely atypical naevi, and MM and SSMDT mandatory review. Approximately two-thirds of the additional workload relates to SSMDT and tertiary review.</p> <p>It is estimated that approximately 1.75 additional consultant histopathologists/dermatopathologists would be required per network to</p>	<p><i>Dermatologen überlegen ist. [17] Es ist allerdings zu bemerken, dass dieses systematische Review durchgeführt wurde, bevor die Dermatoskopie, eine Technik, die zuerst in Europa und Australien entwickelt wurde, größere Verbreitung in den USA fand. Zwei aktuelle Meta-Analysen haben gezeigt, dass die Dermatoskopie bei erfahrenen Dermatologen die diagnostische Leistung verbessert [160, 161]. In der Studie von Bafounta et al. ist der geschätzte positive prädiktive Wert der Dermatoskopie und der klinischen Untersuchung 9,0 [IC95 : 5,9-19,0] bzw. 3,7 [IC95 : 2,8-5,3] [160]. Die Meta-Analyse von Kittler et al. hat diese Daten bestätigt und klar gezeigt, dass nur erfahrene Anwender der Dermatoskopie ihre diagnostische Leistung damit verbessern [161].</i></p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	<p>diagnosis of melanoma compared with specialists. In all studies sample sizes were not large enough to be able to detect potential differences in the sensitivity for melanoma. Further studies are required to assess the impact of automated instruments against human performance in the clinical field.</p> <p>5.7 Total body photography for early melanoma diagnosis in high-risk subjects Total body photography (TBP) is widely used in the follow-up of high-risk patients [42], particularly those with large numbers of melanocytic naevi or dysplastic naevi. TBP has been recommended for the detection of new or changing pigmented lesions. Use of TBP is advocated in the follow-up of high-risk patients by the authors of most studies. [43-50] The technique has been said to reduce the need for unnecessary removal of benign lesions to exclude melanoma [45,46] and to increase the sensitivity and specificity of clinical examination for the detection of melanoma. [46,47]</p>	<p>support the guidance. In addition, there would be an additional requirement for laboratory staff, not calculated here. The additional annual employment costs of the histopathologists will be around £171,991 per network. (This cost has been included in the total cost for additional staff required as a result of the guidance, reported in the 'Organisation of skin cancer services' chapter.)</p>	

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	<p>Several authors point out that TBP was the key factor in the detection of most melanomas in their high-risk populations. [44-46,48] Two authors referred to the role of TBP in enabling the detection of clinically subtle or undiagnosable melanoma. [46,47] No appropriately controlled or randomised study has been undertaken to confirm these observations in a high-risk population. Almost all melanomas are new or changing lesions and baseline images are helpful in identifying a new or changing lesion.</p> <p>Evidence summary From a meta-analysis of nine level II studies prospectively performed in a clinical setting, the diagnostic accuracy for melanoma, as expressed by the relative diagnostic odds ratio, was 15.6 times higher for dermoscopy compared with naked eye examination. Sensitivity of dermoscopy was 18% (95% CI 9%-27%; P=0.002) higher than for eye examination, but there was no evidence of an effect on specificity. LoE: I, References: 21, 22, 24-31</p>		

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	<p>Dermoscopy has been shown to reduce the benign:malignant ratio of excised melanocytic lesions and reduce the number of patients referred for biopsy in a specialist setting LoE: II, References: 22, 23</p> <p>Four level II studies show consistently that sequential digital dermoscopic imaging allows the detection of suspicious dermoscopic change in melanomas that lack dermoscopic evidence of melanoma at a particular time LoE: II, References: 35–38</p> <p>To date only three automated instruments for the diagnosis of primary melanoma have been assessed against clinicians with a reasonable sample size in the clinical field. Here, instrument specificity was either inferior or equivalent to specialist diagnosis, and sample sizes were inadequate to assess differences in sensitivity LoE: II, References: 25, 40, 41</p> <p>Eight level IV studies and one level III-3 study examined surveillance of high-risk</p>		

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	<p>subjects with total body photography but only one included a comparison arm (of lower-risk subjects). All studies on high-risk patients showed early melanoma detection and/or high melanoma incidence.</p> <p>All studies were designed to assess the outcomes of surveillance in high-risk groups rather than the value of TBP.</p> <p>LoE: IV</p> <p>References: 43-51</p>		
Bemerkungen		<p>Diese Leitlinie bezieht sich auf MM und auf NMSC.</p> <p>Referenzen und ausführliche Evidenztabelle dieser Leitlinie werden wegen ihres Umfangs als separates Dokument zur Verfügung gestellt: GB NICE Guideline Evidence Review, S. 174 bis 211.</p>	<p>Das Gutachten der HAS, der Artikel der AHRQ, auf den die Leitlinie sich bezieht, sowie dessen Aktualisierung aus dem Jahr 2009 werden als Zusatzmaterial zu dieser Tabelle zur Verfügung gestellt.</p>

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2.2. Frage I.3. Konfokale Laserscan-Mikroskopie und optische Kohärenztomographie - De-novo-Recherche

Frage I.3. Welche Hilfsmittel oder apparativen Verfahren können die klinische Diagnostik des MM ggf. weiter verbessern

Beantwortung durch Adaptation (s.o. I.2.)

Ergänzende Recherche zu:

- Konfokale Laserscan-Mikroskopie (CLSM)
- Optische Kohärenztomographie (OCT)

2.2.1. PICO, Suchwörter

Suchwörter		
Stichwort	melanoma	Confocal, laserscan microscopy
Synonyme	melanoma	Clsm
Ober-/Unterbegriffe, MESH-Term	s. Suchstrategie	

2.2.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	"melanoma"[tiab] AND ("confocal"[tiab] OR "laserscan microscopy"[tiab] OR "clsm"[tiab]) NOT "uveal"[tiab] NOT "models, animal"[Mesh]	26.01.2012	275
	"melanoma"[tiab] AND ("oct"[tiab] OR "optical coherence tomography"[tiab] OR "optical coherence tomographic"[tiab] OR "multiphoton"[tiab]) NOT "uveal"[tiab] NOT "models, animal"[Mesh]		92
Cochrane Library	melanoma and (confocal or "laserscan microscopy" or clsm).ti,ab.	26.01.2012	1
	melanoma and (oct or "optical coherence tomography" or "optical coherence tomographic" or "multiphoton").ti,ab.	26.01.2012	4

Bemerkungen: Datum der Erst-Recherche für Medline und Cochrane war der 21.09.2010. Eine letzte Update-Recherche erfolgte am 26.01.2012 für Medline bzw. am 19.01.2012 für Cochrane. In den Tabellen angegeben sind die Zahlen der letzten Update-Recherche.

31.08.2012: Aufgrund der eingegangenen Kommentare im Rahmen der Konsultationsphase in Bezug auf die Literaturoauswahl zur konfokalen Laserscanmikroskopie wurde die Literatur, die bei der systematischen Recherche gefunden wurden, reevaluiert. Die Tabelle wurde daraufhin ergänzt entsprechend der angegebenen Ein- und Ausschlußkriterien.

Abschluß Konsultationsphase, Stand 09/2012: Das Statement zur konfokalen Laserscanmikroskopie wurde aus der Leitlinie herausgenommen (Details: s. „Kommentare zur Konsultationsfassung“). Eine Überarbeitung der Evidenztabelle nach erneuter systematischer Literaturrecherche ist für das Update der Leitlinie geplant.

2.2.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	372
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews, Bench Research CLSM: nur Artikel, bei Sensitivität und Spezifität bestimmt wurden
Anzahl nach Abstractscreening	29
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	9

2.2.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Subtopic: Optical coherence tomography (OCT), Multiphoton laser tomography (MLT)							
Dimitrow et al. (2009)	To examine the clinical applicability of	Diagnostic study	83 patients	Sensitivity and specificity in and ex vivo	Overall sensitivity 75% in vivo, 93% ex vivo	Specificity and sensitivity for single criteria: see	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<p>multiphoton laser tomography with regard to statistical evaluation of sensitivity, specificity, accuracy, and reliability.</p>			<p>Accuracy</p> <p>Interobserver reliability</p>	<p>Specificity 80% in vivo, 74% ex vivo</p> <p>Diagnostic accuracy 85% in vivo, 97% ex vivo</p> <p>Interobserver agreement: kappa values for different criteria ranging from 0.6 to 0.8</p>	<p>full-text of publication</p>	
<p>Gambichler et al. (2007)</p>	<p>To visualize and characterize melanocytic skin lesions (MSL) by using OCT in vivo, compare OCT features of benign nevi (BN) and MM, and histologically validate the OCT findings.</p>	<p>Diagnostic study</p>	<p>75 patients with 92 MSL</p>	<p>Frequency of several characteristics of lesions</p>	<p>See full-text for frequency of all investigated characteristics of lesions.</p>	<p>The diagnostic performance of OCT in the diagnosis of MSL could not be fully determined. Sensitivity and specificity studies also including other skin tumors have not been performed</p>	<p>3b</p>
<p>Subtopic: Confocal laser scan microscopy (CLSM)</p>							

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Gerger et al. (2007)	To validate diagnostic confocal examination of melanocytic skin tumours using unselected tumour images.	A total of 3709 unselected CLSM tumour images obtained from 20 malignant melanomas and 50 benign naevi	60 patients	Sensitivity and specificity Positive and negative predictive value (PPV, NPV) Diagnostic accuracy	Sensitivity 97.5% Specificity 99% PPV 97.5% NPV 99% Diagnostic accuracy 92.4% for benign naevi and 97.6% for melanoma images	High risk of verification bias (no histology if diagnosed "on unequivocal clinical and conventional dermoscopic criteria as benign naevi") Computerized images were provided, a loss in sensitivity or specificity through acquisition of the images by an unexperienced examiner could therefore not be observed	3b
Gerger et al. (2005)	To systematically validate CLSM in diagnosing melanocytic skin tumors in an observer-blinded manner, and to evaluate	Diagnostic study	88 patients with 117 lesions (90 benign nevi, 27 melanomas)	Sensitivity, specificity Positive and negative predictive value (PPV, NPV)	5 independent observers without previous experience in CLSM 2 Residents: sensitivity 96.3%, specificity 100%	High risk of verification bias (selective histopathological confirmation of diagnosis)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	morphologic features determined by CLSM for their presence or absence, diagnostic performance, and reliability.				<p>and 99%, PPV 100% and 96.3%, NPV 99%</p> <p>Senior physician without dermatopathologic qualification: sensitivity 92.6% and specificity 99%, PPV 96.2%, NPV 98%</p> <p>2 Dermatopathologists: sensitivity 96.3% and 59.3%, specificity 94% and 96%, PPV 81.3% and 80%, NPV 99% and 89.7%</p> <p>Overall sensitivity 88.2%, specificity 97.6%, PPV 90.7%, NPV 96.9%.</p>		
Gerger et al. (2006)	To systematically investigate the diagnostic impact	Diagnostic study	119 patients with 117 melanocytic and 45 non-	Sensitivity, specificity	Diagnostic differentiation of MM from BCC, BN,	High risk of verification bias (see above)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	and reliability of well described morphologic features in a large series of melanocytic and nonmelanocytic skin tumors.		melanocytic skin lesions	Positive and negative predictive value (PPV, NPV)	and SK reached sensitivity and specificity values of 85.19% and 98.52% (Observer 1), 92.59% and 98.52% (Observer 2), and 92.59% and 99.26% (Observers 3 and 4), respectively with the following overall performance: sensitivity, 90.74%; specificity, 98.89%; PPV, 94.22%; and NPV, 98.17%.		
Gerger et al. (2008)	To assess the applicability of image analysis and a machine learning algorithm on diagnostic discrimination of benign and malignant melanocytic skin tumours in in vivo confocal laser-	Diagnostic study	60 patients (total of 857 CLSM tumour images including 408 benign nevi and 449 melanoma images)	Sensitivity, specificity	Correct classification by CART analysis in 97.55% and 96.32% of melanoma and nevi images, overall performance 96.97% Human observer: sensitivity 85.52%,	Use of pre-selected CLSM images (high risk of selection bias)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	scanning microscopy (CLSM).				specificity 80.15%, overall performance 82.84%, positive predictive value 82.58%, negative predictive value 83.42%		
Koller et al. (2010)	To investigate the applicability of an automated image analysis system using a machine learning algorithm on diagnostic discrimination of benign and malignant melanocytic skin tumours in reflectance confocal microscopy (RCM)	Diagnostic study	178 patients with 16269 RCM tumor images	Diagnostic accuracy	<p>Classification tree analysis: correct classification in 93.60% of melanoma and 90.40% of nevi images of the learning set</p> <p>When applied to the independent test set $46.71 \pm 19.97\%$ (range 7.81–83.87%) of the tumour images in benign melanocytic skin lesions were classified as 'malignant', in contrast to $55.68 \pm$</p>	<p>Risk of verification bias (verification by histopathology dependent on clinical examination)</p> <p>ROC curve: see full-text</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>14.58% (range 30.65–83.59%; t-test: $P < 0.036$) in malignant melanocytic skin lesions</p> <p>78.95% of melanocytic skin tumours (62.50% of the melanoma and 84.50% of the nevi) correctly classified by independent clinical dermatologist</p>		
Langley et al. (2007)	The aim of this study was to evaluate the diagnostic accuracy of CSLM compared to dermoscopy in a prospective examination of benign and malignant melanocytic lesions.	Diagnostic study	125 patients	<p>Sensitivity, specificity</p> <p>Positive and negative predictive value (PPV, NPV)</p>	<p>Dermoscopy: sensitivity 89.2%, specificity 84.1%, PPV 70.2%, NPV 94.9%</p> <p>CSLM: sensitivity 97.3%, specificity 83.0%, PPV 70.6%, NPV 98.6%</p> <p>No melanomas</p>	<p>No verification bias (all diagnoses were confirmed histologically)</p> <p>Clinical, dermoscopic and confocal imaging were performed sequentially by a single observer; result of clinical examination and</p>	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					misidentified when both techniques were used together	dermatoscopy may lead to bias in confocal examination	
Lorber et al. (2009)	To examine the correlation between objectively reproducible image-analysis features und visual morphology in melanocytic skin tumours using CLSM.	Diagnostic study	60 patients with 70 melanocytic skin lesions	Diagnostic accuracy	CART analysis of the whole set of CLSM tumour images correctly classified 97.55% of melanoma images and 96.32% of nevi images.	High risk of verification bias (selective histopathological confirmation of diagnosis).	3b

Anmerkung: Bei Studien, die für zwei oder mehrere Teilfragen relevant sind, ist nur der Ergebnisteil und LoE erneut angegeben, für die übrigen Felder wird auf die erste Erwähnung der Studie in der Evidenztabelle verwiesen.

2.2.5. Literatur

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Gambichler T, Regeniter P, Bechara FG, et al. Characterization of benign and malignant melanocytic skin lesions using optical coherence tomography in vivo. *J Am Acad Dermatol* 2007;57:629-637

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Koller S, Wiltgen M, Ahlgrimm-Siess V, et al. In vivo reflectance confocal microscopy: automated diagnostic image analysis of melanocytic skin tumours. *J Eur Acad Dermatol Venereol* 2010

Langley RG, Walsh N, Sutherland AE, et al. The diagnostic accuracy of in vivo confocal scanning laser microscopy compared to dermoscopy of benign and malignant melanocytic lesions: a prospective study. *Dermatology* 2007;215:365-372
Lorber A, Wiltgen M, Hofmann-Wellenhof R, et al. Correlation of image analysis features and visual morphology in melanocytic skin tumours using in vivo confocal laser scanning microscopy. *Skin Res Technol* 2009;15:237-241

2.3. Frage I.6., I.7., I.8., VII.6. Ausbreitungsdiagnostik bei Patienten mit malignem Melanom – De-novo-Recherche

Frage I.6. Welche Ausbreitungsdiagnostik ist bei asymptomatischen Patientien bei Diagnose des Primärtumors bis Stadium IIA/ab Stadium IIB indiziert?

Frage I.7. Welche Ausbreitungsdiagnostik ist bei Patientien mit Verdacht auf bzw. Nachweis von lokoregionaler Metastasierung indiziert?

Frage I.8. Welche Ausbreitungsdiagnostik ist bei Patientien mit Verdacht auf bzw. Nachweis von Fernmetastasen indiziert?

Frage VII.6. Welche Unersuchungen sind im Rahmen der Nachsorge bei asymptomatischen Patientien indiziert?

Für die Fragen I.7 und I.8 fand 2015 eine Aktualisierungsrecherche statt.

2.3.1. PICO, Suchwörter

Verfahren:

- LK-Sono
- Röntgen-Thorax
- Abdomen-Sono
- MRT
- CT
- PET
- PET/CT
- Szintigraphie
- Labor

PICO-Unterfragen:

- Wie ist die Sensitivität und Spezifität des Verfahrens zur Diagnose von Metastasen des MM bei Primärdiagnose?
- Ändert die Durchführung des Verfahrens bei Patientien mit Primärdiagnose des MM das Krankheitsstadium?
- Ändert die Durchführung des Verfahrens bei Patientien mit Primärdiagnose des MM die Therapie?
- Ändert die Durchführung des Verfahrens bei Patientien mit Primärdiagnose des MM das Überleben?
- Wie hoch sind die zusätzlichen Kosten bei Durchführung des Verfahrens bei Patientien mit Primärdiagnose des MM?

2.3.2. Datenbanken, Suchstrategie, Trefferzahlen

2.3.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche		Der letzten Update-Recherche:	Insgesamt (Update-Recherche)
Medline	<p>"melanoma"[tiab] AND ("staging"[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR "sonography"[all fields]) OR ("lymph nodes"[all fields] OR ("lymph"[all fields] AND "nodes"[all fields]) OR "lymph nodes"[all fields] OR ("lymph"[all fields] AND "node"[all fields]) OR "lymph node"[all fields]))</p> <p>"melanoma"[tiab] AND ("staging"[all fields] OR "diagnosis"[all fields]) AND ("chest X-ray"[all fields] OR "chest radiography"[all fields] OR "Radiography, Thoracic"[Mesh])</p> <p>"melanoma"[tiab] AND ("staging"[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR "sonography"[all fields]) OR "abdomen"[all fields] OR "abdominal"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])</p> <p>"melanoma"[tiab] AND ("staging"[all fields] OR "diagnosis"[all fields]) AND ("Magnetic Resonance Imaging"[Mesh] OR "Magnetic Resonance Imaging"[all fields] OR "mri"[all fields] OR "magnetic resonance"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])</p> <p>"melanoma"[tiab] AND ("staging"[all fields] OR "diagnosis"[all fields]) AND ("Tomography, X-Ray Computed"[Mesh] OR "computer tomography"[all</p>	26.01.2012	3153 83 588 595 936

Datenbank	Suchstrategie	Datum	Treffer
	<p>fields] OR "ct"[all fields] OR "Tomography, Spiral Computed"[Mesh] OR "Tomography Scanners, X-Ray Computed"[Mesh] OR "Positron-Emission Tomography"[Mesh] OR "positron-emission tomography"[all fields] OR "pet"[all fields] OR "Tomography, Emission-Computed, Single-Photon"[Mesh] OR "single-photon emission computed tomography"[all fields] OR "spect"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])</p> <p>"melanoma"[tiab] AND ("staging"[tiab] OR "diagnosis"[tiab]) AND ("scintigraphy"[tiab] OR "scinti*"[tiab]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])</p> <p>"melanoma"[tiab] AND ("LDH"[all fields] OR "lactate dehydrogenase" OR "S100"[all fields] OR "MIA"[tiab] OR "melanoma-inhibiting activity"[tiab]) AND ("staging"[all fields] OR "diagnosis"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])</p>		<p>66</p> <p>594</p>
Cochrane Library	<p>(melanoma and (staging or diagnosis) and ("chest x-ray" or "chest radiography")).ti,ab.</p> <p>(melanoma and (staging or diagnosis) and ("ultrasonography" or "sonography" or "ultrasound" or sonogr*)).ti,ab.</p> <p>(melanoma and (staging or diagnosis) and ("magnetic resonance" or mri)).ti,ab.</p> <p>(melanoma and (staging or diagnosis) and ("computer tomography" or ct or "positron emission tomography" or pet or spect or "single-photon emission computed tomography" or "spect ct" or "pet ct")).ti,ab.</p>	19.01.2012	<p>7</p> <p>7</p> <p>5</p> <p>9</p>

Datenbank	Suchstrategie	Datum	Treffer
	(melanoma and (staging or diagnosis) and (scintigraphy or scinti*)).ti,ab.		4
	(melanoma and (staging or diagnosis) and (ldh or "lactate dehydrogenase" or s100* or mia or "melanoma inhibiting activity")).ti,ab.		10
Embase	(melanoma and (staging or diagnosis) and ("chest x-ray" or "chest radiography")).ti,ab.	23.01.2012	79
	(melanoma and (staging or diagnosis) and ("ultrasonography" or "sonography" or "ultrasound" or sonogr*)).ti,ab.		546
	(melanoma and (staging or diagnosis) and ("magnetic resonance" or mri)).ti,ab.		431
	(melanoma and (staging or diagnosis) and ("computer tomography" or ct or "positron emission tomography" or pet or spect or "single-photon emission computed tomography" or "spect ct" or "pet ct")).ti,ab.		777
	(melanoma and (staging or diagnosis) and (scintigraphy or scinti*)).ti,ab.		142
	(melanoma and (staging or diagnosis) and (ldh or "lactate dehydrogenase" or s100* or mia or "melanoma inhibiting activity")).ti,ab.		317
<p>Bemerkungen: Datum der Erst-Recherche für Medline und Cochrane war der 17.08.2010. Die erste EMBASE-Recherche erfolgte am 11.05.2011. Eine letzte Update-Recherche (initiale Suche, Ergänzungsrecherche) erfolgte am 23.01.2012 für EMBASE, am 26.01.2012 für Medline bzw. am 19.01.2012 für Cochrane. In den Tabellen angegeben sind die Zahlen der letzten Update-Recherche.</p> <p><u>Bezüglich Tumor-Marker:</u> da eine Meta-Analyse (Mocellin et al. 2008) vorliegt, wurden lediglich Studien eingeschlossen, die nicht in der Meta-Analyse enthalten waren, die nach der Metaanalyse erschienen sind oder die bestimmte Teilaspekte abdecken, die in der Meta-analyse nicht berücksichtigt wurden.</p>			

Datenbank	Suchstrategie	Datum	Treffer
<p><u>Bezüglich PET und PET/CT:</u> Die erste systematische Recherche zeigte zwei Meta-Analysen (Krug und Jimenez-Requena). Einzelne Studien wurden nur mit aufgenommen, sofern sie noch nicht in diesen beiden Meta-Analysen enthalten waren oder Aspekte beinhalteten, die aus den Meta-Analysen nicht hervorgingen. Da die Meta-Analyse von Xing erst im Rahmen einer Update-Recherche identifiziert wurde, sind einzelne Studien, die in der Meta-analyse enthalten sind, auch in dieser Tabelle aufgeführt. Die Studien sind jedoch gekennzeichnet und haben einen dementsprechend schlechteren Evidenzgrad.</p> <p>Bei gleicher Suchstrategie zu den Fragen I.6, I.7, I.8 und VII.6 und teils Überschneidungen der Studien sind alle relevanten Recherche-Ergebnisse in dieser Tabelle zusammengefasst. Eine Übersicht über die Zuteilung der Studien zu den verschiedenen Fragestellungen befindet sich am Ende der Tabelle.</p>			

2.3.2.2. Aktualisierungsrecherche 2015 für I.7. und I.8

Datenbank	Suchstrategie	Datum	Treffer
Medline	<p>((("melanoma"[tiab] AND ("staging"[all fields] OR "diagnosis"[all fields]) AND(("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR"sonography"[all fields]) OR ("lymph nodes"[all fields] OR ("lymph"[all fields] AND "nodes"[all fields]) OR "lymph nodes"[all fields] OR ("lymph"[all fields] AND "node"[all fields]) OR "lymph node"[all fields]))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication])))</p> <p>((("melanoma"[tiab] AND ("staging"[all fields] OR "diagnosis"[all fields]) AND("chest X-ray"[all fields] OR "chest radiography"[all fields] OR "Radiography,Thoracic"[Mesh]))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication])</p> <p>((("melanoma"[tiab] AND ("staging"[all fields] OR "diagnosis"[all fields]) AND(("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR"sonography"[all fields]) OR "abdomen"[all fields] OR "abdominal"[all fields])NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh]))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication])</p> <p>((("melanoma"[tiab] AND ("staging"[all fields] OR "diagnosis"[all fields]) AND ("Magnetic Resonance Imaging"[Mesh] OR "Magnetic Resonance Imaging"[all fields] OR "mri"[all fields] OR "magnetic resonance"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh]))) AND ("2012.01.27"[Date -</p>	16.09.2015	716
			14
			170
			192

	<p>Publication] : "3000"[Date - Publication])</p> <p>("melanoma"[tiab] AND ("staging"[all fields] OR "diagnosis"[all fields]) AND ("Tomography, X-Ray Computed"[Mesh] OR "computer tomography"[all fields] OR "ct"[all fields] OR "Tomography, Spiral Computed"[Mesh] OR "Tomography Scanners, X-Ray Computed"[Mesh] OR "Positron-EmissionTomography"[Mesh] OR "positron-emission tomography"[all fields] OR "pet"[all fields] OR "Tomography, Emission-Computed, Single-Photon"[Mesh] OR "single-photon emission computed tomography"[all fields] OR "spect"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication])</p> <p>("melanoma"[tiab] AND ("LDH"[all fields] OR "lactate dehydrogenase" OR "S100"[all fields] OR "MIA"[tiab] OR "melanoma-inhibiting activity"[tiab]) AND ("staging"[all fields] OR "diagnosis"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication])</p>		386	
Cochrane Library	<p>(melanoma and (staging or diagnosis) and ("chest x-ray" or "chest radiography")).ti,ab.</p> <p>(melanoma and (staging or diagnosis) and ("ultrasonography" or "sonography" or "ultrasound" or sonogr*)).ti,ab.</p> <p>(melanoma and (staging or diagnosis) and ("magnetic resonance" or mri)).ti,ab.</p> <p>(melanoma and (staging or diagnosis) and ("computer tomography" or ct or "positron emission tomography" or pet or spect or "single-photon emission computed tomography" or "spect ct" or "pet ct")).ti,ab.</p> <p>(melanoma and (staging or diagnosis) and (scintigraphy or scinti*)).ti,ab.</p> <p>(melanoma and (staging or diagnosis) and (ldh or "lactate dehydrogenase" or s100* or mia or "melanoma inhibiting activity")).ti,ab.</p>	16.09.2015	7	18
			14	20
			4	11
<p>Die Update-Literatur-Recherche erfolgte am 16.09.2015 und schloss alle Studien mit ein, die ab dem 26.01.2012 auf Medline bzw. ab 2012 auf Cochrane erschienen sind. Es wurden nur Studien aufgenommen, die einen hohen Evidenzlevel besitzen. Da in Hinblick auf die apparative Diagnostik keine randomisiert kontrollierten Studien vorliegen, wurde in diesem Fall ein „hohes Evidenzlevel“ bis LoE von 2b definiert.</p>				

2.3.3. Auswahlkriterien

2.3.3.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer	8349
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews, Bench Research
Anzahl nach Abstractscreening	296
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	114

2.3.3.2. Aktualisierungsrecherche 2015

Auswahl der Literatur	
Gesamttreffer	1555
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews, Bench Research
Anzahl nach Abstractscreening	1202
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	3

2.3.4. Evidenztabelle (zusammengefaßt für I.6., I.7., I.8., VII.6.)

2.3.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Subtopic LYMPH NODE ULTRASOUND							
Xing et al. (2011)	To examine the utility of ultrasonography, computed tomography (CT), positron emission tomography (PET), and a combination of both (PET-CT) for the staging and surveillance of melanoma patients.	Systematic review and meta-analysis	10 528 patients with cutaneous melanoma at primary diagnosis or under surveillance (follow-up)	Sensitivity, specificity Diagnostic odds' ratio (OR)	Data for initial staging of regional nodes: Sensitivity 60% Specificity 97% Diagnostic OR 42	Very large patient cohort, but patients under follow-up included	1a
Bafounta et al. (2004)	To investigate whether lymph-node ultrasonography improves detection of nodal invasion during the initial staging	Systematic review and meta-analysis of 12 published diagnostic studies until December 2003	6642 patients Predominantly stage I and II, six studies also stage III, very few (1.9% in one study) stage IV	Sensitivity and specificity Odds' ratios Positive and negative likelihood ratios	Odds ratio of sonography: 1755 (95% CI 726-4238) Odds' ratio of palpation 21 (4-111) Sonography: Positive likelihood	Variations in the definition of false negatives and verification bias in included studies	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	and follow-up of patients with melanoma.				ratio 41.9, negative likelihood ratio 0.024 Palpation: Positive likelihood ratio 4.55, negative likelihood ratio 0.22		
Voit et al. (2010)	The aim of this study was to evaluate a number of specifically defined morphology US patterns and to correlate this with tumor involvement of the SN.	Prognostic and diagnostic study	400 patients with CM before SLNE	Sensitivity, specificity Positive predictive value, negative predictive value Overall and distant-metastasis-free survival	Highest sensitivity and PPV in following combination: presence of peripheral perfusion, loss of central echoes, and balloon-shaped lymph nodes Sensitivity 82% Specificity 80% PPV 52% NPV 94% 5-year OS according to peripheral perfusion 81% and 92% for present and absent 5-year OS for the	Preliminary report (400 of 650 patients)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					loss of central echoes 49% vs. 92% when echoes still present 5-year OS rates for the presence and absence of a balloon-shaped lymph node 48% and 92%		
Sibon et al. (2007)	To evaluate the ability of high-resolution ultrasonography (hrUS) to detect sentinel-node (SN) melanoma metastases preoperatively before sentinel-node biopsy (SNB), to define hrUS resolution, and to evaluate which US criteria should be used.	Diagnostic study	131 consecutive patients with 132 ≥ 1 -mm thick or ulcerated CM	Sensitivity and specificity Positive and negative predictive value Positive and negative likelihood ratios	Targeted high-resolution sonography for the detection of SLN: Stringent criteria: Sensitivity 8.8% Specificity 95.9% PPV 42.9% NPV 75.2% Non-stringent criteria: Sensitivity 20.6% Specificity 89.8% PPV 41.2% NPV 76.5%	Patients with mucosal melanoma included	1b
Saiag et al. (2005)	(1) to compare the respective ability of ultrasonography	Diagnostic study	160 consecutive patients with stage I to stage III CM	Sensitivity, Specificity	Sonography: Sensitivity 76.9% Specificity 98.4%	Patients with mucosal melanoma	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	and palpation to detect nodal metastasis during initial staging and follow-up in patients having melanomas (2) to assess which ultrasound criteria should be used to define metastasis in cases of cutaneous or mucosal melanoma (3), because scar tissue can modify ultrasonographic images, to evaluate whether ultrasonography remains useful once patients have undergone radical LD				Palpation: Sensitivity 41.5% Specificity 95.7%	included	
Stoffels et al. (2011)	to clarify the reliability of preoperative ultrasonography (US) in direct	Diagnostic study	221 patients with primary malignant melanoma with a Breslow index of ≥ 1.0	Sensitivity Specificity PPV NPV	US: Sensitivity: 13.6% Specificity: 96.9% PPV: 97.2% NPV: 12,6%	Reference standard for SLNE not described	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	comparison to the result of SLNE and seeks to identify potential advantages of preoperative ultrasound if performed in conjunction with lymphoscintigraphy in detecting malignant melanoma metastases in sentinel lymph node (SLN).		mm		<p>SLNE alone: Sensitivity: 94% Specificity: 98.6% PPV 100% NPV 98,3%</p> <p>Preoperative US in conjunction with dynamic lymphoscintigraphy, followed by SLNE: detecting ratio: 100% (n = 28) for micrometastases, 98.6% (n = 42/ 43) for macrometastases</p>		
Hinz et a. (2011)	To evaluate whether high-resolution ultrasound combined with power Doppler sonography (PDS) is an appropriate tool for preoperative	Diagnostic study	81 consecutive patients with CM in whom dissection of SLNs was indicated underwent ultrasound examinations before and after the preoperative lymphoscintigraph	<p>sensitivity, specificity, PPV, NPV</p> <p>positive likelihood ratio</p> <p>negative likelihood ratio</p>	<p>A total of 170 SLNs (mean 2.1 per patient) were removed and examined by histopathology.</p> <p>sensitivity, specificity, PPV, NPV of ultrasound: 22.2%</p>	<p>patient cohort with only 9 positive SLNs in total</p> <p>No information about follow-up</p>	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	identification and characterization of sentinel lymph nodes (SLNs) in patients with cutaneous melanoma.		y.		(95% CI = 2.8-60.0), 100% (95% CI = 97.7-100.0), 100.0% (95% CI = 15.8-100.0), and 95.8% (95% CI = 91.6-98.3), respectively. positive likelihood ratio: 0 negative likelihood ratio: 0.78.		
Chai et al. 2011	To assess feasibility and staging results of clinically targeted ultrasound (before lymphoscintigraphy) compared to SLNB.	Diagnostic study	325 patients with melanoma underwent ultrasound before SLNB without palpable lymphadenopathy in regional nodal basins	Sensitivity, specificity, PPV, NPV	sensitivity of ultrasound: 33.8%, specificity: 85.7%, PPV: 36.5%, NPV: 84.2%	No information about time interval between US and SLNB Confidence interval not given	2b
Sanki et al. (2009)	To reassess traditional ultrasound descriptors of sentinel lymph node (SLN)	Diagnostic study	716 CM patients	Sensitivity and specificity Positive and negative predictive value Positive and	Targeted high-resolution sonography for the detection of SLN: Sensitivity 24.3% Specificity 96.8%	Design (retrospective vs. prospective) not described	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastases, to determine the minimum cross-sectional area (CSA) of an SLN metastasis detectable by ultrasound (US), and to establish whether targeted, high-resolution US of SLNs identified by lymphoscintigraphy before initial melanoma surgery can be used as a substitute for excisional SLN biopsy.			negative likelihood ratios Diagnostic accuracy	PPV 60.3% NPV 86.2% Diagnostic accuracy 86.7%		
Testori et al. (2005)	(1) To obtain, using US, a pre-operative indication of the presence or absence of metastatic deposits in the sentinel node (SN); (2) to obtain, using	Diagnostic study	Of 300 melanoma patients who underwent SNB, 88 received sonography of the lymph nodes preoperatively	Sensitivity, specificity Positive and negative predictive value	Sensitivity 94.1% Specificity 89.8% PPV 64% NPV 98.7%	Inclusion criteria for patients who received pre-operative sonography unclear	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	US, the precise pre-operative location of superficial or deep, or peculiarly sited, SNs; and (3) to evaluate the role of US in the early diagnosis of falsenegative SNs (i.e. recurrences in the lymph node basin) during follow-up.						
Hocevar et al. (2004)	The aim of this study was to evaluate the ability of a combination of US and US-FNAB to stage the regional lymph node basins in patients with MM.	Diagnostic study	57 patients with CM, in whom SLN biopsy was planned	Sensitivity and specificity Positive and negative predictive value	Sensitivity 71% Specificity 84% PPV 59% NPV 90%	Risk of verification bias Design of study not described (retrospective versus prospective)	2b
Hafner et al. (2004)	To evaluate the sensitivity and specificity of baseline staging in the early detection	Diagnostic study	100 consecutive patients with CM > 1.0 mm	Sensitivity, specificity Positive and negative predictive value	Sensitivity 8% Specificity 88% PPV 18% NPV 73%	Risk of verification bias	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of regional lymph node metastases or distant metastases in patients with MM.						
Kunte et al. (2009)	The aim of this study was to evaluate the ability of high resolution B-mode ultrasonography (US) for pre-operative identification and characterization of sentinel lymph nodes (SLN) in patients with cutaneous melanoma.	Prospective diagnostic study	25 consecutive patients before SLN for CM	Sensitivity, specificity Positive and negative predictive value	Sensitivity 33.3% Specificity 100.0% PPV 100.0% NPV 87.9%	Risk of verification bias Small patient cohort	3b
Schmid-Wendtner et al. (2004)	to evaluate whether signal enhanced color Doppler sonography (CDS) is superior to native CDS in detection of	Diagnostic study	22 melanoma patients	Sensitivity Specificity	signal-enhanced sonography : sensitivity = 92.3%, specificity=100.0% . For melanoma metastases, a sensitivity of	Prospective two-center study lack of histopathologic correlation in all presumptive sonographic	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	characteristic vascularity patterns that are important for the differentiation between benign and malignant lymphadenopathy in patients with cutaneous melanomas.				90.0% and a specificity of 85.7% was calculated. For both P-values <0.05	diagnoses small study group sensitivity and specificity of native CDS not given study included in Xing et al. 2011	
Uren (1999)	to determine if high-resolution ultrasound could identify metastases in newly palpable lymph nodes found during clinical follow-up for melanoma, and to define the ultrasound features that were associated with this diagnosis	Diagnostic study	52 patients (61 individual node fields)	Ultrasound features in metastatic lymph nodes Sensitivity specificity	specificity = 87% sensitivity = 94% accuracy = 89% If presence of 2 US-features (=node thicker greater than two-third of the length and low-level internal echos) were present: Sensitivity = 94%, specificity = 100%, accuracy 98%	No information about the time interval between ultrasound and FNAB/excision biopsy Small population Different examined fields: axilla, groin, supraclaviculaire, submental, cervical study included in Xing et al. 2011	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Subtopic CHEST X-RAY							
Wang et al. (2004)	To examine the yield of a chest radiograph and serum lactate dehydrogenase (LDH) in the work-up for newly diagnosed localized melanoma, and to investigate how often the results of chest radiograph and LDH alter the initial surgical management.	Diagnostic study	210 CM patients without clinical evidence of metastasis	False positives Alteration of surgical management	False positives 15/210 (7%) Alteration of surgical management in 0%		2b
Hafner et al. (2004)	See above	Diagnostic study	100 consecutive patients with CM > 1.0 mm	Sensitivity, specificity Positive and negative predictive value	Sensitivity - Specificity 96% PPV 0% NPV 100%	study included in Xing et al. 2011	2b
Vermeerenet et al. (2011)	to evaluate therapeutic consequences of preoperative staging with Chest	diagnostic study	248 medical records of patients treated for primary melanoma	False positives	Preoperative CXR did not identify pulmonary metastasis and did not change	Reference standard: complementary radiodiagnostic imaging and/or	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	X-ray (CXR) in patients with a primary melanoma planned for sentinel node biopsy (SNB).		CXR in 227 patients CXRs were made prior to SNB		planned treatment strategies. In 5%, the CXR was inconclusive → false positives	follow-up.	
Panagiotou et al. (2001)	To determine which imaging modalities should be performed during the evaluation of patients with local-regional malignant melanoma	Retrospective study	158 asymptomatic patients submitted to at least a chest X-ray, an abdominal US and a CT of the chest, abdomen and pelvis	true-positive and false-positive rate	TP: 26.6% FP: 7.6% In 12% CT was the only imaging modality depicting metastases highest positive yield During the surveillance period, 118 asymptomatic patients relapsed. Detection of relapse: - in 33.1% by physical examination - in 38.1% by chest X-ray - in 16,9% by		3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					abdominal CT		
Yancovitz et al. (2007)	To investigate whether initial imaging led to a change in stage or treatment plan	Diagnostic study	158 patients, 135 with stage I/II disease and 23 with stage III disease	True and false positives and negatives	True positives 0/7 (0.0%), False-positives 5/7 (71.4%) True negatives 112/126 (88.9%) 2/126 lost to follow-up	study included in Xing et al. 2011	3b
Tsao et al. (2004)	To determine if earlier detection of pulmonary metastasis by routine chest radiography (CR) is associated with a prolonged survival.	Case-control study	994 CM patients in stages I – IV	Overall survival	28/1938 chest x-rays leading to first diagnosis of CM stage IV (1.4%) Overall survival according to Kaplan-Meier curve: no difference between patients with known stage IV at the time of diagnosis and initial diagnosis of stage IV by x-ray False positives (of all x-rays): 3.5%	Cohort consisting of stage I – IV patients	3b
Hofmann et al. (2002)	Assessment of the performance,	Diagnostic study with historical	661 patients (stage I/II: 630	True and false positives and	524 total chest x-rays	Diagnostic standard	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	costs and survival benefits of staging methods (history and physical examination; chest X-ray; ultrasonography of the abdomen; high resolution sonography of the peripheral lymph nodes) at initial staging and during follow-up of stage I/II+III disease.	cohort; economical evaluation	patients, stage III: 27 patients, stage IV: 4 patients)	negatives Detection rate Cost-efficiency of imaging procedures Survival	1 true positive (0.2%) 23 false positives (4.4%) Detection rate 3.2% Cost of chest x-ray at initial staging: 11761 EUR (1887 EUR due to false positive results)	procedures varied over time; no defined gold standard of diagnosis	
Terhune et al. (1998)	To evaluate the use of an initial staging chest x-ray film in asymptomatic patients who present with localized primary cutaneous melanoma.	Diagnostic study	876 CM patients at initial staging	True and false positives .	130/876 (15%) patients with suspicious findings Additional workup led to 1/876 true positives (0.1%) 129/876 false positives (14.7%)	X-rays not obtained from all patients "Initial" chest x-ray up to 6 months after diagnosis	3b
Iscoe et al. (1986)	The description of predictive value of clinical, laboratory and radiologic	Diagnostic study	393 consecutive CM patients	True and false positives Positive and negative predictive	Number of chest x-rays: 345 True positives: 0 False positives: 8	Index tests not carried out on all patients	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	investigations in the staging of patients with clinical stage I melanoma.			value	Positive predictive value: 0% Negative predictive value: 97.6%		
Khansur et al. (1989)	To evaluate the role of staging workup in primary and recurrent malignant melanoma.	Diagnostic study	115 patients with primary CM (72 in localized stage) and 28 patients with recurrent disease	True and false positives	0/72 true positives 2/72 false positives (3%)	Criteria for selecting staging examinations unclear	3b-
Ardizzoni et al. (1987)	To evaluate the yield, in terms of cost-benefit-ratio, of a multimodal staging procedure consisting of multiple nuclear scans, chest X-ray and abdominal ultrasonography to detect silent metastases in asymptomatic melanoma patients	Diagnostic study	116 patients; clinically 93 in stage I and 23 in stage II	True and false positives and negatives	Positive results: 0 of 116 chest x-rays 0% true positives 0% false positives 2 patients with lung metastases later in follow-up => 2% false negatives, 98% true negatives	Design (prospective vs. retrospective) not clear Follow-up time not given	3b-
Meyer and Stolbach (1978)	To evaluate radiographic evaluation for the	Diagnostic study	53 CM patients without symptoms to suggest distant	True and false positives	4/53 true positives (8%) 0 false positives	Cohort probably included patients with lymph node	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	recognition of occult sites of metastatic disease beyond the regional nodes in malignant melanoma.		metastasis			metastases	
Zartman et al. (1987)	To answer the question whether extensive diagnostic staging procedures are justified for patients with primary diagnosis of melanoma	Cohort study	90 CM patients with level III and IV lesions	Positive results	No positive results for chest x-ray	Patients with complete staging included; indications for different staging examinations unclear	4
Goerz et al. (1986)	To investigate which staging and follow-up examinations are necessary for patients with malignant melanoma.	Diagnostic study	378 patients with histologically confirmed CM (stage not given)	True and false positives	0% positive results for chest x-ray at initial staging During follow-up examinations, distant metastasis was proven in 34/378 patients, in 32 of them by physical examination, in 2 by chest x-ray.		3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Kersey et al. (1985)	To determine the value of staging and serial follow-up investigations in newly diagnosed patients with completely excised primary cutaneous malignant melanoma	Diagnostic study	393 patients at primary diagnosis of CM	True and false positives	True positives 0 False positives 8/345 (2%)	Extent of staging examinations and extent/ length of follow-up depended on center and tumor site	3b-
Collins et al. (1993)	to determine whether the detection of metastatic disease would be reduced if the lateral projection were not obtained.	Diagnostic study	follow-up of 227 consecutive patients.	number of suspect lesions in PA and lateral radiographs	In 1 case was an abnormality evident on the lateral radiograph which was not previously detected on the PA films Normal PA and lateral radiograph: 60,8%. Abnormality equally visible on PA and lateral radiograph: 16,7%. Abnormality more easily visualized	Sensitivity and specificity not given No reference test Population not described in detail No information about the study design No information about selection criteria Sensitivity or specificity not given	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>on PA than on lateral radiograph: 11%.</p> <p>Abnormality more easily visualized on lateral than on PA radiograph: 4,4%.</p> <p>Abnormality on PA radiograph not visualized on lateral projection 6,6%. Abnormality on lateral radiograph not visualized on PA projection: 0,44%</p>		
Webb (1977)	to describe the frequency of radiographic patterns of thoracic metastasis in patients with melanoma, and to correlate these patterns with the symptoms, clinical course, and survival of the	diagnostic study	65 patients with malignant melanoma metastatic to the thorax	<p>radiographic patterns of thoracic metastasis</p> <p>Survival rates</p>	<p>Abnormalities in chest x-ray in 42/62 patients</p> <p>Survival: see full-text</p>	<p>11 patients received x-ray and tomogram</p> <p>Tissue specimen in only 31</p> <p>Small population, asymptomatic patients included</p>	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients.						
Subtopic ABDOMINAL ULTRASOUND							
Hafner et al. (2004)	See above	See above	100 consecutive patients with CM > 1.0 mm	Sensitivity, specificity Positive and negative predictive value	Sensitivity - Specificity 97% PPV 0% NPV 100%		2b
Panagiotou et al. (2001)	See above	See above	See above	See above	See above	See above	3b
Hofmann et al. (2002)	See above	See above	661 patients (stage I/II: 630 patients, stage III: 27 patients, stage IV: 4 patients)	True and false positives and negatives Detection rate Cost-efficiency of imaging procedures Survival	487 total abdominal sonographies 2 true positive (0.4%) 25 false positives (5.1%) Detection rate 6.5% Cost of chest x-ray at initial staging: 16618 EUR (6421 EUR due to false positive results)	Diagnostic standard procedures varied over time; no defined gold standard of diagnosis	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Pandalai et al. (2010)	To evaluate the clinical utility of standardized radiographic staging.	Diagnostic study	58 consecutive asymptomatic patients with stage III AJCC melanoma	True-positive (TP) rate false-positive (FP) rate	<p>Initial staging examinations: 9% TP, 91% FP</p> <p>All examinations: 3% TP; 23% FP.</p> <p>Analyzed per patient, in 37 (64%) of 58 patients, ≥ 1 examination was initially reported as positive. 3 patients (5%) had a TP and 34 (59%) had ≥ 1 FP report. The positive reports of the staging scans generated 45 additional examinations (0.78 per patient).</p> <p>analyzed by type of radiograph, the 5 TP findings were found in 3 (13%) of 23 suspicious chest CT scans, 1</p>	<p>Small sample size</p> <p>Sensitivity and specificity not given</p> <p>Small number of MRI/CT of the head, PET and bone scan</p> <p>No routine standardized staging procedure was followed</p>	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(5%) of 20 suspicious abdomen and pelvis CT scans, and in 1 (100%) of 1 PET scans. Of the 5 brain MRIs, 2 head CT scans, and 1 bone scan that were initially reported as "suspicious," none was proven to be TP. ratio of FP:TP: 34:3		
Kuan et al. (1988)	To emphasize the sensitivity and specificity of the examinations both for the detection of space-occupying lesions and for the assessment of extent of metastatic disease	Retrospective cohort study	88 patients with pathologically proven cutaneous melanoma in various clinical stages	Sensitivity specificity	In patients who had all 3 examinations (n=24): Sensitivity in detecting intra-abdominal metastasis:CT: 94% vs. US: 62% (P< 0.05) CT vs. LS: 38% (P< 0.01) In patients with only US and LS	Poor information about selection criteria and population Poor data about patients` follow-up Small population	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(n=64): Sensitivity US: 88% vs. LS 54% (P<0.01). CT detected metastases significantly earlier than US (P=0.03)		
Ardizzoni et al. (1987)	See above	See above	116 patients; clinically 93 in stage I and 23 in stage II	True and false positives and negatives	0/66 positives for liver involvement 1/66 true positives for iliac lymph node involvement (2%) 1/66 false positives for iliac lymph node involvement (2%)	Design (prospective vs. retrospective) not clear from description Follow-up time not given	3b-
Goerz et al. (1986):	See above	See above	378 patients with histologically confirmed CM	True and false positives	0% positive results	Stage of patients not given	3b-
Holloway et al. (1997)	To determine the frequency of gallbladder pathology, other	diagnostic study	464 patients with cutaneous melanoma except one which arose	Detection rate of metastasis	Ultrasound appearances typical of gallbladder	No further information about the population.	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	than gallstones in this group of patients.		on the nasal mucosa.		metastases in 4,1%		
Stutte (1989)	To describe ultrasonographic findings and to evaluate the significance of upper abdominal ultrasonography in assessing the spread of metastasizing malignant melanome during follow up.	Prognostic study Retrospective study	42 patients with distant metastases of CM	Mean overall survival	Mean survival time: - for patients with ≤ 3 liver metastases ≤ 3 cm diameter: 8,4 months - for patients with numerous metastases or metastases > 3 cm diameter: 4,3 months - for patients with isoechoic metastases: 2,6 months.	No information about inclusion criterias Small patient cohort	4
Zartman et al. (1987)	See above	See above	90 CM patients with level III and IV lesions	Positive results	No positive results for abdominal sonography	Patients with complete staging included; indications for different staging examinations unclear	4
Doiron et al. (1981)	To discuss	Diagnostic study	163 patients with	False negatives	Group 1:	Sensitivity and	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	which of these imaging modalities yields the most information in patients with intraabdominal metastatic melanoma		<p>malignant melanoma in clinical stage III examined by RN liver scan, US, and CT in various combinations over a 2-years-period.</p> <p>Patients were divided into 3 groups according to the examinations: (1) RN liver scan, US, and CT (38 patients) (2) RN liver scans and CT (10 patients) (3) US and RN liver scan.(115 patients)</p>	<p>(FN)</p> <p>False positives (FP)</p>	<p>CT, US and RN demonstrated 20, 22 and 23 normal results respectively and 18, 17 and 15 abnormal results respectively</p> <p>1 FN (CT) 1 FN (US) 8 FP and 1 FN (RN)</p> <p>Group 2: CT, RN demonstrated both 7 normal results and both 3 negative results. 2FP and 1 FN (RN)</p> <p>Group 3: US and RN demonstrated 52 and 75 normal results respectively and 43 and 40 abnormal results respectively</p> <p>2 FP (US) 10 FP (RN)</p>	<p>specificity not given</p> <p>No information about follow-up</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Subtopic MRI							
Hausmann et al. (2011)	to compare the diagnostic accuracy of whole-body MRI with the standard diagnostic algorithm (whole-body CT and brain MRI) in patients with stage III/IV MM.	diagnostic study	33 consecutively admitted patients with histologically confirmed diagnosis of stage III or IV MM	Sensitivity specificity	The sensitivity of whole-body MRI was observerdependent. Sensitivity: MRI vs. CT: 73.4 % vs. 78.2 %, $p = 0.0744$. Sensitivity in the detection of small (1–5 mm) pulmonary nodules: MRI vs. CT: 2.9 % vs. 66.9 %, $p < 0.0001$ Overall specificity: MRI vs. CT: 83.4 % vs. 50.4 %, $p < 0.0001$	Data interpretation by two blinded examiners	2b
Pfannenbergl et al. (2007)	to compare the overall and site-based accuracy and impact on	Diagnostic study	64 patients: 25 patients stage III, 39 patients stage IV	Sensitivity Specificity	The overall accuracy: PET/CT: 86.7% wbMRI: 78.8%	Cerebral lesions in wbMRI were recorded, but excluded from the	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patient management of positron emission tomography/computed tomography (PET/CT) and whole-body (wb) magnetic resonance imaging (MRI) in staging of advanced melanoma.			positive predictive value (PPV) negative predictive value (NPV) accuracy	CT: 75.0% PET: 74.3% PET vs. wbMRI: P = 0.0007 PET vs. PET/CT: P < 0.0001 . Sensitivity, specificity, TN, FN, TP, FP: see full text/table 2	analysis because of the lack of comparable PET data. The selection of inclusion criteria led to underestimated calculated specificity, because only the lesions suspicious of malignancy in one of the different methods were included in the study and compared by different methods. Study included in Xing et al. 2011 and Krug et al. 2008	
Dellestable et al. (2011)	to assess the Se and specificity (Sp) of wb-MRI with a diffusion sequence for detecting	Diagnostic study	40 patients were included and a total of 72 metastases were noted	Sensitivity specificity	CT: sensitivity: 80%, specificity: 95% PET/CT	no detailed information about patient cohort small patient	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma metastasis compared to PET/CT.				<p>sensitivity: 74% specificity: 89%</p> <p>Wb-MRI sensitivity: 83% specificity: 96%</p> <p>The sensitivity of MRI was distinctly superior to PET/CT for both hepatic and pulmonary lesions.</p>	cohort	
Laurent et al. (2011)	to compare whole-body MRI with a multi-contrast protocol including a DW (Diffusion Weighted) sequence to PET-CT using (18)FDG for staging advanced melanoma.	Diagnostic study	35 patients	Sensitivity specificity	<p>sensitivity and specificity for whole-body MRI: 82% and 97%</p> <p>PET-CT: 72.8% and 92.7%.</p> <p>DW sequence allowed the detection of 14 supplementary malignant lesions (20%) in comparison with</p>	<p>prospective blinded study</p> <p>small patient cohort</p>	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					standard MRI protocol. DW sequence has been shown to be the most accurate for detecting metastases in the liver, bone, subcutaneous and intra-peritoneal sites.		
Mueller-Horvat (2005)	to compare contrast-enhanced whole-body magnetic resonance imaging (wbMRI) and whole-body computed tomography (wbCT) to detect distant metastases for staging.	Diagnostic study	43 patients AJCC stage III-IV malignant melanoma	Metastasis detection rate	<p>wbCT vs. wbMRI: detection of 522 vs. 730 metastases</p> <p>wbCT vs. wbMRI: -pulmonary metastases: 188 vs. 143 - metastases in kidneys, adrenal glands and lymph nodes: same number of detected lesions - liver: 122 vs. 199. - spleen 26 vs. 54 - subcutaneous</p>	<p>4 patients had choroid malignant melanoma</p> <p>specificity and sensitivity not given</p> <p>no follow-up</p> <p>small population</p> <p>uninterpretable results not described</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					tissue 39 vs. 61 - muscle 4 vs. 11 - bone marrow 23 vs. 132 Brain 15 vs. 25 Therapy was modified as a consequence of wbMRI findings in 10/41 (24%) patients.		
Schlamann et al. (2008)	To investigate the incidence of cerebral metastasis in asymptomatic melanoma patients in relation to the stage of disease to estimate the reasonability of this examination.	Diagnostic study	120 CM patients without other malignancy or neurological disease	Incidence of cerebral metastasis	Stage I: 0/27 positive results Stage II: 1/29 positive results (3%); patient in stage IIC Stage III/IV: 14/64 positive results (22%)	Criteria for patient selection unclear	3b-
Fogarty et al. (2006)	To retrospectively evaluate the use of brain magnetic resonance imaging (MRI) in the initial staging of patients	Diagnostic study	100 of 193 consecutive CM patients without neurological symptoms	Detection rate Upstaging by MRI	Patients in stages I – III: 0% positive results No patients upstaged by staging MRI	Patients in stages I – IV included	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	with cutaneous melanoma						
Subtopic PET							
Xing et al. (2011)	To examine the utility of ultrasonography, computed tomography (CT), positron emission tomography (PET), and a combination of both (PET-CT) for the staging and surveillance of melanoma patients.	Systematic review and meta-analysis	10 528 patients with cutaneous melanoma at primary diagnosis or under surveillance (follow-up)	Sensitivity, specificity Diagnostic odds' ratio (OR)	Data for initial staging of regional nodes: Sensitivity 30% Specificity 96% Diagnostic OR 9.45	Very large patient cohort, but patients under follow-up included	1a
Krug et al. (2008)	To calculate summary estimates of the diagnostic performance of fluorine 18 fluorodeoxyglucose (FDG) positron emission tomographic (PET) imaging in the	Systematic review with meta-analysis	2905 CM patients in 28 studies of which 2096 underwent PET alone and 809 underwent PET/CT	Pooled sensitivity and specificity Positive and negative likelihood ratio (LR+, LR-) Diagnostic odds' ratio (OR) Changes in disease management	Pooled sensitivity: 83% Pooled specificity: 85% LR+: 4.56 LR-: 0.27 Overall diagnostic OR: 19.8 Early-stage subgroup (10 studies, 755	In 17 studies, patients enrolled exclusively for initial staging; in 11 studies, proportion of initial staging patients 18 - 97% Overall, many low-quality studies resp. small	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	initial staging of cutaneous malignant melanoma (CMM)				patients): Pooled diagnostic OR 4.3 (95% CI: 1, 18) Mean sensitivity 60% 8 studies suggested that FDG PET was associated with 33% (range, 15%–64%) disease management changes	patients cohorts	
Jimenez-Requena et al. (2010)	The aim of this study was to perform a systematic review of the literature to evaluate the accuracy of FDG-PET in staging and restaging of cutaneous melanoma.	Systematic review with meta-analysis	444 CM patients (group I = regional staging), stages I – III, in 7 studies	Pooled specificity and sensitivity Positive and negative likelihood ratio (LR+, LR-) Summary receiver-operating curve (ROC)	Group I (regional staging): Pooled specificity: 0.99 No global homogeneity for sensitivity, LR+ or LR- ROC curves grouped in the left margin, indicating global high specificity	Overall, many low-quality studies resp. small patients cohorts	2a
Schwimmer et al. (2000)						Data included in Jimenez-Requena	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						et al. (2010): Meta-analysis of the performance of (18)F-FDG PET in cutaneous melanoma	
Bastiaannet et al. (2009)	to perform a head-to-head-comparison of FDG-PET and CT in staging of patients with melanoma with palpable lymph node metastases (AJCC stage III) in terms of diagnostic accuracy and impact on treatment.	Prospective multicenter study	In total 251 Patients with palpable and histologically or cytologically proven lymph node metastases (after negative sentinel lymph node)	False negatives (FN) true positives (TP) false positives (FP) true negatives (TN) sensitivity	FDG-PET detected more metastatic sites (133 v 112, P = .03), detecting significantly more bone and subcutaneous metastases. CT had more FN results (n=17) than PET (n=11). Numbers of FN, TP, FP and TN: see full Sensitivity to detect distant metastases CT scan 78% PET scan 86%	study included in Xing et al. 2011 and Jimenez-Requena 2008	2b
Pfannenberget al.	See above	See above	See above	See above	See above	See above	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(2007)							
Laurent et al. (2011)	See above	See above	See above	See above	See above	See above	2b-
Koskivuo et al. (2007)	to determine the clinical impact of whole body positron emission tomography (FDG PET) to detect clinically silent metastases in the follow-up of patients with high risk melanoma.	Prospective study	30 asymptomatic melanoma patients (AJCC stage IIB- IIIC) 7-24 months after the primary surgery and sentinel node biopsy.	Sensitivity Specificity PPV NPV Clinical impact	sensitivity and specificity for melanoma recurrence: 86% and 96%, respectively. PPV: 86% NPV: 96% positive PET finding had an impact on treatment decisions in every case: 3 patients underwent surgical resection, 4 patients received chemotherapy or interferon.	Small patient cohort Study included in Xing et al. 2011	2b-
Maubec et al. (2007)	To determine the value of F-18 fluorodeoxy-D-glucose positron	Diagnostic study	25 CM patients with lesions > 4 mm	Sensitivity, specificity	Initial tumor site: 14/19 true negatives (74%) 5/19 false	Prospective design small number of patients	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	emission tomography scanning in the detection of regional and/or distant metastasis				positives (26%) Sensitivity 17%, specificity 74% Microscopic lymph node disease: 12/19 true negatives (63%) 7/19 false negatives (37%) Sensitivity 0%	Study included in Xing et al. 2011	
El-Maraghi and Kiear (2008)	To evaluate PET and PET/computed tomography (CT) compared with SLNB for staging local lymph nodes in patients with intermediate-risk melanoma.	Systematic review without meta-analysis	20 studies; number of patients unclear because some included studies did not report cohort size	True and false negatives and positives Sensitivity and specificity Positive and negative predictive value	Ranges (no meta-analysis): TP 0 – 10% FP 0 – 18% TN 60 – 74% FN 3 – 40% Sensitivity 0 – 92% Specificity 7 – 100% PPV 0 – 100% NPV 20 – 85%	Levels of evidence according to authors: 7 studies 2b, 1 review 3a, 3 review 3b, 3 studies 3b, 3 letters/opinion articles 5 Overall, many low-quality studies resp. small patients cohorts	3a
Pleiss et al. (2007)	to assess the potential of fluor-18-FDGPET in order to	Prognostic and diagnostic study	95 Patients with malignant melanoma who had received a PET	overall 5-year survival sensitivity	Sensitivity, specificity, and accuracy of FDG-PET were 91%,	No information about the final assessment of findings (e.g.	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	evaluate the survival prognosis in melanoma			specificity	86%, and 89%, respectively, and of CT 58%, 91%, and 73%, respectively. survival in patients with - both studies (CT and PET) being negative: 5-year survival, 83% - both studies (CT and PET) being positive: 5-year survival, 61%; $p < 0.02$ - PET being positive but CT still negative: 5-year survival, 73%	histology and/or clinical follow-up) Number of TP and FP etc. missing. Data for the calculation of sensitivity/specificity not given No information about the time-period between PET and CT	
Clark et al. (2006)	To investigate the utility of whole-body PET imaging in 64 patients with T2 to T4 melanomas prior to sentinel lymph node dissection without clinically	diagnostic study	64 CM patients without clinical evidence of metastasis	True and false positives and negatives Change in management	PET scans normal in 60 of 64 patients (94%) 2/64 (3%) false positives 2/64 true positives 19/64 false negatives (regarding	22/64 patients with T4 lesions Study included in Xing et al. 2011	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	suspected metastases				sentinel node status) No change in management by PET results		
Vereecken et al. (2005)	The purpose of this study was to evaluate the impact of extensive initial staging on the management of melanoma patients.	Diagnostic study	43 patients with intermediate/high risk melanoma (Breslow thickness ≥ 1 mm or regression/ulceration)	Evidence of metastasis	Paraclinical investigation (CT scan of the chest, CT of the abdomen, CT or NMR of the brain and whole body FDG PET scan) failed to reveal any sign of evidence of disseminated disease in the series of 43 patients. Positivity:67% Sensitivity: 40% PPV: 9,3%	Results concerning PET already considered in Jimenez-Requena et al. 2010, in Krug et al. 2008 and in Xing et al. 2011 No distinction between results for MRI and CT of the brain. Imaging results validated by 6 months follow-up.	3b
Stas et al. (2002)	to evaluate (1) the sensitivity and specificity of PET scan at a single lesion level compared with	Retrospective diagnostic study CSP= chest X-ray, blood analysis,	100 PET scans on 84 melanoma patients with regional or distant recurrences according to CSP	Sensitivity Specificity Accuracy	At the single lesion level: Sensitivity: PET: 85% CSP: 81% Specificity:	Comparison of PET scan and CSP results at a lesion-based level→ see full-text	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	conventional screening procedures (CSP) – both of these accompanied by clinical examination; and (2) the additional value of the PET scan at the level of the individual patient and its therapeutic impact for different types of melanoma recurrence.	ultrasonography, (US), computed tomography (CT), magnetic resonance imaging (MRI) and nuclear bone scans		Therapeutic impact	PET: 90% CSP: 87% Accuracy: PET 88% CSP: 84% The overall therapeutic impact (PET): 26%	Therapeutic impact of PET scan results → see full text Study included in Jimenez-Requena et al. 2010 and Xing et al. 2011	
Wagner et al. (2011)	To assess the rate of distant metastases in patients with a positive SLN biopsy (SLNB).	Diagnostic study	46 consecutive patients with a positive SLNB underwent PET or PET-computed tomography within 6 weeks of the SLNB procedure and without any clinical sign of nodal involvement or of distant metastasis.	FN	Positive PET-scan: 0% Nonconclusive PET scan 13% Negative PET in 87%, among them 12% presented with distant metastasis within 12 months.	46 PET procedures were performed: In 22 patients: stand-alone PET and aCT scan with a contrast medium. In 24 patients: PET-CT scan without injection of contrast medium. Results: no differentiation	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						between PET and PET/CT Images were interpreted by a specialist aware of all the clinical findings → not blinded	
Constantinidou et al. (2008)	to evaluate the role of PET or PET/computed tomography (CT) as a routine procedure in patients with positive sentinel node biopsy (SNB).	Diagnostic study	30 patients with Breslow thickness of at least 1mm and who had a positive sentinel node biopsy.	Positive rate	Positive PET in 2 patients (6%) LN dissection positive in 5 cases (16%) With a median follow-up of 24 months, 21 patients remained disease free.alteration of melanoma management in none of the 30	Follow-up methods not described in detail Small patient number	3b-
Horn et al. (2005)	To investigate the clinical value of implementing whole-body FDG-	Diagnostic study	33 patients with cutaneous malignant melanoma and	sensitivity specificity NPV	Sensitivity and a specificity for melanoma metastases: 80%	Small patient cohort Only cases with	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	PET as a routine investigation in stage III melanoma patients with sub-clinical regional lymph node metastases diagnosed by SNB.		subclinical lymph node metastases diagnosed by sentinel node biopsy (SNB)		and 88%, respectively. NPV: 96%.	positive PET findings received verification via CT scan, MRI, ultrasonography or biopsy Small population Study included in Krug et al. 2008 and in Xing et al. 2011	
Loffler et al. (2003)	To disclose the diagnostic benefit of scanning the legs and to evaluate the therapeutic benefit resulting.	Diagnostic study	213 consecutive PET studies in 153 patients with suspected or recent melanoma	Detection rate	Suspicious findings at the legs in 53 patients on 76 occasions. 38/53 showed pathologic uptake in the torso as well. In 15/53 patients it was restricted to the legs. 11 of those 15 patients had a previous history in that location. In 1 patient the finding was a new and	Sensitivity and specificity not given	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>clinically relevant metastasis, in 3 other patients the leg manifestations were already known.</p> <p>In 6 other patients a validation of the positive PET findings was not possible</p>		
Krug et al. (2000)	To assess the diagnostic value of fluor-18-Fluorodeoxyglucose positron emission tomography (FDG-PET) in screening for melanoma metastases	Diagnostic study	94 melanoma patients who had been examined by whole-body FDG-PET. 40 patients showed evidence of lymphogenous, 42 of hematogenous metastasis.	Metastases-detection rate	In no case did PET change the staging. In 13 patients, PET agreed with morphological diagnosis in the number of metastatically invaded organs. This included 3 patients without metastases. The estimated number of organs invaded by metastases was higher with PET in 5 patients and	Different reference tests Sensitivity and specificity not given	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>higher with morphological imaging techniques in 6 patients. Among the PET findings with higher or equivocal counts of organs with metastases there were 2 confirmed false-positive findings.</p> <p>(Results for the different organs (lungs, liver...): see full text)</p>		
Dietlein et al. (1999)	To examine if - FDG-PET can improve staging of patients with melanoma when compared with combinations of standard radiological examinations currently used in routine practice?	Diagnostic study	91 FDG-PET examinations performed on 68 patients with advanced melanoma.	<p>True positives</p> <p>False positives</p>	<p>FDG-PET detected more lymph node and bone metastases</p> <p>High proportion of non-verifiable PET findings</p> <p>Comparison of ultrasonographic and radiological</p>	<p>FDG-PET images from various institutes</p> <p>Different staging examinations</p> <p>Sensitivity /specificity not given</p> <p>No data</p>	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	- if the setting of indications for PET can be optimized?				methods with FDG-PET for examining the lungs, abdominal organs, LN and skeleton: see full-text.	concerning follow-up Study included in Jimenez-Requena et al. 2010	
Subtopic CT							
Xing et al. (2011)	See above	Systematic review and meta-analysis	10 528 patients with cutaneous melanoma at primary diagnosis or under surveillance (follow-up)	Sensitivity, specificity Diagnostic odds' ratio (OR)	Data for initial staging of regional lymph nodes: Sensitivity 9% Specificity 92% Diagnostic OR 1.13	Very large patient cohort, but patients under follow-up included	1a
Bastiaannet et al. (2009)	See above	See above	See above	See above	See above	study included in Xing et al. 2011 and Jimenez-Requena 2008	2b
Pfannenbergl et al. (2007)	See above	See above	See above	See above	See above	See above	2b
Dellestable et al. (2011)	See above	See above	See above	See above	See above	See above	2b-
Hausmann et al. (2011)	See above	See above	See above	See above	See above	See above	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Panagiotou et al. (2001)	See above	See above	See above	See above	See above	See above	3b
Sawyer et al. (2009)	The aim of this study was to determine whether CT changes management in AJCC IIB disease or worse with regard to initial staging scans and subsequent follow up scans. A second objective was to determine whether CT of the head and neck should be performed.	Diagnostic study	132 CM patients in stages IIB/C (42 IIB, 90 IIC)	True and false positives Change in clinical management	Region – number of scans with metastases – change in management in % Chest – 3 – 0% Abdomen – 2 – 0% Pelvis – 0 – 0% Head – 3 – 0.7% Neck – 0 – 0% True and false positives of regional CT scans: Chest True positives: 9 (81%) False positives: 2 (19.0%) Abdomen True positives: 7 (53%) False positive: 6 (47%) Pelvis True positives: 3 (38%) False positives: 5 (62%)	No homogenous reference standard Values for true and false positive based on initial and follow-up scans; probably lower if only initial scans were considered	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Head True positives: 6 (100%) False positives: 0		
Yancovitz et al. (2007)	See above	Diagnostic study	158 patients, 135 with stage I/II disease and 23 with stage III disease	True and false positives and negatives	Number of CT studies: 57 chest, 57 abdomen/ pelvis, 57 head Positives: Chest CT 24 of 57 Abdomen/ pelvis 11 Cranial CT 2 True positives: Chest CT 0 of 57 (0.0%) Abdomen/ pelvis CT 0 of 57 (0.0%) Cranial CT 0 of 57 (0.0%) False positives: Chest CT 21 of 57 (37%) Abdomen/ pelvis CT 10 of 11 (18%) Cranial CT 2 of 57 (4.0%) True negatives: Chest CT 50 of 57 (88%)	study included in Xing et al. 2011	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Abdomen/ pelvis CT 46 of 57 (81%) Cranial CT 53 of 57 (93%) (Rest lost to follow-up) No false negatives		
Van den Brekel et al. (1998)	To assess the value of CT scanning in detecting lymph node metastases in the neck from malignant melanoma and to look at possible CT characteristics of such metastases.	Diagnostic study	26 CM patients with neck CT before neck dissection, 8 of them negative for palpation	Sensitivity and specificity True and false positives and negatives	CT scans of the neck: 2/26 (8%) false negatives (slices of 8 mm instead of 5 mm) Sensitivity of both palpation and CT scanning 86%, specificity 100%	Different reference standards (comprehensive and selective neck dissection) Inclusion criteria unclear Only 8 asymptomatic patients	3b
Iscoe et al. (1986):	See above	Diagnostic study	393 consecutive CM patients	True and false positives Positive and negative predictive value (PPV, NPV)	Chest CT: Number of exams: 59 True positives: 0 False positives: 9 PPV: 0% NPV: 98.0% Cranial CT: Number of exams: 52	Index tests not done on all patients	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					True positives: 0 False positives: 9 PPV: / NPV: 98.1%		
Heaston et al. (1983)	First, to determine prospectively the sensitivity and specificity of conventional chest radiography, tomography, and computed tomography in a selected group of patients with high propensity for pulmonary melanoma metastases; second, to evaluate the impact of the discovery of pulmonary nodules on the clinical therapy of melanoma.	Diagnostic study	42 CM patients in stages I – III (11 in stages I – II)	Sensitivity, specificity False-positive and false-negative rate Overall accuracy	Chest CT: Sensitivity 100% Specificity 95% False positives 2% False negatives 0% Overall accuracy 98%	Sensitivity and specificity calculated for a cohort including stage III melanoma patients; not enough data given to calculate for stage I and II alone	3b
Aloia et al. (2006)	To analyse the efficacy of routine	Diagnostic retrospective	270 staged patients with	True positive and False negative rate	TP detection rate of occult distant	Calculation of sensitivity and	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	radiologic staging in asymptomatic patients with microscopic nodal involvement before completion of lymphadenectomy.	cohort study	positive SLNB melanoma		metastases: 1,9% FP: 12%.	specificity not possible False and true negatives not given	
Miranda et al. (2004)	To determine the rate of detectable systemic metastasis at the time of SSL in asymptomatic patients with melanoma in North America	Diagnostic study	185 patients with pathologic evidence of metastasis to at least 1 SLN	Diagnostic yield of imaging studies:	142 patients underwent chest CT: - 1 positive finding - 114 negative - 27 indeterminate 146 patients underwent CT of the abdomen and pelvis: - 1 positive finding, - - 123 negative - 22 indeterminate. 96 underwent MRI imaging (brain), 16 underwent CT	Not in every case of indeterminate findings additional diagnostic was performed Sensitivity/specificity not given	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(brain): - no positive findings - 105 negative - 7 were indeterminate. CT of the chest and abdomen/pelvis/brain: indeterminate rates were 19%, 15% and 6,3% respectively.		
Johnson (1997)	To evaluate the yield and clinical impact of computed tomography (CT) imaging in otherwise asymptomatic patients with stage III melanoma metastatic to the regional nodes	Diagnostic study	127 asymptomatic patients stage III (28 patients: microscopic disease at ELND. 99 patients with palpable disease diagnosed by fine needle aspirate, open biopsy, or TLND)	True (TP) and false positives (FP)	20 patients: TP CT scan revealing unsuspected metastases. 15 patients: abnormal CT scans subsequently shown to be a benign process or second malignancy. No difference in the incidence of TP CT between the	TP and FP rates: see full text FP and FN not given	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>groups of patients with clinically apparent vs. occult nodal disease.</p> <p>significantly higher incidence of abdominal and pelvic metastatic sites identified by CT scan in patients with inguinal nodal disease vs. patients with axillary or head and neck nodal disease.</p>		
Buzaid et al. (1995)	To determine the value of CT scans in the staging of asymptomatic melanoma patients who presented with or developed localregional disease as the first site of recurrence and had both a normal chest radiograph and	Diagnostic study	89 patients who either presented with or developed localregional disease as the first site of recurrence	TP-rate TN-rate	Findings on CT scan were TP for six patients (7%), FP for 20 (22%), and TN for 63 (71%).	<p>No detailed data about the follow-up regime/time of follow up</p> <p>Sensitivity and specificity not given</p> <p>Study included in Xing et al. 2011</p>	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	serum lactate dehydrogenase (LDH) level.						
Khansur et al. (1989)	See above	Diagnostic study	115 patients with primary CM (72 in localized stage) and 28 patients with recurrent disease	True and false positives	Cranial CT: 0 true positives and 0 false positives in patients with localized disease	Criteria for selecting staging examinations unclear	3b-
Kuan et al. (1988)	See above	See above	See above	See above	See above	See above	3b-
Goerz et al. (1986):	See above	Diagnostic study	378 patients with histologically confirmed CM	True and false positives	Whole-body CT: 2/378 true positives (distant metastasis)	Stages not given	3b-
Kersey et al. (1985)	See above	Diagnostic study	393 patients at primary diagnosis of CM	True and false positives	CT chest: 0/59 true positives 9/59 false positives (15%) Cranial CT: 0/51 true positives 0/51 false positives	Extent of staging examinations and extent/ length of follow-up depended on center and tumor site	3b-
Patten et al. (1990)	To determine	Cross-sectional	125 CM patients	Prevalence of bone	Examinations: CT	Not enough data	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	whether the frequency of CT detection of axial skeletal metastases was greater than that reported for plain film radiology and to determine if the thickness and depth of penetration of the primary melanoma (according to the Breslow and Clark classifications) can be used to predict the occurrence of skeletal metastases.	study		metastasis	abdomen (41%), chest (27%), pelvis (25%), and neck (7%) 98/125 patients (78%) with CT evidence of metastatic melanoma 17/98 (17%) skeletal metastases 2/17 only evidence of metastatic disease	given to differentiate between prevalence of bone metastasis in early stage and advanced stage melanoma	
Zartman et al. (1987)	See above	Cohort study	90 CM patients with level III and IV lesions	Positive results	No positive results in cranial CT	Patients with complete staging included; indications for different staging examinations unclear	4
Silverman et al. (1984)	To assess the value of computed	Cross-sectional study	70 CM patients	Prevalence of abdominal	52 scans of abdomen and	Most patients symptomatic at	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	tomography in the detection of abdominal spread of malignant melanoma.			metastases	pelvis, 5 of abdomen, 2 of pelvis, 11 limited to the liver Nodal enlargement in abdomen or pelvis in 30% Liver metastases in 17% Adrenal metastases in 11% Nodular masses in the subcutaneous fat in 8,6% Splenic metastases in 2% Mesenteric metastases in 4%	time of CT scan (abdominal pain, abnormal liver function tests or liver imaging)	
Ginaldi et al. (1981)	To investigate the value of CT as a staging procedure in neurologically asymptomatic melanoma patients, and to describe the neurological features of metastases and their incidence in	Diagnostic study	179 CM patients; 74 of them with no neurological findings	Detection rate	Cranial CT: Positive results in 9/74 patients (11%) 2/9 had known single metastases in the liver and lung, 2/9 others recurrent local disease, 5/9 other systemic metastases	No clear distinction between patients of different stages	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma patients.						
Doiron et al. (1981)	See above	See above	See above	See above	See above	See above	4
Subtopic PET/CT							
Xing et al. (2011)	See above	Systematic review and meta-analysis	10 528 patients with cutaneous melanoma at primary diagnosis or under surveillance (follow-up)	Sensitivity, specificity Diagnostic odds' ratio (OR)	Data for initial staging of regional nodes: Sensitivity 11% Specificity 97% Diagnostic OR 4.39	Very large patient cohort, but patients under follow-up included	1a
Krug et al. (2008)	See above	Systematic review with meta-analysis	2905 CM patients in 28 studies of which 2096 underwent PET alone and 809 underwent PET/CT (4 studies)	Positive and negative likelihood ratio (LR+, LR-) Diagnostic odds' ratio (OR)	LR+ 9.68 LR- 0.10 Diagnostic OR 37.6	4 eligible studies about PET/CT	1a
Essler et al. (2011)	To assess the prognostic value of FDG PET/CT compared to the tumor markers S100B and melanoma	diagnostic and prognostic study	125 consecutive patients Patients who had a Breslow tumor thickness ≥ 2.0 mm, elevated S100B or	specificities sensitivities NPV PPV	Overall specificity for FDG PET/CT: 96.8% (95% CI, 89.1% to 99.1%) corresponding sensitivity: 96.8% (89.0% to 99.1%)		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	inhibitory activity (MIA) in patients with high risk melanoma.		MIA level		NPV for PET/CT 96.8% (89.1% to 99.1%), PPV: 96.7% (89.0% to 99.1%), Patients with elevated S100B- or MIA values or PET/CT positive findings showed a significantly (p,0.001 each, univariate Cox regression models) higher risk of melanoma associated death which was increased 4.2-, 6.5- or 17.2-fold, respectively.		
Etchebehere et al. (2010)	To assess the impact of [F-18] FDG-PET/CT on the restaging and changing management of patients with malignant	Diagnostic study	78 patients (Initial restaging/before PET/CT): local recurrence in 11 patients, locoregional	Impact on patient management Sensitivity Specificity	In 27% of the patients the management was changed after the [F-18] FDG-PET/CT studies. Upstaging in 5 of 23 (22%) patients.	AJCC 2001 staging System was used	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma.		recurrence in 23 patients and distant recurrence in 44 of 78 patients.		sensitivity, specificity, PPV, NPV for lesion detection: 95% accuracy: 94.9%. 2FP, 2 FP		
Klode et al. (2010)	Comparison of SLNE and PET-CT in patients with early-stage malignant melanoma	Diagnostic study	61 CM patients in stages I and II before sentinel biopsy	Sensitivity and specificity Positive and negative predictive value (PPV, NPV)	Sensitivity 5.9% Specificity 100% PPV 100% NPV 78%	50% of eligible patients declined PET-CT	2b
Veit-Haibach et al. (2009)	To evaluate the diagnostic accuracy of contrastenhanced FDG-PET/CT (ce-PET/CT), PET-only, and CT-only in patients with newly diagnosed and resected cutaneous malignant melanoma.	Diagnostic study	56 CM patients after surgical resection who underwent combined PET/CT imaging and had sufficient follow-up; 18 of them in stage III or IV	Sensitivity and specificity Positive and negative predictive value (PPV, NPV)	Sensitivity and specificity regarding N-stage: 38.5% and 100% PPV and NPV regarding N-stage: PET-CT 100% and 84.3% Sensitivity and specificity regarding M-stage: PET-CT 38.5% and 100%	Insufficient data for 24% of patients Study included in Xing et al. 2011	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					PPV and NPV regarding M-stage: PET-CT 41.7% and 93.2%		
Singh et al. (2008)	To evaluate the role of preoperative 18F-fluorodeoxyglucose-positron emission tomography/computed tomography scanning, preoperative lymphoscintigraphy (LS), and sentinel lymph node biopsy in patients with malignant melanoma.	Diagnostic study	52 CM patients initially classified as stage I or II, before sentinel biopsy	Sensitivity and specificity Positive and negative predictive value (PPV, NPV) Overall diagnostic accuracy	18F-FDG PET imaging for the detection of regional lymph node metastases: Sensitivity 14.3% Specificity 94.7% PPV 50% NPV 75% Diagnostic accuracy 73%	Study included in Xing et al. 2011	2b
Lagaru et al. (2007)	To analyse sensitivity and specificity of PET/CT for the detection of metastases of malignant melanoma.	Diagnostic study	106 CM patients who had whole-body FDG-PET/CT, 30 of them with stages IIIc and IV	Sensitivity and specificity	Per patient: Sensitivity 89.3% Specificity 88.0% True positives 50 False positives 6 False negatives 6 True negatives 44 Per lesion:	Studies were done for disease re-staging in all patients; time interval from initial diagnosis not given	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Sensitivity 89.6% Specificity 84.6% True positives 78 False positives 8 False negatives 9 True negatives 44	Studie included in Xing et al. 2011	
Pfannenberger et al. (2007)	See above	See above	See above	See above	See above	See above	2b
Strobel et al. (2007)	To prospectively determine the accuracy of positron emission tomography (PET)/computed tomography (CT) with added CT morphologic information for depiction of metastases in patients with high-risk melanoma and negative findings for metastases at PET, by using histologic findings or additional imaging and/or follow-up findings	Diagnostic study	124 CM patients with tumor thickness > 4 mm; Clark level, III or IV; or known metastases	True and false positives and negatives Sensitivity and specificity Diagnostic accuracy	Without dedicated CT readout: 45/124 true positives (36%) 3/124 false positives (2%) 68/124 true negatives (55%) 8/124 false negatives (6%) Sensitivity 85% Specificity 96% Diagnostic accuracy 91% With dedicated CT readout: 52/124 true positives (34%) 4/124 false positives (3%) 67/124 true	Cohort includes patients with already known metastasis Study included in Xing et al. 2011	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	as reference standard.				negatives (54%) 1/124 false negatives (1%) Sensitivity 98% Specificity 94% Diagnostic accuracy 96%		
Dellestable et al. (2011)	See above	Diagnostic study	See above	See above	See above	See above	2b-
Wagner et al. (2011)	To assess the role of routine staging with FDG PET-CT in melanoma patients with localized high risk melanoma.	Diagnostic study	48 consecutive patients with 1 < BT < 4 mm with ulceration and with BT >= 4 mm were staged with PET-CT (initial staging) prior to SLNB.	sensitivity, specificity, PPV, NPV	For regional nodal assessment: sensitivity, specificity, PPV, NPV of PET: 43%, 100%, 100% and 78%, respectively. For distant metastases: positive PET in 0%, negative PET in 13% and indeterminate PET in 13% of patients	Images were interpreted by a specialist, aware of all clinical findings/not blinded Small patient cohort, not described in detail	2b-
Mansour et al. (2010)	(1) to determine the anatomic scatter plot of false-positive and	Diagnostic study	342 CM patients with PET/CT	True and false positives	True positives: Breslow 0 – 2 mm: 46.9% Breslow 2.01 – 4	Limited purpose of the study (musculo-skeletal findings in	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	true-positive FDG-avid sites; (2) to describe and determine the characteristics of false-positive FDG-avid sites; and (3) to identify patterns that are useful in predicting false-positive findings for patient management and counseling.				mm: 18.8% Breslow > 4 mm: 34.4% Stage II: 3.2% Stage III: 33% Stage IV: 63.8% False positives: Breslow 0 – 2 mm: 30% Breslow 2.01 – 4 mm: 30% Breslow > 4 mm: 40% Stage II: 27.3% Stage III: 45.4% Stage IV: 27.3%	PET/CT) No fixed indications for PET/CT	
Revel et al. (2010)	To assess the utility of PET-CT 18FDG in a group of N patients with cutaneous head and neck melanoma, combined with SLNB.	Diagnostic study	22 patients with N0 cutaneous head and neck melanoma with PET/CT before sentinel biopsy	Sensitivity and specificity	Sensitivity 18% Specificity 84%		3b
Yancovitz et al. (2007)	See above	Diagnostic study	158 patients, 135 with stage I/II disease and 23 with stage III	True and false positives and negatives	Number of PET/CT studies: 42 Positives:	study included in Xing et al. 2011	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			disease		5/42 (12%) True positives 1/42 (2%) False positives: 3/42 (7%) True negatives: 37/42 (88%) False negatives: 0 Lost to follow-up: 1/42		
Wagner et al. (2011)	See above	See above	See above	See above	See above	See above	3b-
Abbott et al. (2011)	to evaluate the role of [18F] fluorodeoxyglucose PET/CT as a surveillance tool in asymptomatic patients with primary cutaneous melanoma	Diagnostic study	34 patients with primary cutaneous malignant melanoma with AJCC stage III	Metastases detection	In 20 patients with microscopic stage 3 disease at diagnosis: PET/CT detected 2 of 3 recurrences and 1 incidental breast carcinoma. In 14 patients with macroscopic stage 3 disease at, or subsequent to, their initial	No reference standard	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					diagnosis: PET/CT detected 4 of 4 recurrences, metastases in 1 patient who remains asymptomatic and 1 incidental thyroid carcinoma.		
Subtopic SPECT/CT							
Van der Ploeg (2009)	To explore whether hybrid SPECT/CT leads to better anatomical localization of sentinel nodes or to the depiction of extra sentinel nodes in patients with melanoma when conventional imaging is inconclusive, and whether this influences the surgical approach.	Cohort study	85 CM patients who underwent both conventional lymphoscintigraphy and subsequent SPECT/CT	Additional diagnostic value of SPECT/CT (change of surgical approach)	Additional diagnostic value of SPECT/CT in 35% (30 patients)	Only patients with questionable results in lymphoscintigraphy or unusual drainage pattern included	2b
Subtopic BONE							

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
SCINTIGRAPHY							
Au et al. (1984)	To evaluate the yield and accuracy of preoperative radionuclide scans in patients with primary melanoma for the detection of occult metastasis to brain, liver and bone.	Diagnostic study	192 CM patients; 171 in stage I (localized) and 21 in stage II (lymph node metastasis according to old AJCC staging)	True and false positives, false negatives	107/112 (96%) true negatives 5/112 (4%) false positives 0 true positives	No information about false negatives (follow-up of patients with negative results unclear)	3b
Hofmann et al. (2002)	See above	Diagnostic study with historical cohort; economical evaluation	661 patients (stage I/II: 630 patients, stage III: 27 patients, stage IV: 4 patients)	True and false positives and negatives Cost-efficiency of imaging procedures	325 total bone scintigraphies 0 true positives 62 false positives (19%) Detection rate / Cost of bone scintigraphy at initial staging: 80654 EUR (4099 EUR due to false positive results)	Diagnostic standard procedures varied over time; no defined gold standard of diagnosis	3b
Khansur et al. (1989)	See above	Diagnostic study	115 patients with primary CM (72 in localized stage)	True and false positives	0/141 true positives 3/141 false	Criteria for selecting staging examinations	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			and 28 patients with recurrent disease		positives (2%)	unclear	
Ardizzoni et al. (1987)	See above	Diagnostic study	116 patients; clinically 93 in stage I and 23 in stage II	True and false positives and negatives	68/73 (93%) true negatives 5/73 (7%) false positives 0 true positives	Design (prospective vs. retrospective) not clear Follow-up time not given	3b-
Kersey et al. (1985)	See above	Diagnostic study	393 patients at primary diagnosis of CM	True and false positives	True positives 0 False positives 7/116 (6%)	Extent of staging examinations and extent/ length of follow-up depended on center and tumor site	3b-
Zartman et al. (1987)	See above	Cohort study	90 CM patients with level III and IV lesions	Positive results	No positive results for bone scintigraphy	Patients with complete staging included; indications for different staging examinations unclear	4
Subtopic TUMOR MARKERS							

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Mocellin et al. (2008)	Analysis of the prognostic value of S100B serum levels in patients with melanoma, with special regard to stages I - III (AJCC)	Meta-analysis of 20 prognostic studies containing 22 series of 3393 patients 5 series considered patients in stages I - IV 8 series considered patients in stage IV only 6 series considered patients in stages I - III only Other combinations in the remaining 3 series	3393 patients with melanoma, stages I - IV	Summary hazard ratio for survival	Summary hazard ratio for survival 2.23 (95% CI 1.92 - 2.58) Summary hazard ratio considering only patients in stages I - III: 2.28 (95% CI 1.8-2.89)	High degree of heterogeneity, which is not present when only studies of stages I - III are included Publication bias present (shown with a funnel plot), but after correction, Hazard Ratio still significantly higher for patients with elevated S100B Publication bias not present when only studies of stages I - III included	1a
Balch et al. (2009)	To revise the staging system for cutaneous melanoma on the basis of data from an expanded American Joint Committee on	Prognostic study	30,946 patients with stages I, II, and III melanoma and 7,972 patients with stage IV melanoma	Survival rate	Elevated serum LDH: The updated AJCC Melanoma Staging Database demonstrated that an elevated serum LDH is an	Study included just for reference here; no data about LDH in earlier stages than IV	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	Cancer (AJCC) Melanoma Staging Database.				independent and highly significant predictor of survival outcome among patients with stage IV disease. Thus 1- and 2-year overall survival rates for those stage IV patients in the 2008 AJCC Melanoma Staging Database with a normal serum LDH were 65% and 40%, respectively, compared with 32% and 18%, respectively, when the serum LDH was elevated at the time of staging ($P < .0001$). Therefore, serum LDH should be measured at the time stage IV disease is documented, and if the LDH level is		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					elevated, those patients are assigned to M1c regardless of the site of their distant metastases.		
Nowecki et al. (2008)	to assess the prognostic value of multimarker reverse transcriptase-polymerase chain reaction (RT-PCR) assay in lymphatic drainage (LY) after lymph node dissection (LND) and of preoperative serum lactate dehydrogenase (LDH) levels in AJCC stage III melanoma patients.	Prognostic study	255 consecutive patients with histological diagnosis of CM and regional (inguinal or axillary) LN involvement who underwent radical LND	Overall survival Disease-free survival Recurrence rate	<p>estimated 3-year OS rate for patients with increased preoperative serum LDH level: 41.3% (95% CI: 28.4–54.6%), vs. 55.3% (95% CI: 45.8–64.9%) for patients with a normal baseline serum LDH level (P = 0.007).</p> <p>disease recurrence in 70% of patients with an increased preoperative serum LDH level compared with 53% patients with a normal serum LDH level (P =</p>	Results for RT-PCR: see full-text	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					0.01). Negative impact of increased pre-lymphadenectomy serum LDH level on OS of melanoma patients with macrometastases after TLND. Serum LDH level does not differentiate the prognostic groups in patients with micrometastases		
Vereecken et al. (2009)	To investigate the prognostic significance of galectin-3 in comparison to S100B, LDH and CRP	Prognostic study	83 patients in stage III and IV	Overall survival	3 groups of patients were defined according to Gal-3 levels: <8 ng/ml (group 1), 8-10 ng/ml (group 2), >10 ng/ml (group 3). Group 1 and 2: similar overall survival, group 3: worst outcome. median	LDH was omitted from the analysis because only 8 patients showed elevated LDH serum levels	1b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>survival was 4.1 months.</p> <p>multivariate Cox proportional hazards model: AJCC stage and CRP serum levels =most important independent prognostic factors [HR =9.60, P=0.0002 and HR=2.75, P=0.002, respectively].</p> <p>At a cut-off value of 10 ng/ml for Gal-3, (on quatrivariate analysis) serum Gal-3: strong independent prognostic value, superior to the other markers (HR=4.64, P=0.0001).</p>		
Essler et al. (2011)	To assess the prognostic value	Retrospective diagnostic and	125 consecutive patients	specificities sensitivities	S100B: Overall specificity 85.7%		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of FDG PET/CT compared to the tumor markers S100B and melanoma inhibitory activity (MIA) in patients with high risk melanoma.	prognostic study	Patients who had a Breslow tumor thickness ≥ 2.0 mm, elevated S100B or MIA level	NPV PPV	<p>(75.0% to 92.3%) corresponding sensitivity: 45.2% (33.4% to 55.5%), NPV 61.4% (50.9% to 70.9%). PPV: 75.7% (59.9% to 86.6%)</p> <p>MIA: Overall specificity 95.2% (86.9% to 98.4%). corresponding sensitivity 36.1% (25.2% to 48.6%), respectively. NPV: 60.6% (50.8% to 69.7%), PPV: 88.0% (70.0% to 95.8%).</p> <p>Patients with elevated S100B- or MIA values or PET/CT positive findings showed a significantly ($p < 0.001$ each, univariate Cox regression models) higher risk of melanoma</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					associated death which was increased 4.2-, 6.5- or 17.2-fold, respectively.		
Kruijff et al. (2011)	Aim was to assess the correlation and the prognostic value of S-100B and Standardized Uptake Values (SUV) of Fluorodeoxyglucose (FDG)	Retrospective cohort study	62 patients with palpable nodal metastases, without distant metastases	DFS and DSS	<p>No relation was found between S-100B and SUV.</p> <p>DFS for patients with an elevated vs. normal S-100B: 31% vs. 44,6% (HR = 3.1; p = 0.02)</p> <p>DFS for patients with normal vs. elevated SUV: 42% vs. 29% (HR = 1.1; p = 0.8).</p> <p>DSS for patients with normal vs. elevated S100B: 60.7% vs. 44.7% (HR = 2.2; p = 0.07).</p> <p>DSS for patients with normal vs.</p>		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>elevated SUV: 59.1% vs. 43.5% (HR = 1.1; p = 0.8).</p> <p>S-100B is associated with tumor load and a strong predictor for DFS in stage III melanoma</p>		
Neuss et al. (2011)	To evaluate the correlation to clinical and pathological data of the following preoperative serum tumour markers: S100, NSE, Albumin, LDH and CRP	Prognostic study	patients in tumour stage III before radical lymph node dissection	Serum levels	<p>The serum level of CRP correlated with increasing number of LN node metastases.</p> <p>Significant elevated serum levels of S100 in patients with more than one positive SLN</p>		2b
Bouwhuis et al. (2011)	To determine the prognostic value of S100B based on updated information using serial determinations in	Prognostic study	918 serum samples of 211 Patients who participated in the EORTC 18952 trial, evaluating efficacy of	<p>distant metastasis-free interval (DMFI)</p> <p>distant metastasis-free survival (DMFS)</p>	<p>Multivariate analyses: DMFS: HR of S100B \geq 0.2 versus S100B $<$ 0.2 was 5.57 (95% CI 3.81-</p>		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	stage IIb/III melanoma patients.		<p>adjuvant intermediate doses of interferon α2b (IFN) versus observation</p> <p>Serum S100B levels were measured during treatment and follow-up</p>	<p>OS</p> <p>HR</p>	<p>8.16), $P < 0.0001$, after adjustment for stage, number of lymph nodes and sex.</p> <p>In stage IIb patients: HR adjusted for sex=2.14 (95% CI 0.71, 6.42)</p> <p>In stage III patients: the HR adjusted for stage, number of LN and sex=6.76 (95% CI 4.50-10.16).</p> <p>OS: HR: 4.73 (95% CI 3.14-7.12), $P < 0.0001$.</p> <p>In stage IIb patients: HR 2.73 (95% CI 0.79-9.44; $P = 0.11$).</p> <p>In stage III patients: 5.46 (95% CI 3.52-8.45; $P < 0.0001$).</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Serial determination of S100B in stage IIb-III melanoma is a strong independent prognostic Marker, the prognostic impact of S100B ≥ 0.2 lg/l is more pronounced in stage III disease than in stage IIb.		
Paschen et al. (2009)	To investigate the correlation between sULBP2, sMICA and S100B levels and the prognostic value of sULBP2 levels	Prognostic study	208 patients (25 in stage I/II, 54 in stage III, 129 stage IV) 50 healthy controls	Clinical stage Tumor load Overall survival	S100B serum concentrations significantly correlated with stage of disease Patients with measurable tumor significantly higher serum concentrations of S100 than patients with clinically non-apparent tumor		2b
Andrés et al. (2008)	To compare the value of tyrosinase	Prospective diagnostic and	90 CM patients in stages I – IV	Sensitivity Progression-free	Sensitivity of S100: 22.2% for stage I	Very small control group for S100 (2	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	mRNA by reverse transcription polymerase chain reaction (RT-PCR) in peripheral blood and of serum S-100 protein in patients with melanoma at different stages of disease.	prognostic study		survival Overall survival	10.5% for stage II 7.4% for stage III 94.1% for stage IV Median follow-up: 312 days or to death Median progression-free survival 213 days for elevated serum S100; not reached for patients with normal S100 Median overall survival 282 days for elevated serum S100; not reached for patients with normal S100 level	healthy subjects, 3 patients with breast cancer, Hodgkin lymphoma and Ewing's sarcoma, respectively) Also contains data on tyrosinase Patients in stage I - IV	
Kruijff et al. (2009)	To investigate whether the perioperative measurement of the tumor markers S-100B has prognostic value in FDG-PET and spiral CT staged patients with stage III melanoma who are	Prognostic study	56 patients with clinically and cytologically proven regional nodal metastases of melanoma	Disease-free survival Prognostic factors	2-year DFS in patients with - elevated vs. non-elevated preoperative S-100B concentrations: 34% vs. 61% (HR:2.6, P=0.03) - elevated vs. non-elevated	Follow-up diagnostic procedures and follow-up intervals not stated in article Design not described (prospective/retrospective)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	selected for therapeutic lymph node dissection				<p>postoperative S-100B concentrations: 30% vs. 51% (HR:2.0, P =0.1).</p> <p>In multivariate analysis: extranodal growth (HR 0.4, P = .05), and elevated preoperative S-100B concentrations (HR 2.6, P = .03) were significantly associated with decreased DFS.</p>		
Wang et al. (2004)	See above	Diagnostic study	210 CM patients without clinical evidence of metastasis	True and false positives and negatives	LDH results available in 96 patients with melanoma > 1 mm 82/96 (85%) within institutional normal range 14/96 patients with elevated LDH, but no detection of systemic disease or		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					alteration in surgical management (15% false positives) No true positives		
Kaskel et al. (1999)	To evaluate the clinical and prognostic value of S-100 in peripheral blood of patients with melanoma as a marker for metastasis.	Diagnostic study	1396 samples of 570 patients with melanoma and 53 control subjects (397: melanoma in situ or stage I or II, 104: stage III, 69: stage IV)	Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), determination of optimal threshold (ROC).	For a cut-off of 0.114 µ/L Sensitivity: 94% specificity: 91%. For a cut-off of 0,2µg/L: sensitivity and specificity both 92% PPV value (cut-off 0,114 µg/L) for newly occurring metastases: 65%, NPV (no metastases): 99%. FN results included patients with unknown primary melanoma and those with amelanotic melanoma metastases.	Part of the data on S-100 levels obtained in Munich have also been evaluated in a different study by Berking et al. follow-up performed in 197 patients only ROC: see full text	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hofmann et al. (2009)	To determine the value of MIA testing in early-stage melanoma	Diagnostic study	1079 CM patients in stages I and II Reference group: 313 dermatological patients without history of melanoma or other malignancy	Mean values Sensitivity Specificity	Mean MIA value did not increase based on stage Sensitivity of MIA for metastasis: 67.6% in stage I and 65.6% in stage II Specificity: 76.9% for stage I and 66.7% for stage II More frequent false-positive values in elderly women and in men with an increased Breslow thickness	Different reference standard for patients with abnormal laboratory values	2b-
Garbe et al. (2003)	To evaluate the diagnostic accuracy of protein S-100B, melanoma-inhibitory activity (MIA), LDH, AP, and tyrosinase/MART-1 reverse	Diagnostic and prognostic study	296 consecutive AJCC Stage II or III clinically disease-free melanoma patients 120 healthy controls without melanoma or other known	Sensitivity Specificity Diagnostic accuracy	Cutoff levels: S100: 0.12 µg/L MIA: 10.49 ng/mL Sensitivity: S- 100: 29%, PCR: 24%, MIA: 22%, AP: 17%, LDH: 2% Specificity: S-100:	Different reference standard (CT) for patients with abnormal laboratory values (may lead to a higher sensitivity of the tumor markers than in reality)	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	transcription-polymerase chain reaction (RT-PCR).		malignancies.		<p>93%, PCR : 80% MIA: 97%, AP: 89% LDH: 90%</p> <p>Diagnostic accuracy: MIA: 86%, S100: 84%, AP: 79%, LDH: 77% RT-PCR: 72%</p> <p>ROC analysis: diagnostic accuracy: S-100: 66%, MIA: 62%, LDH: 53%, AP: 51%</p> <p>Significant P values for S-100 (0.001) and MIA (0.011), but not for LDH (0.571), AP (0.807), and PCR (0.519).</p> <p>Somer's Dxy : S-100 had the highest predictive value</p> <p>Kaplan–Meier</p>	Detailed description of follow up; no drop-outs	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>survival curves: highly significant difference in recurrence-free survival time in the time period after the follow-up examinations between patients with normal and pathologic values for both MIA and S-100.</p>		
Agarwala et al. (2009)	To assess each of the three stratification factors in this study (performance status, metastatic site and LDH) for an interaction with treatment on survival.	Prognostic study	760 patients (in study 301) and 760 (in study 18951)	Overall survival	<p>LDH was within the upper range of normal for a large number of patients.</p> <p>highly ordered and monotonic relationship between LDH and survival: survival worsened as LDH became more elevated, even when LDH remained within normal range.</p>	Post-hoc analysis of two randomised trials (Oblimersen GM301 and EORTC 18951)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>LDH and tumour size poorly correlated; elevated LDH was not associated with any one disease site. LDH was highly predictive of oblimersen effect.</p> <p>Kaplan-Meier survival curves: see full-text</p>		
Deichmann et al. (2004)	LDH was compared to CRP to evaluate, if LDH is of value in discriminating melanoma patients entering AJCC stage IV from patients staying in AJCC stages I, II or III.	Diagnostic study	91 patients with histologically proven melanoma progressing into stage IV, 125 patients stage I, II or III in follow-up examinations	Sensitivity specificity	<p>LDH not significantly elevated in patients entering stage IV melanoma (P=0.785), whereas CRP was (P<0.001).</p> <p>LDH did not discriminate between the defined groups of patients</p>	<p>Sensitivity and specificity for LDH not given</p> <p>Small population</p> <p>No information on blinding</p>	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>(AUC=0.491; 95% CI, 0.410, 0.581), whereas CRP did (AUC=0.933; 95% CI, 0.900, 0.966; P<0.001).</p> <p>CRP in diagnosing AJCC stage IV entry: cutoff =2,1 or 2,2mg/dl: specificity=80%, sensitiviti=83,5%.</p> <p>cutoff 2,4 or 2,5mg/dl: specificity = 83,2% and 85,66, respectively. sensitivity of 81,3%.</p> <p>Cutoff=2.9mg/dl: Specificity=89,6% sensitivity=79,1</p> <p>cutoff point=3.0mg/dl: specificity=90,4 sensitivity=76,9</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Deichmann (2001)						Same data as in: Deichmann et al. (1999): S100-Beta, melanoma inhibiting activity, and lactate dehydrogenase discriminate progressive from non-progressive american joint committee on cancer stage IV melanoma	
Stoitchkov et al. (2003)	To define the potential use of this new marker for the follow-up of melanoma patients by means of serial measurement (before and after treatments, and during follow-up)	Diagnostic study	60 melanoma patients (24: stage I-II, 18 stage III, 18 stage IV)	Overall survival Change in serum concentrations by therapeutic interventions	In stage III patients with elevated marker concentration, LN dissection decreased the S100B level (from 0.27 to < 0.13 g/l, P= 0.008), but not the L-dopa/L-tyrosine ratio. Chemotherapy decreased the ratio by	Small patient numbers divided into many subgroups Study included here in addition to S100 meta-analysis because of results about L-dopa/L-tyrosine ratio	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>38% (P 0.04) and the S100B level by 45% (P 0.02) in stage IV responders.</p> <p>increase in one or both markers during follow-up in patients with progressive disease:</p> <p>shorter survival in stage IV patients with high vs. normal L-Dopa/L-Tyrosine ratio at inclusion (3 vs. 15 months). Levels of S100B had no impact on survival, in stage IV patients.</p> <p>No correlation between L-dopa/L-tyrosine ratio and S100B.</p>		
Stoitchkov et al.	Prospective	Diagnostic study	89 melanoma	Sensitivity and	overall sensitivity	Precursor study to	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(2002)	evaluation of the potential of the serum L-dopa/L-tyrosine ratio in the management of melanoma, with an emphasis on staging, tumour burden and prognosis (the predictive value for disease progression in metastatic patients and survival).		<p>patients with histologically proven primary and/or metastatic melanoma or measurable metastatic disease (by imaging).</p> <p>(9 stage I, 33 stage II, 19 stage III, 28 stage IV).</p>	specificity	<p>for melanoma: 51% for the ratio and 66% for S100B. (range: 33% (stage I) to 71% (stage IV) for the ratio, 56–89% for S100B)</p> <p>no statistical difference between stages I, II and III patients for both markers. Significant higher median ratio in stage IV.</p> <p>In stage III–IV patients, both markers were significantly higher in evolutive patients than in stable ones.</p> <p>The ability (sensitivity/specificity) of markers to predict disease progression in</p>	<p>Stoitchkov et al., 2003</p> <p>Patients lost to follow-up are not included in analysis (risk of bias)</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastatic patients: 78%/67% for the ratio, 74%/83% for S100B (select cut-off) and 87%/33% using the manufacturer's reference values.		
Krahn et al. (2001)	To evaluate tumor markers S100, MIA, LDH and albumin in peripheral blood of melanoma patients	Diagnostic study	373 melanoma patients (284 with melanoma in situ or stage I/II and 89 with melanoma stage III/IV; 54 of these tumor free and 29 with newly occurred metastases) 10 control subjects	Sensitivity Specificity	Presence of lymph node, visceral and brain metastases: Sensitivity (for newly occurred metastases) for LDH 48%, for MIA 80%, for S100 86% Specificity for LDH 98%, for S100 91%, for MIA 62% No false positive results in the control group	No follow-up as reference standard (cross-sectional design)	2b-
Deichmann et al. (1999)	serum levels of S100-beta (S100b) and melanoma-inhibiting activity (MIA) were assessed for the	Diagnostic study	71 consecutive patients with stage IV melanoma Control group: 38 healthy adult	Sensitivities and specificities discrimination ability	Cut-offs: S100b 0.12 µg/L, MIA 6.50 ng/mL All tested serum parameters were significantly	Patients received different therapies Small population No information	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	ability to discriminate progressive from nonprogressive disease.				<p>elevated in patients with progressive disease.</p> <p>Sensitivity: S100b=91% MIA=88% LDH=79%</p> <p>Specificity: S100b=76% MIA=73 LDH=92%</p> <p>In calculating Somers' Dxy and ROC-AUC values, S100b, MIA, and LDH showed high discrimination ability. Multiple logistic regression: LDH was the only statistically significant marker for progressive disease.</p>	about follow-up	
Hofmann et al. (2011)	to assess the utility of	Diagnostic study	138 melanoma patients in stage III	Sensitivity	MIA cut-off value of 12 ng/mL:	No information about time interval	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma inhibitory activity (MIA) serum marker in the follow up and primary diagnosis of stage III melanoma patients		at time of primary diagnosis and during periodical routine follow up	Specificity 5-year survival rate	sensitivity: 69.2%, specificity: 69.9%. PPV for relapsing disease: 67.2%, NPV: 72.0% 5-year survival rate: 78.1% (MIA <12 ng/mL) vs. 72.7% (MIA ≥12 ng/mL). (P = 0.230).	between blood sample and staging/restaging examinations "relapse" not described in detail, staging results not given.	
Garnier et al. (2007)	L-DOPA/tyrosine ratio (an index of tyrosinase activity), melanoma antigens S100B and MIA, lactate dehydrogenase (LDH) and their combinations were evaluated for clinical value as tumour markers in melanoma.	Diagnostic study	170 CM patients (stage I-II: 57, III: 54, IV: 59)	Sensitivity Specificity Increase with disease progression Overall survival	At inclusion: Sensitivity/ specificity of L-DOPA/tyrosine ratio with S100: 73%/70% L-DOPA/ tyrosine ratio with LDH: 69%/69% L-DOPA/ tyrosine ratio with MIA: L-DOPA/ tyrosine ratio with MIA and LDH: 74%/68% During follow-up: Disease progression (11		3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					stage I-II, 7 stage III patients) increased the L-DOPA/ tyrosine ratio by +35.7%, but not other marker levels (MIA: +18%, S100B: -20%, LDH: -9.7%) Cox regression model: survival predictors were S100B and MIA		
Tas et al. (2004)	To investigate the clinical value of S100 and MIA as tumor markers for malignant melanoma.	Diagnostic and prognostic study	48 CM (5 in stage I and II, 22 stage III, 21 in stage IV) Control group: 15 healthy subjects	Sensitivity, specificity Overall survival	Only 5 patients in stages I and II included; none of them had increased MIA, 2 had increased S100 Only sensitivity of serum MIA statistically significantly correlated in Cox analysis, the prognostic significance of MIA	Small patient sample in stage I Small patient sample, especially in stage I Small control group of healthy people, no details given Details of staging and follow-up (e.g. time intervals, examinations at follow-up) not	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					level was lost	reported	
Banfalvi et al. (2002)	to compare the prognostic values of serum 5-S-Cysteinyldopa, S-100B and LDH concentrations in Stage III-IV melanoma patients	Retrospective diagnostic and prognostic study	<p>Data from 179 patients Stage III-IV melanoma patients at diagnosis: (37 in Stage III, 142 in Stage IV).</p> <p>The age of patients ranged from 22 to 88 years (mean 59.8). Median follow up time was 15 months.</p> <p>63 patients (with other skin diseases) were enrolled as control group.</p>	<p>Specificity Sensitivity PPV</p> <p>Overall Survival</p>	<p>Stage III: 5-S-CD was 60 % sensitivity, 91.6 % specificity, 93.8 % PPV</p> <p>Stage IV: LDH: Sensitivity=48.5 %, Specificity =83.3, PPV= 98.5. S 100B: Sensitivity=70.5, Specificity = 100, PPV= 100. 5-S-CD Sensitivity=69.1 Specificity =50, PPV= 96,9</p> <p>calculated median survival: 4.6 months. Kaplan-Meyer analysis of the survival of patients with elevated vs. normal marker</p>	<p>In stage III data for sensitivity and specificity for S100B and LDH not given</p> <p>No further information about staging (reference standard)</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					levels indicated significant differences in case of all the 3 markers, with the shortest survival of patients with elevated S 100B or LDH levels (p<0.05).		
Meral et al. (2001)	To investigate the hypothesis that the decline in serum melanoma-inhibiting activity (MIA) levels following initiation of treatment might have prognostic value	Prognostic study	35 patients with advanced stage melanoma (11 stage III, 24 stage IV) mean age 52.2 years Control group consisting of 20 adults without degenerative diseases of cartilage or joint pain	Overall survival	The mean serum LDH, S100 and MIA levels of the patients with MM before treatment were significantly higher than in the control group. Patients with visceral dissemination vs. patients with nodal spread: MIA-levels 30.1 ng/ml vs.14.5 ng/ml. mean serum MIA level in the control group: 12.4 ± 3.2 ng/ml. (cut-off	See original article for overall survival curves (Kaplan-Meier) Survival analysis were not performed with serum S100 levels Analysis of LDH kinetics revealed no useful information.`	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>level: 8.7 ng/ml (mean + 2SD).</p> <p>1-year OS rates: no change according to the site of the primary tumour, the type of surgical or radiation treatment or the chemotherapy regimen.</p> <p>Advanced stage MM patients in whom serum MIA levels did not decrease during systemic treatment had a less favourable prognosis.</p>		
Brouard et al. (2000)	To determine if serial PS100B is a marker for metastatic evolution by observation of its level/variation/eva	Diagnostic study	239 blood samples were taken in 122 patients with cutaneous melanoma (56 patients in complete	Sensitivity and specificity	The threshold to separate patients with metastases from those in complete remission was 0,09µg/L	Only results of 90 patients are presented. Drop outs are not commented.	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	evaluation in patients in complete remission and patients receiving chemotherapy		remission, 56 patients with melanoma in progression		(Specificity 92%, sensitivity 70%). PPV (Stage III/IV): 77%, NPV 89%		
Schmitz et al. (2000)	To analyse the serum levels of S100B and MIA in non-melanoma control patients and melanoma patients to report on the sensitivity and specificity of both tumor markers	Diagnostic study	87 CM patients	Specificity Positive results	Specificity for S100B regarding the diagnosis of melanoma: 85.8% with a cut-off value of 0.12 µg/l 94.6% with a cut-off value of 0.20 µg/l Specificity for MIA: 89.9% with a cut-off of 6.5 µg/l 97.4% with a cut-off of 8.5 µg/l Values > 6.5 µg/l for MIA prior to treatment: 0% for stage I/ II 53.8% for stage III 68.3% for stage IV Values > 6.5 µg/l for MIA post treatment: 11.7% for stage I/II	No follow-up (cross-sectional design)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					9.7% for stage III 6.9% for stage IV Values > 0.12 µg/l for S100 prior to treatment: 50% for stage III 80% for stage IV Values > 0.12 µg/l for S100 post treatment: 16.1% for stage I/II 18% for stage III 14.3% for stage IV		
Stahlecker et al. (2000)	To evaluate whether MIA is a reliable tumor marker in terms of course of disease, therapy-monitoring and prognostic value	Diagnostic study	326 melanoma patients: 250 stage I, 52 stage II, 5 stage III and 19 stage IV Control group of 100 healthy blood donors	Positive results Sensitivity Specificity	Increased MIA levels: 4.4% in stage I (n = 250) 11.5% in stage II (n = 52) 60.0% in stage III (n = 5) 89.5% in stage IV (n = 19). Elevated MIA 22 patients with no clinical evidence of disease (stage I, II or stage III, IV after metastatic surgery)		3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					8 of them had detection of metastases at the same time, 5 of them 2 - 6 months later 9 stayed free of clinically detectable disease (false positives = 3%)		
Bosserhoff et al. (1997)	To investigate whether MIA provides a clinically useful parameter in patients with malignant melanomas, and to compare this with the diagnostic value of S100.	Diagnostic study	112 CM patients (38 stage I, 13 stage II, 6 stage III, and 44 stage IV) 350 clinically tumor-free patients during a follow-up period after removal of a primary stage I or II melanoma Controls: 72 healthy blood donors Additional controls: 50 patients with sepsis, 23 patients	Positive rates TP FN	Positivity of MIA: - 100% of sera from 50 patients with stage III and IV - 13% of sera from stage I - 23% of sera from stage II patients - 9% of clinically tumor-free patients; 15 (4%) of these patients developed metastases MIA-levels in patients with other malignancies: see	Sample of stage II and III patients small 5 patients during chemotherapy of stage IV melanoma Sensitivity/specificity not given	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			with brain tumors, 243 patients with advanced epithelial and mesenchymal tumors		full-text S100-positivity, cut-off: 0.15 ng/ml - 30/49 (61%) sera from stage III and IV patients - 0% of stage I and II sera - 4% of sera from healthy donors - 20% from septic patients, 16% from patients with gliomas, and 5% from patients with advanced carcinomas positive		
Bosserhoff et al. (1999)						Same patient cohort as Bosserhoff et al. (1997), less data	
Henze et al. (1997)	To examine serum S100 concentrations of	Diagnostic study	Blood samples from 73 patients with malignant	sensitivity	1/25 stage I/II patients, 3/14 stage III patients	Small population Choroid melanoma	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with different stages of malignant melanoma and to determine the value of serum S100 in the follow-up of melanoma patients during treatment		melanoma (25 patients: stage I/II, 14: stage III, 34: stage IV) Control group: 130 healthy patients.		(sensitivity 21,4%) and 27/34 stage IV patients (sensitivity 79,4%) showed detectable S100 levels. For metastatic melanoma (stage III/IV): sensitivity 62,5%. Correlation between serum S100 and clinical stage (p=0,0899 stage I/II versus p<0,0001 stage III/IV)	included (n=1) No information about staging given	
Dumitrascu et al. (2009)	To investigate S-100B and MIA in relation to disease development	Diagnostic study	51 patients with skin melanoma (34% stage I, 40% stage II, 15% stage III and 11% stage IV) and 72 healthy volunteers	True and false positives	Mean serum level of S100 in healthy volunteers: 0.172 µg/l 5.55% FP Mean serum level of MIA in healthy volunteers: 7.28 µg/l No false positives S-100B significantly	Low patient numbers for each stage Selection criteria for patients and healthy volunteers not given	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					elevated only in stage IV patients (p = 0.02) MIA significantly elevated both stage II, III and IV MIA levels decreased after surgical removal of tumors and/or after good response to specific therapy; increase followed tumor progression and poor clinical response to treatment		
Vucetic et al. (2008)	To investigate whether MIA serum level will be elevated in patients with metastases or local spreading of the disease before any symptom of such progression is clinically apparent	Diagnostic study	140 patients: (50 with positive SN, 50 with negative SN, 20 controls with dysplastic nevi 20 controls with basal cell carcinoma Exclusion criterion: palpable	Mean values Sensitivity Specificity	Mean MIA value in patients with positive sentinel nodes: 14.53 ng/ml Mean MIA value in patients with negative sentinel nodes: 7.32 ng/ml At a cutoff value of 8.5 ng/ml, 82%	No follow-up as reference standard (cross-sectional design)	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			lymph nodes		sensitivity and 82% specificity of MIA		
Arenberger (2007)	quantification of the following five melanoma markers by establishing a quantitative multimarker real-time RT-PCR assay: melanoma antigen recognized by T cells (Melan-A/MART-1), melanosomal matrix protein (gp100), melanoma antigen-A3 family (MAGE-3), melanoma inhibitory protein (MIA), and tyrosinase. Additionally human telomerase reverse transcriptase (hTERT) was focused on	Prospective study	65 patients with resected cutaneous melanoma stage IIB-III 33.9% stage IIA, 24.6% stage IIB, 12.3% stage IIC, 15.4% IIIA, 9.2% stage IIIB and 4.6% stage IIIC. Control group: 23 healthy donors	Detection rate	Tumour marker mean levels in patients with progression: MIA, 4.272±2.183 (statistically significant difference compared with cut-off value, P<0.01); Melan-A, 0.026±0.016 (P>0.05); MAGE 3332.927±196.239 (P<0.01); gp100, 0.953 ±0.827 (P<0.05). MAGE-3 was the most frequent positive marker (17x), than gp100 (10x), MIA (9x) and tyrosinase (1x). Melan-A did not show any significant elevation compared with cut-off.	Small population Elevation of tumour markers varies strongly (e.g. patient 35: MAGE-3= 36.4, in patient 2: MAGE-3=40 580). poor information about the patients` follow-up after the study.	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	The final aim is the routine usage of this method for rapid screening of early metastasis and treatment response in high-risk melanoma patients.				In patients with progression, in 39% three markers were concomitantly positive, in 28% two markers and in 33% one marker were positive.		
Arenberger (2007)	See above	See above	See above	See above	See above	Same population/same results as in the previously described study (Arenberger P (2007): Multimarker real-time reverse transcription-PCR for quantitative detection of melanoma-associated antigens: a novel possible staging method)	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Smit et al. (2008)	<p>to evaluate S-100B for monitoring response to chemoimmunotherapy followed by surgery and its predictive value for relapse and overall survival in patients with clinically detectable localized disease.</p> <p>Another aim was to analyze the expression of S-100B in the lymph nodes and in-transit metastases of the included patients and to compare these findings with the values of S-100B in the serum.</p>	Prognostic study.	44 patients with locoregional-lymph node or intransit metastases (cytologically proven, clinically detectable regional metastases of melanoma without evidence of distant metastases.	Overall survival Reissionrate	Correlations between the pattern and intensity of S-100B expression in the tumor specimen and the value of serum the S-100B did not reach statistical significance	Small population	3b-
Lugovic et al. (2007)	To determine and compare levels of S100, MIA, LDH	Diagnostic study	50 melanoma patients (30% in stage I, 52% in	Positive results	Increased MIA in 26% of stage I patients, 26% of	No follow-up as reference standard	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	and tyrosinase in the serum of patients with MM in different disease stages, and to conclude whether these might be useful prognostic tools for MM progression		stage II, 16% in stage III and 8% in stage IV)		stage II patients, 0% of stage III patients and 50% of stage IV patients Increased S100 in of stage I patients, 9% of stage II patients, 0% of stage III patients and 50% of stage IV patients Increased LDH in 26% of stage I patients, 4% of stage II patients, 13% of stage III patients and 25% of stage IV patients		
Auge et al. (2005)	To compare the sensitivity and specificity of S-100 and MIA and their combination in advanced melanoma, and the relationship with prognostic factors such as	Diagnostic study	182 CM patients: 96 patients with no evidence of disease (NED, stages I and II) and 86 patients with stages III, IV	Sensitivity	Sensitivity of S100 (cutoff > 0.2 µg/l): 53.8% for SSM, 40% for ALM, 75% for NM Sensitivity of MIA (cutoff > 14 ng/l): 61.5% for SSM, 40% for ALM, 65% for NM	No data given for specificity Reference test not described in detail	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	growth patterns and site of metastases.				Slightly elevated levels of S100 (< 0.24 µg/l) and MIA (< 16.4 ng/ml) in 1.2% and 3.2% of NED patients, respectively Sensitivity of S100 for LN metastasis 58.3%, for multiple metastases 58.3%, for multiple with liver metastasis 70%, for brain metastasis 77% and for lung metastasis 30% Sensitivity of MIA for LN metastasis 54.1%, for multiple metastases 62.5%, for multiple with liver metastasis 70%, for brain metastasis 66.6% and for lung metastasis 23%		
Guba et al. (2002)	To evaluate the association between pre- and	Diagnostic and prognostic study	70 patients with histologically confirmed	Overall-survival Specificity	Mia positivity concentrations: >8,8ng/l.:	No data for sensitivity given	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	posttreatment levels of MIA and survival in 70 patients with advanced melanoma.		metastatic melanoma. (50 stage III, 17 stage IV)		<p>- stage III: 46% - stage IV: 65%</p> <p>Median OS in MIA positive patients (stage III/IV): 13 vs. 28 months in patients with negative pre-treatment MIA levels.</p> <p>staging-related analysis: stage III: median OS: 14 months in MIA positive patients vs. 28 months in negative patients. stage IV: 12 vs. 19 months respectively.</p> <p>Specificity (cut-off > 8,8 ng/l) = 95%</p>	Small population	
Klimek et al. (2002)	To evaluate the sensitivity of serum MIA levels in predicting the	Diagnostic study	39 patients with stage II, III and IV melanoma 14 patients with	Sensitivity False positives	MIA: 17% sensitivity for recurrence 6% false positives	MIA values taken at different intervals after diagnosis and	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	risk of relapse in patients with AJCC stage II, III and IV melanoma		clinically advanced melanoma (IV or unresectable III) as positive controls Serum from 20 patients with prostate or small cell lung cancer to establish a background reference range		No significant difference in the proportion of patients with elevated MIA levels between the group of patients who relapsed (17%) and those who did not relapse (6%)	treatment of melanoma	
Matsushita et al. (2002)	To compare the usefulness of the serum markers 5-S-cysteinyldopa (5-S-CD) and melanoma inhibitory activity (MIA) in the monitoring of postsurgical melanoma patients	Diagnostic study	45 CM patients (7 in stage I, 20 in stage II, 18 in stage III) 30 age-matched healthy volunteers	Sensitivity False positives	Sensitivity for detection of relapse: 64% for MIA False positives (non-progressive patients) for MIA 8.3% (6/72)	No selection criteria for the included patients given Evaluation per sample, not per patient No description of follow-up	3b-
Dreau et al. (1999)	To measure plasma MIA concentration in patients with metastatic melanoma or	Diagnostic study	84 CM patients (16 in stage II, 29 in stage III and 39 in stage IV) under treatment Most of stage II	Sensitivity and specificity	At a threshold of 4.5 ng/ml values for discrimination between progression and no progression	Low patient numbers for each treatment modality Method of assigning patients to treatment	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients at high risk for recurrence treated with various immunotherapy regimens		and III patients (36/45) were treated with polyvalent melanoma vaccine after surgical resection; all patients treated with IL-2 were stage IV		were: Sensitivity of 82% and specificity of 71% before treatment Sensitivity of 67% and specificity of 79% after treatment	regimens not described	
Tofani et al. (1997)	To assess the reliability of NSE and S100 as indexes of disease activity.	Diagnostic and cross-sectional study	53 consecutive patients with melanoma 24 patients presented with local disease (stage I or II), 29 had metastases (stage III or IV). Twenty healthy volunteers were used as a control group.	Prevalence of increased NSE and S100 levels Sensitivity and specificity	In the whole group, elevation of S-100 in 30% of patients. No elevated levels in the subgroup of 24 patients stage I and II. Increased levels in 55% of patients stage III and IV Serum NSE: elevated in 26%. 4/24 patients (16%) with melanoma in stages I and II had increased NSE values. Increased	Small patient samples Study included in addition to S100 meta-analysis because of results about NSE No details about reference standard for the calculation of sensitivity and specificity	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>levels in 34% of patients stage III and IV.</p> <p>For the whole group: sensitivity of S100 and NSE: 30 and 26%, respectively</p> <p>For patients I and II: Poor sensitivity for NSE, S-100 values were normal in all patients.</p> <p>For patients stage III and IV: sensitivity for S-100 and NSE: 55% and 34% respectively (p < 0.5).</p>		

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Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Rodriguez Rivera et al. 2014	To review the collective experience and utility of FDG-PET scans in the detection of systemic metastases in patients with stage III melanoma	Systematic review and meta-analysis	A total of 623 patients with stage III melanoma	<p>Sensitivity</p> <p>Specificity</p> <p>Positive and negative likelihood ratios</p> <p>SROC</p> <p>DOR</p> <p>Change of management</p>	<p>Sensitivity of FDG-PET: 89.42% (95% CI: 65.07 - 97.46)</p> <p>Specificity: 88.78% (95% CI: 77.04 - 94.91).</p> <p>Pooled positive likelihood ratio: 7.97 (95% CI: 3.58 - 17.71)</p> <p>Negative likelihood ratio: 0.12 (95% CI: 0.03 - 0.47).</p> <p>Area under the summary receiver operating curve (SROC): 0.94 (95% CI: 0.92 - 0.96)</p> <p>Diagnostic odds ratio (DOR): 66.84 (95% CI: 10.66 - 418.89).</p>	<p>Small sample size, 9 studies included</p> <p>Confirmation bias possible: adequate reference test was not applied properly (biopsy, further radiological studies and/or follow-up)</p> <p>67% of the patients had clinically evident stage III disease → findings possibly more relevant for patients stage IIIb/c disease</p>	Ila

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Change in stage and/or management was noted in 22% (126/573) of patients when FDG-PET was utilized.		
Bastiaannet et al. 2012	- to assess predictive value of FDG-PET and CT - to analyze their cost-effectiveness in several diagnosis-treatment combinations.	Cohort study	253 melanoma patients with palpable, proven lymph node metastases	Sensitivity Specificity Accuracy PPV NPV Cost-consequence analysis	FDG-PET: Sensitivity: 86,1% (CI: 78.4-93.7) Specificity: 93,1% (CI: 89.3-96.9) CT Sensitivity: 78,2% (CI: 69.0-87.4) Specificity: 93,7% (CI: 90.1-97.3) PPV, NPV, accuracy: see table 2/full-text Cost of diagnostic work-up: With CT: -5,5% With FDG-PET: +7,2% With both: +15,1%	True-positive upstaging in 61 patients (CT) respectively in 68 patients (FDG-PET)	IIb

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bronstein et al. 2012	To determine how often unexpected FDG PET-CT findings result in change of management of stage IV and clinically evident stage III melanoma patients with resectable disease based on conventional imaging	Cohort study	patients with stage IV and clinically evident stage III melanoma	Metastases detection rate change in surgical management	unexpected melanoma metastases in 12 % of scans As a result the surgery was cancelled in two patients, and the planned approach was altered in another two patients to address the unexpected sites	Small population	IIb

2.3.5. Literatur

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII .6
Abbott et al. (2011)	x	x		x
Agarwala et al. (2009)			x	
Aloia et al. (2006)		x		
Andrés et al. (2008)	x	x	x	
Ardizzoni et al. (1987)	x			
Arenberger (2007)	x	x		
Au et al. (1984)	x			
Auge et al. (2005)	x	x	x	
Bafounta et al. (2004)	x	x	x	x
Balch et al. (2009)	(x)	(x)	(x)	x
Bastiaannet et al. (2009)		x		x
Bastiaannet et al. (2012)		x	x	

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII .6
Bosserhoff et al. (1997)	x	x	x	x
Bouwhuis et al. (2011)	x	x		x
Bronstein et al. (2012)		x	x	
Brouard et al. (2000)	x	x	x	x
Buzaid et al. (1995)		x		
Chai et al. (2011)	x			
Clark et al. (2006)	x			
Collins et al. (1993)				x
Constantinidou et al. (2008)		x		
Deichmann et al. (2004)	x	x	x	x
Dellestable et al. (2011)			x	
Dietlein et al. (1999)		x	x	x
Doiron et al. (1981)			x	

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII .6
Dreau et al. (1999)	x	x	x	
Dumitrascu et al. (2009)	x	x	x	
Etchebehere et al. (2010)		x	x	
El-Maraghi and Kielar (2008)	x			
Essler et al. (2011)	x	x	x	x
Fogarty et al. (2006)	x	x	x	x
Garbe et al. (2003)				x
Garnier et al. (2007)	x	x	x	
Ginaldi et al. (1981)	x		x	x
Goerz et al. (1986)	x	x	x	x
Guba et al. (2002)		x	x	
Hafner et al. (2004)	x			
Hausmann et al. (2011)		x	x	x

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII .6
Heaston et al. (1983)	x	x		
Henze et al. (1997)				x
Hinz et al. (2011)	x			
Hocevar et al. (2004)	x			
Hofmann et al. (2002)	x			x
Hofmann et al. (2009)				x
Hofmann et al. (2011)		x		x
Holloway et al. (1997)		x	x	x
Horn et al. (2005)		x		
Lagaru et al. (2007)m	x	x	x	x
Iscoe et al. (1986)	x			
Johnson (1997)		x		
Kaskel et al. (1999)	x	x	x	x

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII .6
Kersey et al. (1985)	x			x
Khansur et al. (1989)	x	x	x	x
Klode et al. (2010)	x			
Koskivuo et al. (2007)	x	x		x
Krahn et al. (2001)	x	x	x	x
Krug et al. (2000)		x	x	x
Krug et al. (2008)	x	x	x	x
Kruijff et al. (2009)		x		
Kruijff et al. (2011)		x		
Kuan et al. (1988)	x	x	x	
Kunte et al. (2009)	x			
Laurent et al. (2011)			x	
Löffler et al. (2003)		x	x	x

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII .6
Lugovic et al. (2007)	x	x	x	
Mansour et al. (2010)	x	x	x	x
Matsushita et al. (2002)	x	x	x	
Maubec et al. (2007)	x			
Meyer and Stolbach (1978)	x			
Miranda et al. (2004)		x		
Mocellin et al. (2008)	x	x	x	x
Mueller-Horvat (2005)		x	x	x
Neuss et al. (2011)		x		
Panagiotou et al. (2001)	x			x
Pandalai et al. (2010)		x		
Paschen et al. (2009)	x	x	x	x
Patten et al. (1990)	x	x	x	x

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII .6
Pfannenbergl et al. (2007)		x	x	x
Pleiss et al.(2007)	x	x	x	x
Revel et al. (2010)	x			
Rodriguez et al. (2014)		x	x	
Saiag et al. (2005)	x	x		x
Sanki et al. (2009)	x			
Sawyer et al. (2009)	x			x
Schlamann et al. (2008)	x	x	x	x
Schmid-Wendtner et al. (2004)	x	x		
Schmitz et al. (2000)	x	x	x	
Sibon et al. (2007)	x			
Silverman et al. (1984)	x		x	x
Singh et al. (2008)	x			

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII .6
Smit et al. (2008)		x		x
Stahlecker et al. (2000)	x	x	x	x
Stas M et al. (2002)		x	x	
Stoffels et al. (2011)	x	x		
Stoitchkov et al. (2003)	x	x	x	
Strobel et al. (2007)	x	x	x	x
Stucky et al. (2010)	x	x		
Stutte (1989)		x	x	x
Tas et al. (2004)	x	x	x	x
Terhune et al. (1998)	x			
Testori et al. (2005)	x			x
Tofani et al. (1997)	x	x	x	x
Tsao et al. (2004)	x			x

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII .6
Uren (1999)		x		
Van den Brekel et al. (1998)	x	x		x
Van der Ploeg (2009)	x			
Veit-Haibach et al. (2009)	x	x	x	
Vereecken et al. (2005)	x			
Vereecken et al. (2009)		x	x	
Vermeerenet al. (2011)	x			
Vucetic et al. (2008)	x			
Wagner et al. (2011)		x		
Wang et al. (2004)	x			
Webb (1977)	x	x	x	x
Xing et al. (2011)	x	x	x	x
Yancovitz et al. (2007)	x	x		

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII .6
Zartman et al. (1987)	x			

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2.4. Frage I.9. Ausbreitungsdiagnostik beim metastasierten okkulten Melanom - Adaptation

Frage I.9. Welche Untersuchungen sind beim metastasierten okkulten Melanom zur Primärtumorsuche und Ausbreitungsdiagnostik indiziert?

Die Frage wurde letztendlich Konsens-basiert beantwortet.

2.4.1. Synopse Quelleitlinien (kurz)

Thema/Fragestellung	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
14. Welche Untersuchungen sind bei metastasiertem okkultem Melanom zur Primärtumorsuche und Ausbreitungsdiagnostik indiziert?	Klinische Untersuchung: Augen, Gehörgang, Kopfhaut, evtl. Koloskopie (IV); PET zur weiteren Ausbreitungsdiagnostik (IV)	Keine Angaben	Keine Angabe	nur relevant für medikamentöse Therapien

2.4.2. Empfehlung, Hintergrundtext und Literatur Australische Quell-Leitlinie

(mit Seitenangaben der Quelleitlinie)

	LL Australien New Zealand Guidelines Group 2008
Schlüsselempfehlungen	<p>Recommendation</p> <p>Patients with metastases and no obvious primary tumour be examined for primary melanomas in obscure sites. If none are found, assume that the primary melanoma has completely regressed.</p> <p>Recommendation grade:</p> <p>D</p>
Evidenzgrundlage	<p>Evidence summary</p> <p>Patients with occult primary melanoma usually present with lymph node disease, a soft tissue metastasis, or widespread systemic disease, in the absence of a primary tumour and the diagnosis is made by pathological examination of the lymph node, or metastasis which shows the characteristics of melanoma. Such patients should be examined</p>

	<p>LL Australien New Zealand Guidelines Group 2008</p>
	<p>carefully to exclude the possibility of a hidden primary by examination of the eyes, inner ears and scalp, and possibly colonoscopy. The presenting lymph nodes or metastases should be treated appropriately regardless of the inability to detect the primary tumour and a PET scan should be performed Level IV , Referenz 1, 2</p>
<p>Hintergrundtext</p>	<p>Melanoma is among a number of cancers in humans where the primary tumour cannot always be found. In some patients the primary may be in an obscure site such as the eye, ear or the intestine, but in the majority it is likely that the primary tumour has been destroyed by the host's immune system via lymphocyte activation.^{1,2} It is likely that total regression occurs in 10–20% of melanomas, though only those where there have been metastases are diagnosable (about 5% of melanomas). Partial regression of primary tumours is more common and is often reported on pathology reports (30–50%). Two recent studies have shown that those patients with metastases and an occult primary melanoma have a better prognosis than those with metastases and a known primary melanoma.^{3,4} This suggests an intrinsically superior host tumour interaction in those with occult primary melanoma.</p>
<p>Referenzen</p>	<ol style="list-style-type: none"> 1. Tefany FJ, Barnetson RS, Halliday GM, McCarthy SW, McCarthy WH. Immunocytochemical analysis of the cellular infiltrate in primary regressing and non-regressing malignant melanoma. J Invest Dermatol 1991; 97(2):197–202. 2. Lowes MA, Bishop GA, Crotty K, Barnetson RS, Halliday GM. T helper 1 cytokine mRNA is increased in spontaneously regressing primary melanomas. J Invest Dermatol 1997; 108(6):914–919. 3. Vijuk G, Coates AS. Survival of patients with visceral metastatic melanoma from an occult primary lesion: a retrospective matched cohort study. Ann Oncol 1998; 9(4):419–422. 4. Lee CC, Faries MB, Wanek LA, Morton DL. Improved survival after lymphadenectomy for nodal metastasis from an unknown primary melanoma. J Clin Oncol 2008; 26(4):535–541.

Literatur :

1. Lee CC, Faries MB, Wanek LA, et al. Improved survival after lymphadenectomy for nodal metastasis from an unknown primary melanoma. J Clin Oncol 2008;26:535-541
2. Lowes MA, Bishop GA, Crotty K, et al. T helper 1 cytokine mRNA is increased in spontaneously regressing primary melanomas. J Invest Dermatol 1997;108:914-919
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2.4.3. Ergänzende Recherche, Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	<p>("occult melanoma"[tiab] or "melanoma" AND "unknown primary" [tiab]) AND ("staging"[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR "sonography"[all fields]) OR ("lymph nodes"[all fields] OR "lymph"[all fields] AND "nodes"[all fields]) OR "lymph nodes"[all fields] OR ("lymph"[all fields] AND "node"[all fields]) OR "lymph node"[all fields]))</p> <p>("occult melanoma"[tiab] or "melanoma" AND "unknown primary" [tiab]) AND ("staging"[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR "sonography"[all fields]) OR ("lymph nodes"[all fields] OR "lymph"[all fields] AND "nodes"[all fields]) OR "lymph nodes"[all fields] OR ("lymph"[all fields] AND "node"[all fields]) OR "lymph node"[all fields]))</p> <p>("occult melanoma"[tiab] or "melanoma" AND "unknown primary" [tiab]) AND ("staging"[all fields] OR "diagnosis"[all fields]) AND ("chest X-ray"[all fields] OR "chest radiography"[all fields] OR "Radiography, Thoracic"[Mesh])</p> <p>("occult melanoma"[tiab] or "melanoma" AND "unknown primary" [tiab]) AND ("staging"[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR "sonography"[all fields]) OR "abdomen"[all fields] OR "abdominal"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])</p>	26.01.2012	9 9 0 0

Datenbank	Suchstrategie	Datum	Treffer
	<p>("occult melanoma"[tiab] or "melanoma" AND "unknown primary" [tiab]) AND ("staging"[all fields] OR "diagnosis"[all fields]) AND ("Magnetic Resonance Imaging"[Mesh] OR "Magnetic Resonance Imaging"[all fields] OR "mri"[all fields] OR "magnetic resonance"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])</p>		3
	<p>("occult melanoma"[tiab] or "melanoma" AND "unknown primary" [tiab]) AND ("staging"[all fields] OR "diagnosis"[all fields]) AND ("Tomography, X-Ray Computed"[Mesh] OR "computer tomography"[all fields] OR "ct"[all fields] OR "Tomography, Spiral Computed"[Mesh] OR "Tomography Scanners, X-Ray Computed"[Mesh] OR "Positron-Emission Tomography"[Mesh] OR "positron-emission tomography"[all fields] OR "pet"[all fields] OR "Tomography, Emission-Computed, Single-Photon"[Mesh] OR "single-photon emission computed tomography"[all fields] OR "spect"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])</p>		8
	<p>("occult melanoma"[tiab] or "melanoma" AND "unknown primary" [tiab]) AND ("staging"[tiab] OR "diagnosis"[tiab]) AND ("scintigraphy"[tiab] OR "scinti*"[tiab]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])</p>		0
	<p>("occult melanoma"[tiab] or "melanoma" AND "unknown primary" [tiab]) AND ("LDH"[all fields] OR "lactate dehydrogenase" OR "S100"[all fields] OR "MIA"[tiab] OR "melanoma-inhibiting activity"[tiab]) AND ("staging"[all fields] OR "diagnosis"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])</p>		3

Auswahl der Literatur	
Gesamttreffer	25
Gesamttreffer nach Dublettenelimination	
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews, Bench Research
Anzahl nach Abstractscreening	1
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	1
Bemerkungen: Eine Ergänzungsrecherche für den Zeitraum nach 2008 wurde am 26.10.2011 auf Medline durchgeführt, die Update-Recherche erfolgte am 26.01.2012. Oben aufgeführt sind die Trefferzahlen der letzten Recherche. Hierbei wurde eine weitere relevante Studie identifiziert.	

2.4.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Tos T et al. (2011): Extensive Screening for Primary Tumor is Redundant in Melanoma of Unknown	this article questions whether extensive physical examinations (ophthalmoscopy, otoscopy, rhinopharyngoscopy,	retrospective study	103 patients diagnosed with unknown primary tumor during the period 1986–2006	Metastases detection rate	39 (38%) presented primarily with a cutaneous or a subcutaneous Metastasis, 63 (61%) with a lymph node metastasis. 1		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Primary	laryngoscopy, sigmoideoscopy, and in women, gynecological examination) are necessary.				patient presented with a bone metastasis (1%). 87 patients (84%) were examined by an ophthalmologist. A choroidal melanoma was suspected as the primary tumor in 1 patient. 84 patients (82%) were examined by an oto-rhino-laryngologist, whereby no primary tumor was found. 95 patients (92%) were examined by sigmoideoscopy/rectoscopy. No primary tumor was found. Of the 36 women, 32 had a gynecological examination (89%), revealing no primary tumor.		

2.4.5. **Literatur:**

Tos T, Klyver H, Drzewiecki KT. Extensive screening for primary tumor is redundant in melanoma of unknown primary. J Surg Oncol 2011;104:724-727

3. AG Sentinel Node Biopsie

3.1. Frage II.1. Sentinel-Node-Biopsie – De-novo-Recherche

Frage II.1. In welchen Fällen ist die Sentinel-Biopsie indiziert?

3.1.1. PICO, Suchwörter

PICO-Unterfragen:

- Senkt die Durchführung einer Sentinel-Biopsie die Rezidivrate
- Senkt die Durchführung einer Sentinel-Biopsie die Mortalität
- Wie ist die Sensitivität und Spezifität einer Sentinel-Biopsie zum Nachweis einer lokoregionären Lymphknotenmetastasierung?

Suchwörter: s. hierfür auch Suchstrategie

Ober-/Unterbegriffe, Mesh Term	melanoma	survival, mortality, relapse, recurrence, sensitivity, specificity, accuracy, outcome, prognos*, predict*, assoc*	s. Suchstrategie
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3.1.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	"melanoma"[tiab] AND ("sentinel"[tiab] OR "Sentinel Lymph Node Biopsy"[MeSH]) AND ("survival"[tiab] OR "mortality"[tiab] OR "relapse"[tiab] OR "recurrence"[tiab] OR	26.01.2012	1039

Datenbank	Suchstrategie	Datum	Treffer
	"sensitivity"[tiab] OR "specificity"[tiab] OR "accuracy" OR "outcome"[tiab] OR "prognos*"[tiab] OR "predict*"[tiab] OR "assoc*"[tiab])		
Cochrane Library	(melanoma and (sentinel or "sentinel lymph node biopsy" or snb or slne or sln) and (survival or mortality or relapse or recurrence or sensitivity or specificity or accuracy or outcome or predict* or prognosis or assoc*)).ti,ab.	26.01.2012	43
Embase	(melanoma and (sentinel or "sentinel lymph node biopsy" or snb or slne or sln) and (survival or mortality or relapse or recurrence or sensitivity or specificity or accuracy or outcome or predict* or prognosis or assoc*)).ti,ab.	23.01.2012	1751
2. Suche/Ergänzungen			
Medline	(sentinel[title] OR "snb"[title] OR "slne"[title] OR "sln"[title]) predict* melanoma[title]	26.01.2012	1176

Bemerkungen:

Eine erste Literaturrecherche in Medline und und Cochrane erfolgte am 07.10.2010 bzw. für Embase am 11.05.2011. Die zweite Recherche (Ergänzungsrecherche) wurde am 18.04.2011 durchgeführt. Die Update-Recherche wurde am 23.01.2012 für Embase bzw. am 26.01.2012 für Medline und am 19.01.2012 für Cochrane durchgeführt. In der Tabelle angegeben sind die Trefferzahlen der letzten Recherche.

Die Beantwortung der Frage stützt sich in erster Linie auf die Meta-Analysen. Weitere Studien wurden hinzugezogen, wenn sie Aspekte abdecken, die in der Meta-Analyse nicht berücksichtigt wurden bzw. die nach der letzten Meta-Analyse veröffentlicht wurden. Im Rahmen der Update-Recherche wurde, neben einzelnen Studien, weitere Systematische Reviews bzw. Meta-Analyse identifiziert. Einzelne relevante Studien wurden mit aufgenommen, da nur spezielle Melanompopulationen in der Metaanalyse bzw. im Review eingeschlossen wurden (Patienten mit Melanomen >4mm bzw. SNB im Kopf/Hals-Bereich)

3.1.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	2970
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews
Anzahl nach Abstractscreening	77
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	48

3.1.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Valsecchi et al. (2011)	To perform a meta-analysis of all published studies of sentinel lymph node (SLN) biopsy for staging patients with melanoma.	Systematic review with meta-analysis	Melanoma patients; 53.4% male, median age 54 years	Proportion of successfully mapped (PSM) False-negative rate (FNR), post-test probability negative (PTPN) and positive predictive value (PVP) in the same nodal basin	Weighted PSM: 98.1% (improved in more recent studies and in articles with better quality scores) Distribution of FNR among studies ranged from 0.0% to 34%, weighted summary estimate	Very large number of patients (25240). No significant differences in results were seen when data from three large clinical trials or from certain geographic regions were	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				recurrence and for distant/all recurrences	<p>12.5%</p> <p>PTPN for same nodal basin recurrence ranged from 0.0% to 10.4%, summary estimate across studies 3.4%</p> <p>Weighted summary estimate of PVP for nodal recurrence 7.5%</p> <p>Weighted estimate for FNR for distant recurrence 17.4%, for total recurrences 29.9%</p> <p>Weighted estimate for PTPN for distant recurrence 4.4%, for total recurrence 10.5%</p> <p>Probability of additional nodal involvement in CLND for patients</p>	<p>excluded, or in other subgroup analyses.</p> <p>No statement possible about proportion of patients with positive SNB experiencing subsequent nodal recurrence despite CLND.</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					with positive SNB: 20.1%		
					PVP for distant and any recurrence 21.0% and 35.9%		
Warycha et al. (2009)	To estimate the risk, potential predictors, and outcome of SLN positivity in patients with thin melanomas.	Systematic review with meta-analysis	Patients with thin (≤ 1 mm) primary melanoma Total number of patients: 3651	SLN positivity rate Heterogeneity Melanoma-related deaths	Pooled SLN positivity rate 5.6% Significant heterogeneity among studies; remained significant in subgroups of studies with high vs. low quality scores, indicating other covariates or patient selection criteria that are responsible for heterogeneity No statistical evidence of publication bias 4 melanoma-related deaths	Unclear source of heterogeneity in this meta-analysis (may hint to unknown prognostic factors in patients with thin melanoma which need further investigation) Ulceration and Clark level > III have been correlated with a worse prognosis in patients with thin melanoma, but might not be associated with positive SLN	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					were reported		
Kunte et al. (2010)	To assess which factors predict the occurrence of micrometastasis and overall prognosis and whether SLNB should also be performed in patients with thin primary tumors.	Prognostic study	854 patients with malignant melanoma (56.8% male, 43.2% female), mean age 52.9 years	SLN status Disease-free survival (DFS) Overall survival (OS)	Rate of positive SLNs: 24.9% Probability of finding a positive SLN 5.7% in patients with tumor thickness \leq 0.75 mm, 57.3% in patients with tumor thickness > 4 mm SLN positive in 36.8% of patients with nodular melanoma (NM), 27.1% of patients with secondary nodular superficial spreading melanoma, 26.1% in acral lentiginous melanoma, 13.4% in superficial spreading melanoma, 8.8% Spitzoid melanoma and 38.3% of	Prospective design For detailed p values according to tumor thickness etc. see original file. Prospective design and large patient numbers Patients lost to follow-up not described for key characteristics (potential source of selection/attrition bias)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>ulcerated melanomas</p> <p>In multivariate analysis, tumor thickness and histological tumor type significantly associated with SLN status</p> <p>Melanoma with tumor > 4 mm revealed 11.68-fold risk for a positive SLN in comparison with tumors < 1 mm</p> <p>9.8% (63/641) of SLN negative patients had a recurrence of the disease, 8.4% (54/641) died of the disease (5-year survival rate: 90.1%, mean DFS 117.9 months, OS 119.8 months)</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Of SLN positive patients, 39.4% had a recurrence, 28.6% died of the disease (mean DFS 80.75 months, OS 94.91 months, 5-year survival rate: 58.1%)		
Mays et al. (2010)	To evaluate prognostic factors in the subset of patients with a melanoma Breslow thickness between 1 and 2 mm and to determine whether all such patients require SLN biopsy.	Prognostic study	1110 patients with cutaneous melanoma between 1 mm and 2 mm in thickness	Rate of positive and negative SLNs Overall survival Disease-free survival	Group A: melanoma from 1 mm to 1.59 mm in thickness Group B: melanoma from 1.60 mm to 2.0 mm in thickness (n = 348) On multivariate analysis, Breslow thickness, age and lymphovascular invasion were predictive of positive SLN	Post-hoc analysis of the multi-center, randomized Sunbelt Melanoma Trial See full text (p. 1539) for complete partition tree	1b
Testori et al.	To investigate the	Observational	1313 consecutive	Overall survival	Overall SLN	Large patient	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(2009)	relationship between primary tumor characteristics, SLN findings, and the clinical outcome	study	patients	Predictors of SLN positivity and survival	<p>identification rate 99.3%</p> <p>Patients were categorized into four different subgroups: (1) patients with negative SLN after pathological examination who never developed regional lymph node metastases during follow-up; (2) patients with pathological diagnosis of metastasis in the SLN without any positive NSLNs; (3) patients with positive SLNs and secondary deposits in NSLNs at CLND; and (4) patients with negative SLNs who developed clinically detectable regional metastases in the</p>	<p>cohort</p> <p>Long median follow-up</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>SNB lymphatic basin during follow-up.</p> <p>5-year OS rates were 93%, 71.3%, 50.4% and 49.8% for groups A, B, C, and D, respectively</p>		
Morton et al. (2006)	Same study as Morton et al. (2005)	Same study as Morton et al. (2005)	Same study as Morton et al. (2005)	<p>Relapse rate</p> <p>Disease-free survival</p> <p>Melanoma-specific mortality and survival</p>	<p>Frequency of relapse at any site: 26.8% in the observation group and 20.7% in the biopsy group</p> <p>Disease-free survival rate at 5 years: in the biopsy group 78.3%; in the observation group 73.1%</p> <p>Melanoma-specific death: 13.8% in the observation group and 12.5% in the biopsy group</p>	Here, an intention-to-treat analysis was performed (missing in Morton et al., 2005)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>Melanoma-specific survival rate: 90.1% and 93.2%, respectively, at 3 years, and 86.6% and 87.1%, respectively, at 5 years</p> <p>Melanoma-specific mortality rate in the biopsy group: 9.7% when sentinel tumor-free and 26.2% if sentinel positive</p> <p>Estimated disease-free survival rate at 5 years: 53.4% for positive and 83.2% for negative sentinel; corresponding values for melanoma-specific survival 72.3% and 90.2%, respectively</p>		
McMasters et al. (2001)	To identify prognostic factors	Prognostic study	Total of 1058 patients evaluated;	Positive sentinel node	SLN identification rate 99.7%	Prospective design	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	that are predictive of sentinel lymph node (SLN) metastasis in melanoma.		961 patients had complete data and were included in the statistical analysis		SLN positivity 22% Independent predictors of SLN metastasis, in order of importance: Breslow thickness, Clark level, ulceration, and patient age	Subgroup analysis of Melanoma Sunbelt Trial (multi-center, randomized trial); therefore patients partially identical with patients in Mays et al. (2010)	
Rondelli et al. (2011)	to assess the prognostic role of SLN in thick melanoma in terms of disease-free survival (DFS) and overall survival (OS).	Systematic review with meta-analysis	9 studies included with a total of 1261 patients	DFS OS IRR incidence rate ratios (IRD) incidence rate difference (IRD)	Overall, DFS: 71% in patients with a negative SLN, 39% in patients with a positive SLN after a median follow-up of 33 months (IRR 1.83, 95% CI = 1.56-2.14). OS: 71% in patients with a negative SLN, 49% in patients with a positive SLN (IRR 1.44, 95% CI = 1.25-1.65).	Only retrospective studies included in meta-analysis	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Smith et al. (2012)	to compare melanoma-specific survival among patients with head and neck desmoplastic melanoma based on SLN status	Prognostic study	244 patients with desmoplastic melanoma of the head and neck who underwent SLNB	5-year disease-specific survival (DSS)	On univariable and multivariable analysis, SLN positivity did not significantly affect DSS in head and neck desmoplastic melanoma (P = .19 and P = .48, respectively).		2b
Burton et al. (2011)	to determine whether regression predicts nodal metastasis, disease-free survival (DFS), or overall survival (OS).	Prognostic study	2220 patients who underwent SLN biopsy; those with tumor-positive SLN underwent completion lymphadenectomy (261 with regression; 1959 without regression)	DFS OS Prognostic factors	On multivariate analysis, factors independently predictive of DFS included Breslow thickness, ulceration, and SLN status (P < 0.05 in all cases); the same factors along with age, gender, and anatomic tumor location were significantly associated with OS (P < 0.05 in all cases). Regression was not significantly	Post hoc analysis of a multicenter prospective randomized trial	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					associated with DFS (risk ratio [RR], 0.94; 95% confidence interval [CI], 0.67-1.27; P = 0.68) or OS (RR, 1.01; 95% CI, 0.76-1.32; P = 0.93).		
De Vries et al. (2011)	To assess the long-term outcome after sentinel lymph node biopsy (SLNB) in melanoma patients.	Prognostic study	450 melanoma patients who underwent SLNB (Survival and prognostic factors were analyzed for 429 patients)	Relapse rate FN-rate Prognostic factors	In 29% relapse during follow-up; 46% in the SLN-positive group who underwent CLND and 22% in the SLN-negative group (p < 0.001). FN- rate 11%. On multivariate analysis strongest prognostic factors for DFS: primary melanoma ulceration and SLN positivity (HR: 2.2 and 2.3; p < 0.001). For DSS the same was found, HR of 2.1 for	CLND was performed in 119 patients and these patients were analyzed for recurrence and survival.	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>ulceration and 2.0 for SLN positivity (p=0.001 and p=0.002 respectively).</p> <p>10-Year DFS was 71% for SN-negative patients compared with 48% for SLN-positive patients (p < 0.001). 10-Year DSS was 77% for node-negative patients compared to 60% for SLN-positive patients (p < 0.001).</p>		
Murali et al (2011)	To investigate in detail the influence of SN tumor characteristics and clinical and primary tumor parameters on regional lymph node recurrence, distant metastasis, and survival.	Prognostic study	409 patients with primary cutaneous melanoma who underwent SNB	DFS melanoma-specific survival (MSS)	Primary tumor features (presence of ulceration and satellites) and presence of ENS in SNs were independent predictors of DFS, DMFS, and MSS. In addition, poorer DFS was	Same patient cohort as Murali et al. (2010): Non-Sentinel Node Risk Score (N-SNORE): A Scoring System for Accurately Stratifying Risk of Non-Sentinel Node Positivity in Patients With	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					independently associated with primary tumor site (head/neck and limbs vs. trunk), SN tumor features (MaxSize >2 mm, presence of PLI) and positive NSN in CLND; other factors independently predictive of DMFS were male sex, primary tumor features (absence of TILs), and SN tumor MaxSize >10 mm; and age ≥50 years was an additional independent predictor of MSS. CLND status was not an independent predictor of DMFS or MSS.	Cutaneous Melanoma With Positive Sentinel Lymph Nodes	
Göppner et al.	To investigate the	Prognostic study	87 patients	Recurrence-Free	Multivariate		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(2011)	prognostic relevance of SLNB and other risk factors in the subgroup of melanomas > 4.0 mm and to compared it to previously published results.		with thick melanomas \geq 4.0 mm (T4).	Survival Overall survival	analysis: SLN and ulceration, analyzed as separate risk factors as well as their combination, predicted a highly reduced life expectancy in terms of recurrence-free survival (RFS). SLN, but not ulceration, also predicted overall survival (OS)		
Koskivuo et al. (2011)	to evaluate the accuracy and prognostic value of the routine use of SNB in elderly patients with cutaneous melanoma.	Prognostic study	423 consecutive patients \geq 70 years with CM AJCC stage I-II	FN-rate Sensitivity Diagnostic accuracy Relapse-free survival rate Cancer specific survival rate Prognostic factors	Recurrence in 18.9% of patients (median follow-up: 2.5 years) FN-rate: 8.3% Sensitivity: 91.7% overall diagnostic accuracy: 98.0 % at 5 years: relapse-free survival rate: 80.0% in SN-negative patients		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>and 39% in SN-positive patients</p> <p>cancer-specific survival rates: 88.6% and 46% respectively ($P < 0.001$).</p> <p>multivariable analysis: SN metastasis ($P < 0.001$), a Breslow thickness of ≥ 2.0 mm ($P = 0.007$) and presence of ulceration ($P = 0.012$) were independent prognostic factors for cancer-specific survival.</p>		
Tejera-Vaquerizo et al. (2012)	To determine whether growth rate (GR) of cutaneous melanoma predicts the histological sentinel lymph node (SLN)	Prognostic study	698 patients with invasive primary cutaneous melanoma in whom the SLN was identified	Growth rate Prognostic factors	Multivariate logistic regression analysis: GR, Breslow thickness, and the presence of microscopic satellitosis	surrogate measure for GR in primary invasive melanoma was calculated as the ratio of Breslow thickness to time to melanoma	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	positivity				<p>independently associated with SLN positivity.</p> <p>probability of SLN positivity: 8.2% for slow growth melanomas (<0.10 mm/mo) compared with 19.8% for intermediate-growth melanomas (0.10-0.50 mm/mo) and 37.7% for fast-growth melanomas (>0.50 mm/mo).</p> <p>SLN positivity was the most important prognostic factor for DFS (HR, 2.13; 95% CI, 1.20-3.76) and for OS (HR, 3.99; 95% CI, 1.67-9.53).</p>	development.	
White et al. 2011	Prognostic study	undergoing sentinel lymph node (SLN) biopsy	3463 patients (561 (16.3%) had a positive SLN	Predictive factors	multivariate analysis: increasing Breslow	retrospective and prospective data	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		for primary melanoma	biopsy)		thickness, lymphovascular invasion, ulceration, younger age, the absence of regression, and tumor location on the trunk were statistically significant predictors of a positive SLN	multivariate analysis performed with data of 1526 patients (with complete records)	
Yonick et al. (2011)	To elucidate pathologic factors that are predictive of SLN positivity	Prognostic study	1199 patients	Correlation between histopathological features and SLN positivity	Thin melanomas in 39%; of these, 31% underwent SLNB Positive SLNs found in 11% Multiple logistic regression: ulceration and thickness associated with SLN positivity For scoring system, see full article	Retrospective study No defined inclusion criteria for SNB	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Cadili and Dabbs (2010)	To identify the predictors of SLN melanoma metastasis.	Prognostic study	348 patients with malignant melanoma	Relative risk	73% negative and 27% positive SLN Breslow thickness and nodular type significantly correlated with positive SLN; head and neck tumour location significantly correlated with negative SLN	Retrospective design Correlation of head and neck tumour and negative SLN result may be caused by insufficient experience in head and neck SLNEs in this institution.	2b
Kretschmer et al. (2010)	To investigate the impact of the constitutional factor age on the clinical courses of melanoma patients with sentinel lymph node (SLN) biopsy.	Prognostic study	2,268 consecutive patients	Correlation between histological parameters/SNB status and age Melanoma-specific overall survival Adjusted relative risk	According to multivariate analysis, factors predictive for poor overall survival: age, micrometastasis to SLN, Breslow thickness and epidermal ulceration In multivariate logistic regression analysis, age of < 40 years was significantly	Retrospective design Large patient sample	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					related to a 2-fold probability of SLN-positivity		
Roach et al. (2010)	To investigate the significance of mitotic rate (MR) in melanoma	Prognostic study	551 patients had MR data reported	Overall survival Disease-free survival Odds' ratio (OR) for SLN positivity	High MR: thicker tumors, higher rate of ulceration, twice as many positive SLNs (31.3% vs. 14.7%) Tumor thickness and ulceration significant survival predictors upon multivariate analysis For SLN-negative and nonulcerated patients, MR groups were not significant for OS	Retrospective design	2b
Mandala et al. (2009)	To investigate if the tumour infiltrating lymphocytes (TILs) are able to predict the sentinel lymph node (SLN)	Prognostic study	1251 consecutive patients with CM	Overall survival Disease-free survival Correlation between TIL status	TIL status of lesion correlated with the Breslow thickness, Clark level and regression No difference in	Retrospective analysis (though of prospective database)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	positivity, the disease-free survival (DFS) and overall survival (OS) in clinical stages I-II AJCC primary cutaneous melanoma (PCM).			and SLN status	<p>other variables evaluated, including SLN status or the presence of ulceration, among patients with brisk, non-brisk and absent TILs</p> <p>SLN identified in 394 patients (97.5%)</p> <p>18.8% positive SLNs</p> <p>In multivariate analysis, increasing Breslow thickness, anatomical site and absence of TILs independently associated with positive SLN</p> <p>5-year DFS 75.9% in negative SLNs, 35.2% in positive SLNs</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					5-year OS 88.7% versus 42.9%, respectively		
Socrier et al. (2009)	To determine if regression in melanoma is associated with an increased risk of sentinel lymph node (SLN) metastasis.	Prognostic study	397 consecutive melanoma patients	Odds' ratio (OR)	SLN positive in 16% of melanomas with regression and 29% without regression Adjusted OR for regressive melanoma: 0.9	Retro- or prospective design unclear	2b
Gutzmer et al. (2008)	To investigate the value of the status of the sentinel lymph node (SLN) in patients with thick melanomas (Breslow thickness ≥ 4 mm)	Prognostic study	152 patients	Recurrence-free survival Overall survival Correlation between histological properties of primary tumour and SLN positivity Relative risk (RR) for SLN positivity	Probability of recurrence-free 5-year-survival: 42.5 \pm 5% overall, 26.3 \pm 6.6 % for SLN+ and 58.7 \pm 7.1 % for SLN- In multivariate analysis the pathological status of the SLN had a highly significant prognostic value (p = 0.000009); relative risk (RR)	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					3.3 The 5-year overall survival 53.2 ± 5.4 % (37.5 ± 8.1 % with positive SLN and 67.6 ± 6.7 % with negative SLN)		
Roulin et al. (2008)	To confirm the accuracy of sentinel node biopsy (SNB) and its morbidity, and to investigate predictive factors for SN status, disease-free survival (DFS) and disease-specific survival (DSS).	Prospective prognostic study	327 consecutive patients with primary melanoma	Recurrence rate Sensitivity and false-negative rate of SNB 5-year disease-free survival (DFS) 5-year disease-specific survival (DSS)	Success rate of SNB 99.1% Overall SNB + WE morbidity 7.6% SNB positivity rate 22.6% Mean Breslow thickness of primary melanoma 1.95 mm for SN-negative cases and 3.22 mm for SN-positive cases Breslow thickness only statistically significant predictor for metastases	Follow-up presumably too short to discover all recurrences (median follow-up 33 months; median time of recurrence 30 months, mean 34 months) No control group	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>46% of positive and 11% of negative SN patients recurred</p> <p>False-negative rate 8.6%, sensitivity 91.4%.</p> <p>5-year DFS 43% for patients with positive SN and 83.5% for patients with negative SN</p> <p>5-year DSS 49.1% for SN-positive patients and 87.4% for SN-negative patients</p>		
Cecchi et al. (2007)	To report the experience with lymphatic mapping (LM) and sentinel lymph node biopsy (SLNB) in a selected group of patients with thin primary cutaneous	Prospective cohort study	50 patients with thin melanomas	Prevalence of SLN-positivity in thin melanomas	SLN positivity rate 4%	CLND only performed on SLN-positive patients (risk of verification bias)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanomas.						
Kaur et al. (2008)	To understand the significance of regression in melanoma and provide further information on whether patients should be subjected to sentinel lymph node biopsy (SLNB) on the basis of regression.	Prognostic study	146 consecutive melanoma patients	Correlation between histopathologic parameters and SLN positivity	<p>Statistically significant greater proportion of individuals without regression showed sentinel lymph node (SLN) positivity (p=0.028) compared with patients without regression</p> <p>Correlation of age, sex, site and presence of tumour infiltrating lymphocytes (TIL) with regression and sentinel node status not statistically significant</p>	Retrospective design, but 1 - 6 years prospective follow-up in 79% of the patients (recording survival and metastasis)	2b
Morris et al. (2008)	To assess whether the presence of RG was associated with a higher probability of a	Prognostic study	1349 patients with cutaneous melanoma	Correlation between regression and SLN positivity	10% of patients with RG and 18% of patients with NRG who underwent SLN	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	positive SLN or an increased risk of local or distant recurrence.			Overall survival Disease-free survival	biopsy had a positive SLN When stratified by Breslow depth category, there was no evidence of an increased risk of a positive SLN in those with RG OS not significantly different between the two groups DFS significantly longer for those with RG		
Paek et al. (2007)	To verify previous results in which increasing mitotic rate and decreasing age predicted sentinel lymph node (SLN) metastases in patients with melanoma, and to create a prediction	Prognostic/ diagnostic study	910 patients with cutaneous melanoma	Correlation between histological features and SLN positivity OR for SLN positivity	≥1 positive SLNs identified in 26.7% of patients The best multivariate model included the following single variables: patient age, Breslow depth, the	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	model for the better selection of which patients with melanoma should undergo SLN biopsy.				presence of angiolymphatic invasion, the number of mitoses, and body site location of the melanoma		
Taylor et al. (2007)	To evaluate the prognostic implications of tumor-infiltrating lymphocytes (TILs)	Prognostic study	887 patients who underwent SLN mapping for cutaneous melanoma	Correlation of histopathologic features with SLN positivity Overall survival Disease-free survival	SLN identification rate 98.6% SLN positivity rate 17.6% By multivariate logistic regression analysis, male sex, thickness, presence of ulceration, and absence of TILs were independently associated with positive SLN When brisk and nonbrisk TILs were analyzed separately, both levels were		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>significant predictors of a negative SLN compared with absent TILs, by univariate and multivariate analysis</p> <p>Histologic status of SLN was the most significant predictor of DFS and OS</p> <p>Negative SLN: 5-year DFS 80.0%</p> <p>Positive SLN: 5-year DFS 32.8%</p> <p>When stratified by SLN status, no survival advantage present with TILs</p>		
Morton et al. (2005)	The objective of this study was to evaluate, in an international multicenter phase	Randomized controlled clinical multi-center trial	2001 patients with invasive primary cutaneous melanoma	Accuracy of sentinel node identification Dissected-basin	Overall rate of SN identification: 95.3% 6.3% of patients	Method of randomization described in Morton et al. (2006)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	III trial, the accuracy, use, and morbidity of intraoperative lymphatic mapping and sentinel node biopsy (LM/SNB) for staging the regional nodal basin of patients with early-stage melanoma.			recurrence in patients with negative sentinel node Surgical morbidity	with tumor-negative SNs developed regional nodal recurrence at a median followup of 54 months Incidence of at least one local wound complication: 13.9% in the WEO arm and 13.8% in the LM/SNB arm Surgical morbidity: 37.2% for LM/SNB with immediate CLND vs 10.1% for LM/SNB without CLND	No intention to treat analysis (ITT); instead an as-treated analysis was performed	
Roka et al. (2005)	To investigate the accuracy of SLNB and the clinical outcome of patients.	Prognostic study	309 patients with malignant melanoma	Disease-free survival Overall survival	SNB success rate: 96.8% SLN positivity rate: 23% False-negative SLNB rate: 9.2%	Prospective design Relatively short mean follow-up time	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>Among patients with one or more metastatic SLN, 21% had further metastases in non-SLNs in the dissected basin</p> <p>Micrometastasis in SLN in 68%, macrometastasis in 32%</p> <p>3-year DFSI for negative and positive SLN patients: 82 and 55%, respectively</p> <p>3-year overall survival for negative and positive SLN: patients 93% and 83%, respectively</p> <p>By multivariate analysis, Breslow thickness the only statistically</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					significant prognostic factor with respect to overall survival		
Cuéllar et al. (2004)	To describe independent prognostic factors other than tumour thickness useful in SLN candidate selection.	Prognostic study	94 MM patients	Correlation between potential prognostic factors and SLN positivity	<p>SLN positivity rate 20.2%</p> <p>No positive SLN in MM ≤ 1.0 mm and in patients with regression $> 50\%$</p> <p>Small cell and ulceration were significant prognostic factors in multivariate analysis</p> <p>SLN positivity rate for small cell: 56.9%</p> <p>SLN positivity rate for ulceration: 35.5%</p> <p>SLN positivity rate for small cell and ulceration: 86.3%</p>	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Macripo et al. (2004)	To analyse the parameters associated with a higher risk of occult nodal metastases, to evaluate the clinical outcome of melanoma patients who underwent SLN procedure, and to identify by means of multivariate analysis the prognostic parameters with independent predictive value on disease-free survival (DFS) in node-positive and negative patients.	Prognostic study	274 melanoma patients with melanoma \geq 1 mm or ulceration, regression or Clark level IV/V	Status of SLN (negative, micrometastasis or macrometastasis) Disease-free survival	SLN positivity rate 16.8% Subsequent radical node dissection revealed further melanoma metastases in 33% of patients with macrometastases and 10% of patients with micrometastases Relapse rate of SLN-positive patients: 54.3% Relapse rate of SLN-negative patients: 10.9% 5-year DFS and OS 42% for SLN+ and 69% for SLN- SLN status (micrometastases/macrometastases) and thickness were independent	Prospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>prognostic factors in the SLN-positive group</p> <p>Low-risk group: micrometastases and Breslow thickness ≤ 2 mm; 2-year DFS 100%</p> <p>Intermediate-risk group: macrometastases or Breslow thickness >2 mm; 2-year DFS 71%</p> <p>High-risk group: macrometastases and Breslow thickness >2 mm; 2-year DFS 28%</p>		
Stitzenberg et al. (2004)	To investigate if lymphatic mapping and sentinel lymphadenectomy (LM/SL) with a focused examination of the sentinel node (SN)	Prognostic study	146 patients with a melanoma tumor thickness of ≤ 1.0 mm	Correlation of histopathological factors and SLN positivity	<p>SLN positivity rate 4%</p> <p>On multivariate analysis, none of the clinical or histopathologic factors examined</p>	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	will detect a significant number of SN metastases in patients with thin melanoma and which clinical or histopathologic factors may serve as predictors of SN tumor involvement.				<p>significantly associated with SN tumor involvement in patients with thin melanoma</p> <p>None of the patients had non-SN tumor involvement</p>		
Mraz-Gernhard et al. (1998)	To develop a prognostic model, based on clinical and pathological data, to estimate the probability of micrometastasis in the sentinel lymph node in patients with malignant melanoma.	Prognostic study	215 patients with AJCC stages I and II cutaneous malignant melanoma	Incidence of SLN positivity depending on histological features	<p>SLN positivity rate 21.4%</p> <p>Only tumor thickness significantly correlated with SLN positivity</p> <p>Incidence of positive SLN according to number of high risk features (HRFs): 14% with no HRF 31% with 1 HRF 47% with 2 HRFs 75% with 3 or</p>	<p>Retrospective design</p> <p>Similar rate of SLN positivity in melanomas between 1.0 and 2.9 and > 5 mm may be due to selection bias (exclusion of patients with evidence of regional lymph node metastasis) => may also be true for other studies</p>	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					more HRFs		
Satzger et al. (2011)	To analyze the possible effect of SLND on the prognosis of melanoma patients.	Prognostic study	673 consecutive melanoma patients	Overall survival Recurrence-free survival	Pre-SLN group: 25.7% melanoma related deaths SLN group: 17.6% 5-year melanoma-specific survival rates: 80.3% in pre-SLN patients, 84.8% in SLN patients 5-year survival rates: 72.8% in SLN positive patients, 89.9% in SLN negative patients 89.9% Relapse rate 39.0% in pre-SLN patients, 23.6% in SLN patients	Retrospective design Historical control group	2b-
Ellis et al. (2010)	To clarify indications, predictive factors, and outcomes of	Prognostic and diagnostic study	397 patients with melanomas	Correlation between histological properties and SLN	Breslow thickness > 2 mm, upper extremity primaries, and	Retrospective design Difficult definition	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	sentinel node biopsy.			positivity Sensitivity and specificity, NPV and PPV	ulceration were predictive for SLN+ status SLN positivity rate 12%; for lesions > 1 mm 16% False-negative rate 4.0% Sensitivity of SLNB 75.4%, with a negative predictive value of 95.4% and accuracy of 96.0%; specificity and positive predictive value 100%	of "false-positives" (here declared as 0, but not defined)	
Kretschmer et al. (2008)	To determine surgical morbidity in melanoma patients with sentinel lymphnodectomy and complete regional lymph node dissection	Cohort study	315 melanoma patients	Complication rate	Mortality 0% Morbidity rate related to general anaesthesia 0% Complication rates: 65.5% after CLND, 13.8% after SLNE	Most data prospectively recorded (325 vs. 40 nodal basins) Surgical morbidity not recorded for all patients who underwent SLNE or CLND (possible source of bias)	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					19.5% in inguinal dissection, 9.2% in axillary dissection		
de Rosa et al. (2011)	to examine the test performance of sentinel node biopsy in head and neck melanoma, including the identification rate and false-negative rate	Systematic review without meta-analysis (32 studies eligible for analysis)	3442 patients	predictive value positive (PPV) and negative (PVN) for nodal recurrence posttest probability FN-negative rate	Positive sentinel node biopsy: in 15% of patients. Subsequent completion neck dissection revealed additional positive nodes in 13.67%. predictive value positive for nodal recurrence: 13.1%, posttest probability negative: 5%. Median FN-negative rate for nodal recurrence was 20.4%.	Distinct portions of the included studies were used to determine PVP, PTPN... 32 studies clinically heterogeneous	3a
Doeden et al. (2009)	We directly compared the relative	Prognostic study	94 patients with primary cutaneous melanoma, 57 of	Overall survival Disease-free	SLN positivity rate 75% in LI-positive patients, 39% in LI-	Small sample size (57 with known SLN status)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	contribution of lymphatic and hematogenous pathways in a cohort of patients with primary cutaneous melanoma with 3 years of clinical follow up.		which had a known SLN status	survival Correlation between lymphatic invasion (LI) resp. vascular invasion (VI) and SLN positivity	negative patients Presence of LI was independent of tumor thickness and not associated with distant metastasis Kaplan-Meier analyses did not detect a significant difference in the overall or disease-free survival in LI-positive or LI-negative patients By multivariate analysis, LI was not a significant risk factor for SLN metastasis	Retrospective design	
Leiter et al. (2010)	To investigate the potential survival benefit of sentinel lymph node dissection (SLND).	Prognostic study	879 patients with primary cutaneous melanoma	Incidence of metastasis Overall survival Recurrence-free survival	Rate of regional lymph node metastasis: 16.5% in non-SLND collective, 7.3% in SLND collective; no difference in	Retrospective design Historical control group without consistent reporting of	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					satellite/in-transit metastases and distant metastases Disease-free survival improved in the SLND collective	ulceration	
Massi et al. (2006)	To evaluate whether tumour lymphangiogenesis and the expression of vascular endothelial growth factor C (VEGF-C) is related to the risk of SLN metastasis and to clinical outcome in a case-control series of patients with melanoma.	Case-control study	15 patients affected by primary cutaneous melanoma with metastasis to SLN were matched with a group of 30 patients without SLN metastasis.	Correlation between LV and SLN positivity Overall survival	Number and area of peritumorous and intratumorous lymphatics was significantly higher in melanomas associated with SLN metastasis than in non-metastatic melanomas No significant difference in VEGF-C expression by neoplastic cells between metastatic and non-metastatic melanomas In multivariate	Retrospective design Small patient sample	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					analysis, peritumorous LV density was an independent variable affecting overall survival		
Dadras et al. (2005)	To investigate whether the extent of tumor lymphangiogenesis can predict melanoma metastasis to sentinel lymph nodes.	Prognostic study	45 consecutive patients with nonmetastatic (n = 27) or metastatic (n = 18) primary cutaneous melanoma to the SLN.	Odds' ratio	<p>Mean tumor thickness in SLN-positive patients $3.01 \pm 0.52\text{mm}$, in SLN-negative patients $1.70 \pm 0.31\text{mm}$</p> <p>Additional prognostic parameters such as tumor ulceration, mitotic activity, regression and number of tumor infiltrating lymphocytes did not differ between groups</p> <p>Frequency of intratumoral lymphatics in SLN-positive patients</p>	<p>Small patient sample</p> <p>Retrospective design</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					83.3 ± 0.09%, in SLN-negative patients 59.3 ± 0.09%		
Roaten et al. (2005)	To investigate the assumption that SLNB has fewer complications than elective regional lymph node dissection (RLND).	Cohort study	339 consecutive patients undergoing SLNB for melanoma	Complication rates	SLN positivity rate 19.6% Complication rate 5.9% for SNB, 19.5% for RLND	Retrospective design No clear inclusion criteria and different characteristics (thicker tumors, more men, longer follow-up) in control group who received RLND Role of closed suction to be investigated further	3b
Leong et al. (2003)	To examine the role of sentinel lymph node biopsy (SLNB) in patients with a previous wide local excision (WLE).	Prospective case-control study	168 patients with clinically nodenegative truncal or extremity melanoma and Breslow thickness of ≥ 1 mm.	Number of positive SLNB False-negatives Disease-free survival	SLN positivity rate 32.3% both for cases and controls No significant difference in relapse-free survival: 72.3% for	Follow-up time span too short for reliable assessment of survival	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			A total of 103 of the 168 patients were referred after their WLE.	Overall survival	cases, 81.7% for controls at 2 years; No significant difference in overall survival: 94.7% incases, 96.8% in controls at 2 years		
McCready et al. (2001)	To document experience with sentinel lymph-node biopsy in patients who have already undergone a wide local excision for melanoma because in many centres previous wide excision has been a contraindication for sentinel lymph node biopsy.	Prospective cohort study	100 patients with cutaneous melanoma	Accuracy of biopsy False-negative rates	SLN positivity rate 31% At completion lymphadenectomy, 29% rate of other positive nodes in the dissected basin	Only a historical control group available Small patient numbers, especially in the false-negative group	3b
Nguyen et al. (2001)	To determine whether primary melanoma histopathologic features could be	Prognostic study	112 consecutive melanoma patients	Correlation between histological features and SLN positivity	SLN positivity rate 20% False-negative rate 2.4%	Retrospective design No explicit information about	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	applied to predict sentinel node status.				<p>In multivariate analysis, the most significant cutoff for prediction of node positivity was a thickness of 1.5 mm</p> <p>Additional histologic features significantly predictive of occult micrometastases: ulceration and lymphovascular invasion</p>	inclusion criteria for SLNE	
Pasquali et al. (2011)	To test the discrimination, the calibration and the NPV of MSKCC nomogram in 543 patients	Diagnostic study	543 patients		<p>positive SN in 147 patients (27%).</p> <p>Mean predicted probability: 17.8% (95%CI: 16.8-18.8%). Nomogram discrimination was significant (area under the curve = 0.68; P < 0.0001) (R(2) = 0.99).</p>		3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>Cut-off values between 4% and 9% led to a NPV, SNB reduction and overall error rates ranging between 100 and 91.2%, 2.2 and 27.2%, and 0 and 2.3%, respectively.</p> <p>incidence of SN metastasis was higher than that observed in the MSKCC series (27% vs 16%).</p>		

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3.2. Frage II.5. und III.4. Tumorlast am Sentinel-Node und komplettierende Lymphadenektomie – De-novo-Recherche

Frage II.5. Hat die Tumorlast am Sentinel-Node eine prognostische Bedeutung?

Frage III.4. Ist eine komplettierende LAD bei Mikrometastasen am SLN indiziert?

3.2.1. Datenbanken, Suchstrategien, Trefferzahlen

3.2.1.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
Medline	melanoma[title] AND (("sentinel"[tiab] OR "sentinel lymph node"[tiab] OR sln[tiab] OR slne[tiab]) AND (("tumor load"[tiab] OR "tumor burden"[tiab]) OR (prognosis[tiab] OR survival[tiab]))) OR starz OR dewar OR rotterdam OR s-classification)	26.01.2012	747
Cochrane Library	(melanoma and (sentinel or "sentinel lymph node" or sln or slne) and ("tumor load" or "tumor burden" or prognosis or survival or starz or dewar or rotterdam or "s classification")).ti,ab.	19.01.2012	27
Embase	(melanoma and (sentinel or "sentinel lymph node" or sln or slne) and ("tumor load" or "tumor burden" or prognosis or survival or starz or dewar or rotterdam or "s classification")).ti,ab.	23.01.2012	872

Bemerkungen: Eine erste Literaturrecherche in Medline und und Cochrane erfolgte am 01.02.2011 bzw. für Embase am 11.05.2011. Die Update-Recherche wurde am 23.01.2012 (Embase) bzw. am 26.01.2012 (Medline) und am 19.01.2012 (Cochrane) durchgeführt. In der Tabelle angegeben sind die Trefferzahlen der letzten Recherche.

Da die Literaturlbasis für die Fragen II.5 und III.4 die gleiche ist (bei gleicher Suchstrategie), diente die Tabelle sowohl der AG chirurgische Therapie als auch der AG Sentinel als Grundlage zur Beantwortung der Fragen III.4 bzw. II.5.

3.2.1.2. Aktualisierungsrecherche 2015

Datenbank	Suchstrategie	Datum	Treffer
Medline	"melanoma"[tiab] AND ("sentinel"[tiab] OR "Sentinel Lymph Node Biopsy"[MeSH]) AND ("survival"[tiab] OR "mortality"[tiab] OR "relapse"[tiab] OR "recurrence"[tiab] OR "sensitivity"[tiab] OR "specificity"[tiab] OR "accuracy" OR "outcome"[tiab] OR "prognos*"[tiab] OR "predict*"[tiab] OR "assoc*"[tiab]) AND ("2011.01.11"[Date - Publication] : "2015.09.16"[Date - Publication])	16.09.2015	499
Cochrane Library		16.09.2015	51

Bemerkungen: Die bisherige Empfehlung aus der S3-Leitlinie Melanom zu der Schlüsselfrage „Hat die Tumorlast am Sentinel-Node eine prognostische Bedeutung?“ (AG Sentinel) basiert auf Studien mit einem Evidenzlevel von 2b. Da es nur wenige Studien gibt mit einem höheren Evidenzlevel, wurden auch diesmal Studien in die Evidenztabelle aufgenommen, die ein Evidenzlevel bis schlechtestens 2b haben.

Da die Literaturlbasis für die Fragen II.5 und III.4 die gleiche ist (bei gleicher Suchstrategie), diente die Tabelle sowohl der AG chirurgische Therapie als auch der AG Sentinel als Grundlage zur Beantwortung der Fragen III.4 bzw. II.5.

Die Suche in Cochrane erbrachte ein relevantes Review, was wiederum nur eine Studie inkludierte.

3.2.2. Auswahlkriterien

3.2.2.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer (inkl. Dupletten)	1646
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt

Ausschlusskriterien	Case Reports, narrative Reviews
Anzahl nach Abstractscreening	79
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	25

3.2.2.2. Aktualisierungsrecherche 2015

Auswahl der Literatur	
Gesamttreffer (inkl. Dubletten)	550
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews
Anzahl nach Abstractscreening	408
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	11

3.2.3. Evidenztabelle#

3.2.3.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Mocellin et al. (2007)	To investigate the prognostic value of PCR status of SLN.	Systematic review and meta-analysis	4019 patients who underwent SLN biopsy for clinical stage I to II	Recurrence rate Overall survival	Pooled positivity rate: 20.3% pathology-based	Funnel plot did not show publication bias	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			cutaneous melanoma	Sensitivity, specificity, positive and negative predictive value (PPV, NPV)	<p>In patients with pathology-negative SLN: PCR positive in 42.3%</p> <p>In patients with pathology-positive SLN: PCR negative (false negative) in 49%</p> <p>PCR positivity in patients with pathology-positive SLN: 95.1%</p> <p>In patients with pathology-negative SLN: 46.6%</p> <p>Disease recurrence rate: 16.8% among PCR-positive patients; 8.7% in PCR negative patients</p> <p>PCR sensitivity 57.4%, specificity 61.1%, accuracy 60.6%, PPV 16.8%, NPV 91.3%</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Elsaesser et al. (2012)	investigated survival probabilities and prognostic factors in sentinel lymph node biopsy (SLNB) staged patients with cutaneous melanoma (CM) with the aim of defining subgroups of patients who are at higher risk for recurrences and who should be considered for adjuvant clinical trials.	Cohort study	1909 SLNB staged patients with primary CM	5-year-OS Prognostic factors	5-year OS in SLNB negative patients: 90.3% (IB 96.2%, IIA 87.0%, IIB 78.1%, IIC 72.6%). 5-year OS in patients with micrometastases (stage IIIA/B): 70.9% which was clearly less favorable than for stages I-II. Multivariate analysis revealed tumor thickness, ulceration, body site, histopathologic subtype and SLNB status as independent significant prognostic factors.		2b
Quaglino et al. (2011)	to evaluate which prognostic variables could predict NSLN invasion in SLN-	Cohort study	603 patients who had undergone SLNB for melanoma	OS prognostic variables on CLND results and disease	Breslow thickness, ulceration and micro/macrometastatic pattern of SLN invasion carried a	Retrospective chart review	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	positive patients and their impact on the overall survival (OS).			course.	significantly independent higher likelihood of NSLN involvement; Starz classification did not maintain a statistical significance in multivariate analysis. NSLN involvement, was found in 33.3% of patients with one and 55.9% with \geq adverse parameters ($p = 0.0001$).		
Van der Ploeg et al. (2011)	To determine the role of tumor load and tumor site in the SN as prognostic factors for survival and as predictive factors for NSN positivity.	Cohort study	1080 patients with positive SLN	NSN status Overall survival	Significant factors regarding NSN status: age, study center, histology and location of the primary, Clark level, Breslow thickness, Rotterdam criteria, Rotterdam criteria	Retrospective design Large patient cohort For detailed survival rates see original article	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					II, III, and IV, Dewar criteria, Dewar criteria II, and RDC criteria Rate of additional positive lymph nodes in the group of patients with submicrometastases (≤ 0.1 mm, Rotterdam criteria): 9% Patients with 0.1 to 1.0 mm: 16%		
Murali et al (2011)	To investigate in detail the influence of SN tumor characteristics and clinical and primary tumor parameters on regional lymph node recurrence, distant metastasis, and survival.	Cohort study	409 patients with primary cutaneous melanoma who underwent SNB	DFS melanoma-specific survival (MSS)	Primary tumor features (presence of ulceration and satellites) and presence of ENS in SNs were independent predictors of DFS, DMFS, and MSS. In addition, poorer DFS was independently associated with primary tumor site (head/neck and	Same patient cohort as Murali et al. (2010): Non-Sentinel Node Risk Score (N-SNORE): A Scoring System for Accurately Stratifying Risk of Non-Sentinel Node Positivity in Patients With Cutaneous Melanoma With Positive Sentinel Lymph Nodes	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					limbs vs. trunk), SN tumor features (MaxSize >2 mm, presence of PLI) and positive NSN in CLND; other factors independently predictive of DMFS were male sex, primary tumor features (absence of TILs), and SN tumor MaxSize >10 mm; and age ≥50 years was an additional independent predictor of MSS. CLND status was not an independent predictor of DMFS or MSS.		
Balch et al. (2010)	To determine the survival rates and independent predictors of survival using a	Cohort study	2313 patients with stage III disease	Overall survival	5-year survival for patients with micrometastases: 67%	Patient cohort partially identical with Balch et al. 2004 and 2009	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	contemporary international cohort of patients with stage III melanoma.				<p>When stratified by tumor thickness, ulceration, and number of involved nodes, 5-year-survival rates were: 87% for a single nodal micrometastasis arising from a nonulcerated primary melanoma ≤ 2.0 mm in thickness, 23% for patients with four or more nodal macrometastases from an ulcerated primary melanoma greater than 6.0 mm in thickness</p> <p>For patients with nodal micrometastases independent predictors of survival were patient age, sex, tumor thickness, ulceration, primary</p>	For survival curves see original article	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>anatomic site, and number of tumor-bearing lymph nodes</p> <p>For patients with nodal macrometastases, age, ulceration, anatomic site, and number of tumor-bearing lymph nodes independently predicted survival</p>		
Meier et al. (2010)	To compare the RFS and OS of 697 melanoma patients as predicted by various classification systems.	Cohort study	697 consecutive patients with primary cutaneous melanoma (Breslow tumor thickness ≥ 1 mm)	<p>Recurrence-free survival</p> <p>Overall survival</p>	<p>CLND positivity rate 15.4%</p> <p>21% recurrence rate</p> <p>14% mortality rate (causes related to melanoma)</p> <p>In multivariate analysis, independent predictors for RFS were greatest</p>	Suggestion of new classification system Hannover II	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					dimension of the largest tumor cell deposit (cutoff point, <0.1 mm vs ≥ 0.1 mm), TPD (cutoff point, ≤ 2 mm vs >2 mm), and capsular involvement; TPD and capsular involvement also for OS		
Balch et al. (2009)	To revise the staging system for cutaneous melanoma on the basis of data from an expanded American Joint Committee on Cancer (AJCC) Melanoma Staging Database.	Cohort study	3,307 stage III patients.	Overall survival	Independent predictors for survival: number of tumor-bearing nodes, tumor burden at the time of staging (ie, microscopic v macroscopic), presence or absence of primary tumor ulceration, and thickness of the primary melanoma 5-year survival rates: 70% for	For stage III survival curves, see Fig. 1 in the publication. Patient cohort partially identical with Balch et al. 2004	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients with T1-4N1M0 melanomas, 39% for patients with T1-4N3M0 melanomas		
van Akkooi et al. (2008)	to evaluate the survival rate of minimal SN tumor burden	Cohort study	388 SN positive patients	overall survival (OS)	<p>SN tumor burden increased significantly with tumor thickness.</p> <p>estimated 5-year overall survival:</p> <ul style="list-style-type: none"> - for SUB-micrometastases <0.1 mm SN tumor burden: 91% - for 0.1- to 1.0-mm SN tumor burden: 61% - for >1 mm SN tumor burden: 51% - for ≤ 0.2 mm: 89%. <p>Independent prognostic factors in OS (multivariate analysis):</p> <ul style="list-style-type: none"> - SN tumor burden 	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- T4 primary tumors		
Satzger et al. (2008)	To compare different parameters of the SLN and to identify the parameters that are most important for the prediction of non-sentinel lymph node (NSLN) involvement.	Cohort study	180 patients with primary cutaneous melanoma	NSLN involvement	<p>NSLN involvement in the CLND specimen in 16.0% of patients</p> <p>Primary melanomas significantly thicker, more often ulcerated, and regressive in patients with NSLN involvement compared with patients without NSLN involvement</p> <p>Upon multivariate analysis, the three significant parameters were positivity by H&E (versus immunohistochemistry alone), relative tumor area > 10%, and presence of perinodal</p>	Patient population subgroup of Meier et al. (2010)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					intralymphatic tumor		
Debarbieux et al. (2007)	To confirm the prognostic value of SLN biopsy (SLNB); to correlate patient prognosis to the micromorphometric features of SLN metastasis in SLN-positive patients; and to correlate these micromorphometric features to the likelihood of positive completion lymph node dissection (CLND).	Cohort study	455 patients	Overall survival Disease-specific survival	SLN positivity rate 22% Survival significantly shorter in SLN-positive than in SLN-negative patients Prognostic factor of disease-free survival: extracapsular invasion Prognostic factors of disease-specific survival: ulceration, maximum diameter of largest metastasis	10 patients lost to follow-up	2b
Satzger et al. (2007a)	To determine the prognostic relevance of histopathological	Cohort study	169 patients with primary cutaneous melanoma (Breslow's tumour	Overall survival (OS) Relapse-free	Relapse rate 30% Mortality rate 20% (15% melanoma-	Patient population subgroup of Meier et al. (2010)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	characteristics of micrometastases in the SLN.		thickness ≥ 1 mm) and positive SLN diagnosed from April 2000 to December 2004.	survival (RFS)	related, 5% unrelated) Independent prognostic factors in multivariate analysis: invasion of capsule (present versus absent), tumor penetrative depth (TPD) with a cut-off of 2 mm (< 2 mm versus ≥ 2 mm) and deposit size (< 30 cells versus ≥ 30 cells)		
van Akkooi et al. (2006)	to identify a SN positive patient group, which can be spared CLND	Cohort study	77 SN-positive patients	Disease-free survival Estimated 5-year survival Non-SN-positivity	Estimated 5-year OS rates: <0.1 mm SN tumor burden: 100% 0.1–1.0 mm SN tumor burden: 63% >1.0 mm SN tumor burden: 35% Distant metastases in $<0,1$ mm SN-positive patients:	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>1/16 = 6.3%</p> <p>Distant metastasis-free survival in <0,1 mm SN positive patients: 91% (identical to the 5-yr OS of SN negative patients)</p> <p>no additional non-SN positivity for SN-micro-metastases <0.1 mm.</p> <p>multivariate analysis: SN tumor burden was the most important prognostic factor for DFS (P = 0.005) and OS (P = 0.03).</p>		
Shivers et al. (2007)	To determine the relevance of low-volume disease of the sentinel lymph node detected only by RT-PCR-based	Cohort study	311 Patients with melanoma	Overall survival Relapse-free survival Sensitivity and	<p>SLN positivity rate: 19% in histology, 67% by PCR</p> <p>Recurrence rate: 42% of</p>	<p>Very long follow-up time (up to 15 years)</p> <p>Change in technique during</p>	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	assays.			specificity of histology and PCR regarding the prediction of recurrence/death	<p>histologically and PCR positive patients 22% of histologically negative, but PCR positive patients 6.6% for histologically and PCR negative patients</p> <p>Prediction of death: Sensitivity of histology 47%, specificity 87% Sensitivity of PCR 88%, specificity 38%</p>	the course of time	
Baehner et al. (2012)	To (1) quantitate tumor burden in sentinel lymph nodes (SLNs), and (2) assess the independent contributions of SLN tumor burden and primary melanoma	Cohort study	63 patients with one or more positive SLNs were available	<p>Progression-free survival (PFS)</p> <p>OS</p>	Cox proportional-hazard regression model: After adjusting for age and gender, both MMS maximum metastasis size (MMS) and PMT primary melanoma thickness were		2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	thickness (PMT) with respect to progression-free survival (PFS) and overall survival (OS).				highly significant and provided independent prognostic information.		
Fink et al. (2011)	to predict the likelihood of further non-SN metastases on the basis of earlier published micromorphometric classifications of SN metastases	Cohort study	Specimens of 124 positive-SN basins and subsequent complete lymph node dissection (121 patients)	NSN-positivity	metastases in non-SNs were found in 30 lymph node basins (24.2%). Classification according to Dewar: Significant correlation between the microanatomic location of the metastases and non-SN involvement (P=0.004). Classification according to Starz: Significant correlation between S.classification of	Retrospective study	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>SN and non-SN status ($P < 0.001$)</p> <p>Classification of the size of the SN metastases according to the Rotterdam criteria for SN tumor burden: significant correlation with additional non-SN involvement ($P = 0.007$)</p> <p>no statistically significant difference between the three classifications ($P = 0.6$).</p>		
Murali et al. (2010)	To investigate clinicopathologic factors that predict NSN positivity in an attempt to identify patients who may be safely spared completion	Cohort study	409 patients	NSN positivity	Predictive of NSN status in multivariate analysis: clinical characteristics (sex), primary tumor	Retrospective design For details of the score, see original article	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	lymph node dissection (CLND).				characteristics (ulceration and regression), and %PosSN		
Riber-Hansen et al. (2009)	To use objective stereological techniques to correlate accurately total SLN tumour burden with recurrence and patient survival.	Cohort study	335 consecutive melanoma patients	Recurrence rate Overall survival	SLN positivity rate 30.3% Benign naevus inclusions in 36.1% of SLN patients Recurrence rate 10.4% (25.3% for patients positive in histology, 3.9% for negative patients) Mortality rate from metastatic disease 6.7% (14.1% for patients positive in histology, 3.5% for negative patients)	Description of study drop-outs described in another publication	2b-
Van der Ploeg et al. (2009)	To evaluate the micromorphometric Starz classification in melanoma patients.	Cohort study	70 patients with a cutaneous melanoma	Disease-free survival (DFS)	Lymph node recurrence rate: 0% in S-I, S-II 12% in S-III Overall 3-year	Small patient cohort	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>survival: 100% in S-I, S-II 80% in S-III</p> <p>3-year disease-free survival rates: were 83% in S-I, S-II 60% in S-III</p>		
Frankel et al. (2008)	To examine whether the size and location of the metastases within the SLN may help further stratify the risk of additional positive NSLN.	Cohort study	144 melanoma patients	Presence of metastatic non-sentinel nodes	Independent predictors of additional disease in CLND: primary location on the head and neck or lower extremity, Breslow thickness > 4 mm, the presence of angiolymphatic invasion, satellitosis, extranodal extension, three or more positive SLN and tumor burden within the SLN > 1% surface area	Design not consequently prospective	2b-
Satzger et al. (2007b)	To determine the prognostic	Cohort study	477 patients with primary cutaneous	Overall survival (OS)	3 groups were differentiated	Patient population subgroup of Meier	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	significance of isolated HMB45 and/or Melan A positive cells (immunohistochemically positive cells, IPC) in melanoma SLN.		melanoma	Relapse-free survival (RFS)	<p>according to the findings in the SLN: Group 1 included 308 patients with histologically and immunohistochemically negative SLN, group 2 included 47 patients with IPC, and group 3 included 122 patients with micrometastases.</p> <p>Relapse rate: 11.7% of SLN negative patients, 12.8% of IPC+ patients, 37.7% of histology+ patients</p> <p>Mortality rate: 5.5% of SLN negative patients, 6.4% of IPC+ patients, 23.8% of histology+ patients</p>	et al. (2010)	
Namikawa et al. (2012)	to re-evaluate microscopic	Cohort study	450 patients, including the 149	LN positivity-rate	additional LN positivity rate of	retrospective study	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	classifications of metastatic sentinel lymph nodes (SLN) in the Japanese population		cases with SLN metastasis,		<p>0% only in patients with a maximum diameter category of less than 0.1 mm.</p> <p>As compared with that in the SLN metastasis-negative cases, the prognosis was poorer in cases with SLN metastasis, even those with lesions falling under the maximum diameter category of less than 0.1 mm, invasion depth category of SI (≤ 0.3 mm) and microanatomic location category of subcapsular.</p>		
Starz et al. (2004)	to identify the relevant predictors for the presence versus absence of nonsentinel lymph	Cohort study	<p>SLNE cohort: 324 patients</p> <p>pre-SLNE cohort:274</p>	<p>Overall survival</p> <p>survival without distant metastases</p>	S-classification was the most significant independent predictor of the	Patients who underwent SLNE → same population as in Starz et al. 2001 (see above)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	node metastases in CLND specimens		consecutive melanoma patients		<p>presence/absence of NSN-metastases in binary logistic regression: (P = .010; adjusted relative risk = 3.31).</p> <p>survival without distant metastases: Highly significant divergence of the Kaplan-Meier curves of the pre-SLNE- and SLNE-cohort (P = .0057 by log rank test).</p> <p>Overall survival: Kaplan-Meier curves diverge after about 4 years of follow-up (P = .03).</p> <p>Cox regressions: S-classification is a significant independent predictor for</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					distant metastasis (P = .014) and overall survival (P = .009)		
Bogenrieder et al. (2011)	to predict the absence of non-SN metastases in a multicentre study of patients with a positive SN based on primary melanoma features and SN tumour load.	Cohort study	70 SN positive patients	NSN-positivity	<p>18/70 patients had non-SN metastases.</p> <p>No non-SN-metastases in patients with:</p> <ul style="list-style-type: none"> - a Breslow thickness <2.0 mm and an SN tumour load <0.2 mm² - a Breslow thickness <2.0 mm and SN penetrative depth <600 μm - a Breslow thickness <2.0 mm and a diameter of the largest SN deposit <500 μm <p>logistic regression: the SN metastatic area was the only independent factor</p>	<p>Differences in survival between different microanatomic locations of sentinel node metastases not investigated</p> <p>No follow-up</p>	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					predicting the presence of non-SN metastases		
Dewar et al. (2004)	to identify criteria that might be used in selecting patients who should undergo CLND	Cohort study	146 SN-positive patients	NSN-positivity	<p>evidence of melanoma metastases in NSN in 24 of CLND specimens (16.4%)</p> <p>significant correlation between the microanatomic location and NSN involvement (subcapsular metastatic deposits in 26%: no NSN-involvement. SN-metastases with different microanatomic location: NSN-involvement in 22,2%)</p> <p>strong correlation between depth of metastatic deposit</p>	<p>Retrospective study</p> <p>differences in survival between different microanatomic locations of sentinel node metastases not investigated</p> <p>No follow-up</p>	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					from the capsule of the SN and NSN involvement (3/24 patients (12.5%) with positive NSNs had deposits less than 1mm in depth.)		
Starz et al. (2001)	predictive capacity of S-classification	Cohort study	342 patients with primary melanoma and SLNE (389 lymph node Regions) 62 patients with positive SLNs: 42 received RCLND	Presence of metastases survival	325 SLNs: S0 24 SLNs: S1 22 SLNs: S2 18 SLNs: S3. Correlation of the S categories with the T categories (of the pTNM classification) (Spearman correlation; P = 0.0001), occurrence of melanoma-positive non-SLN significantly increased from 0 of 12 in S1 SLNs to 2 of 13 in S2 SLNs	Short follow-up Ulceration of the primary melanoma not included in this analysis (multivariate analysis directly using the T and S classifications as variables was not possible)	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>and 9 of 15 in S3 SLNs (P = 0.001; chi-square test).</p> <p>The risk of developing distant metastases was dependent on the T classification (P < 0.0001; log rank test) and S-classification (P < 0.0001)</p> <p>T classification of the primary melanoma and S-classification= highly significant predictor for distant metastasis (P < 0.001).</p> <p>It turned out to be an independent factor of influence on distant metastasis and survival in multivariate Cox analyses, which</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					included tumor thickness, primary tumor site, patient gender, and patient age as covariates.		

3.2.3.2. Aktualisierungsrecherche 2015

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Morton et al. 2014	To evaluate the outcomes in melanoma patients (SNB vs. nodal observation)	RCT	Melanoma patients (CL III and a Breslow thickness ≥ 1 mm and CL \geq IV and any Breslow thickness) 1661 patients underwent randomization: Observation group: wide excision and nodal observation with lymphadenectomy for nodal relapse	5- and 10-year-Melanoma specific survival 5- and 10-year disease-free survival Survival with tumor-positive and tumor-negative SN Incidence of SN-metastases and incidence of clinically detected nodal metastases	Melanoma specific survival rate: 20.8% with and 79.2% without nodal metastases intermediate-thickness melanomas: - 10-year disease-free survival rates: biopsy group 71,3 +/- 1,8% vs. observation group 64,7 +/- 2,3% - distant disease-free	10-year follow-up/ 215 patients were lost to follow-up Different sentinel mapping procedures Different follow-up procedures in participating sites High rate of false negative biopsy results Ascertainment bias	1b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			<p>biopsy group : wide excision and SNB with immediate lymphadenectomy for nodal metastases detected on biopsy</p>		<p>survival: significantly improved when patients with nodal metastases received immediate rather than delayed lymphadenect omy</p> <ul style="list-style-type: none"> - 10-year melanoma- specific survival rates: biopsy group 81.4±1.5% vs. observation group 78.3±2.0% - 10-year melanoma- specific survival rate: 62.1±4.8% for patients with metastasis vs. 85.1±1.5% for patients without metastasis <p>thick melanomas:</p> <ul style="list-style-type: none"> - 10-year disease-free 	For further details and survival curves: see full- text and appendix	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>survival rates: biopsy group 50,7 +/- 4,0% vs. observation group 40,5+/- 4,7%</p> <ul style="list-style-type: none"> - 10-year melanoma- specific survival rates: no significant treatment- related difference between the biopsy and the observation group (data see full-text) - 10-year melanoma- specific survival rate: 48.0±7.0% for patients with metastases vs. 64.6±4.9% for patients without metastases <p>Similar rates of nodal metastases</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					in biopsy and observation group		
Nagaraja et al. 2013	to determine which of the clinicopathologic prognostic factors could be used to predict the presence of positive non-SLNs.	Systematic research with meta-analysis	54 studies included with a total number of patients of 8388		The pooled estimates significantly associated with the high likelihood of NSN metastases were: ulceration (OR: 1.88, 95% CI: 1.53-2.31), satellitosis (OR: 3.25, 95% CI: 1.86-5.66), neurotropism (OR: 2.51, 95% CI: 1.39-4.53), >1 positive SLN (OR: 1.77, 95% CI: 1.2-2.62), Starz 3 (old) (OR: 1.83, 95% CI: 0.89-3.76), angiolymphatic invasion (OR: 2.46, 95% CI: 1.34-4.54), extensive location (OR: 2.22, 95% CI: 1.74-2.81), macrometastases >2 mm (OR: 1.95,	differences in sample size, populations studied, protocols for pathologic processing and examination of primary tumors and SNs, and methods of data analysis, as well as the effects of interobserver variation in pathologic interpretation. Retrospective studies included	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>95% CI: 1.61-2.35), extranodal extension (OR: 3.38, 95% CI: 1.79-6.40) and capsular involvement (OR: 3.16, 95% CI: 1.37-7.27).</p> <p>Characteristics associated with low risk of NSN metastases: subcapsular location (OR: 0.51, 95% CI: 0.38-0.67), Rotterdam Criteria <0.1 mm (OR: 0.29, 95% CI: 0.17-0.50) and Starz I (new) (OR: 0.44, 95% CI: 0.22-0.91).</p>		
Egger et al. 2014	to determine the classification scheme that best predicts nonsentinel node (NSN) metastasis,	Retrospective study	157 patients with melanoma ≥ 1.0 mm Breslow thickness who underwent SLN biopsy	<p>N-SN metastases after CLND</p> <p>Overall survival</p> <p>Disease free</p>	<p>independent predictors of a positive NSN: maximum diameter, maximum area,</p>	This study reviewed pathologic slides of tumorpositive SLNs from the Sunbelt Melanoma	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	disease-free survival (DFS), and overall survival (OS).			survival	nonsubcapsular location according to Dewar's, and the SIII class according to Starz (significant for cut-off of 1 mm) multivariate analysis: maximum diameter (cut-off of 3 mm) was the only classification system that was an independent risk factor predicting DFS (hazard ratio 2.31, p = 0.0181) and OS (hazard ratio 3.53, p = 0.0005).	Trial and the University of Louisville Melanoma Database	
Satzger et al. 2014	to determine the therapeutic impact of CLND	Retrospective study	305 SLN-positive patients Matched-pair analysis between groups : - 58/305 did not undergo CLND	Recurrence-free survival Overall survival	Matched-pair-analysis: CLND vs. non-CLND: Recurrence-free survival (P= 0.765)	Small patients number	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			<p>- 58/305 underwent CLND</p> <p>Subgroup analysis in patients with SLN micrometastases < 0,1 mm :</p> <p>- 72/106 patients underwent CLND</p> <p>- 34/106 did not undergo CLND</p>	Recurrence rates	<p>Overall survival (P = 0.844)</p> <p>Recurrence rates 17/58 (29%) vs. 15/58 (26%) (P=1.000).</p> <p>Subgroup analysis: CLND vs. non-CLND:</p> <p>Overall survival P=0.610</p> <p>Recurrence-free-survival: P=0.346</p> <p>Recurrence rates: 5/72 (7%) vs. 4/34 (9%)</p> <p>Multivariate analysis: independent prognostic factors:</p> <ul style="list-style-type: none"> - ulceration of the primary melanoma (absent versus present) - the largest 		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					dimension of tumor cell deposit (</=0.1 versus >0.1 mm) - age of patients (</=60 versus >60 years),		
Van der Ploeg et al. 2012	to evaluate the impact of immediate CLND on the outcome of patients with SN-positive melanoma	Retrospective study	1174 Patients with SLN metastases, 1113 underwent CLND, 61 did not	Disease-free-survival	Matched pair analysis: CLND did not significantly influence disease-specific survival (HR 0.86, 0.46 to 1.61; P = 0.640). Multivariate analysis: DSS: - SN tumour burden characteristic was significant prognostic factor, - CLND had no significant influence on prognosis 3- and 5-year DSS	Selection bias: patients who did not undergo CLND had more favourable prognostic factors Small number of patients without CLND	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>rates: Non-CLND: 74% and 66% CLND: 76,9% and 66,9% (HR 0.89, 0.58-1.37; P=0.600) Matched-pair-analyses CLND: 79% and 69% (HR 0.86, 0.46-1.61; P=0.640)</p>		
Van der Ploeg et al. 2014	To evaluate indices of SN tumour burden (intranodal location, tumour penetrative depth (TPD) and maximum size of SN tumour deposits)	Retrospective study	11 melanoma centers : 1539 patients with positive SLN, CLND in 1381 patients	Disease-free survival Melanoma-specific survival N-SLN metastases-rate	Breslow thickness, ulceration, Clark level of invasion, number of SNs removed and all micromorphometric parameters were significant predictors of NSN status (p < 0.05) As continuous variables measured in millimetres,	Heterogeneity in SN biopsy protocols and clinicopathologic features of the patient cohorts Not all patients with micrometastases <0,1mm in the SLN underwent CLND 11 melanoma centers used various	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>maximum SN metastasis size (odds ratio (OR) = 1.11, 95% confidence interval (CI): 1.07-1.15, $p < 0.001$) and tumour penetrative depth (OR = 1.26, 95% CI: 1.15-1.38, $p < 0.001$) were significant predictors of NSN status in the overall cohort</p> <p>Patients with subcapsular micrometastases <0.1 mm in maximum dimension had the lowest frequency of NSN metastasis (5.5%).</p> <p>Significant prognostic factors</p>	<p>classification systems</p> <ul style="list-style-type: none"> → Variation in the prediction of N-SLN-positivity → 4 different multivariate regression models for MSS <p>Further details: see full-text</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>for poorer MSS in the multivariate models included the presence of nonsubcapsular metastases, TPD > 1 mm and maximum SN tumour size > 1 mm</p> <p>A maximum SN tumour size > 1 mm was the most consistent independent predictor of NSN-positivity and poorer DFS and MSS in individual centres, and in the combined cohort.</p>		
Bamboat et al. 2014	to - determine the pattern of initial	Retrospective study	495 patients with positive SLN 167 patients (34%)	Recurrence rates survival	Recurrences in 81 patients (49 %), no-CLND, with a median time to	Patient selection bias (e.g. patients in the no-CLND group were	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	recurrence between the no-CLND and CLND groups - determine melanoma-specific survival of both patient groups		underwent nodal observation 328 (66%) underwent CLND		recurrence of 9 months, and in 179 patients (55 %), CLND, with a median time of 12 months (p = 0.46) regional recurrence rates: 16 %, no CLND, vs. 18 %, CLND; p = 0.58 - nodal only: (15 %, no CLND, vs. 6 %, CLND; p = 0.002) - systemic only (8 %, no CLND, vs. 27 %, CLND; p<0.001) median recurrence-free survival: 34.5 , CLND, vs. 20.9 months, no CLND; p = 0.02 melanoma-specific	significantly older than those undergoing CLND (66 vs. 56 years; p<0.001) patient, tumor and SLN characteristics see tables/full text big differences in median follow-up time between groups: 23 and 80 months for the no-CLND and CLND groups, respectively	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					survival: not reached, no CLND vs. 110 months, CLND; p = 0.09.		
Feldmann et al. 2013	To validate the accuracy of N-SNORE in melanoma patients with positive SLN	Retrospective study	106 melanoma patients with positive SLN, who had undergone complete lymph node dissection (CLND) subsequently,	Non-sentinel-lymph-node-positivity rate	<p>13 patients: score 0 63 patients: score 1-3 19 patients: score 4-5 6 patients: score 6-7 5 patients: score >8.</p> <p>NSLN positivity rates for these 5 risk groups were: 7.7%, 18.2%, 21.1%, 33.3%, and 80%, respectively.</p> <p>contingency coefficient: 0.322; p-value: 0.025</p>	Small patient cohort	2b-
Kibríté et al. 2015	to evaluate the significant	Retrospective study	957 patients who underwent SLNB	Factors for predicting SLN	multivariate analysis: 3 factors	Bias: not all patients with	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	factors associated with positive sentinel and subsequent lymph nodes status.		Subsequent lymphadenectomy in 171 patients	positivity	<p>demonstrate a significant effect ($P < 0.05$) for predicting SLN positivity : Breslow thickness, LVI, tumor location.</p> <p>Breslow thickness ≥ 2 mm or SLN with macroscopic burden ≥ 2mm are the only statistically significant variables predicting the completion lymphadenectomy lymph nodes status (multivariate analysis):</p> <p>Subsequent positive lymph nodes in</p> <ul style="list-style-type: none"> - 9/100 (9%) patients with tumor load < 2mm - 24/71 (33,8%) 	positive SN underwent lymphadenectomy	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients with tumor load \geq 2mm		
Kim et al. 2015	To examine the prognostic role of tumor burden in SLN on overall survival (OS) and disease-free survival (DFS) in patients with cutaneous melanoma using different microscopic classifications and to assess clinical and histological predictors of additional NSLN metastases.	retrospective study	138 patients with positive SLN status 111 patients underwent CLND	Overall survival disease-free survival	Most significant cut-off point for both OS ($p < 0.0001$) and DFS ($p = 0.0064$): 1mm Estimated 5-year-OS: 75.6% in patients with SLN tumor burden \leq 1mm vs. 34.6% in patients with SLN tumor burden $>$ 1mm. only statistically significant predictor of metastatic disease in NSLNs (by multivariate analysis): the number of positive SLN (OR=4.27; 95%	Different pathological protocols used to examine SLN Small patient cohort	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					CI=1.15-15.82; p=0.03)		
Wevers et al. 2013	To identify factors predicting NSN positivity and to assess the validity of the N-SNORE in an independent patient cohort.	Retrospective study	130 patients who underwent CLND after a positive SNLB		<p>Presence of regression was associated with a positive NSN in multivariable logistic regression (OR 6.3; 95%CI 1.1-36.1; p = 0.04).</p> <p>The N-SLN positivity rates for the N-SNORE risk groups were 5.9%, 19.8%, 24.5%, and 47.6%, respectively (p= 0.04) (after adjustment because of missing data on perinodal lymphatic invasion: p = 0.003)</p>	missing data were imputed to enable multivariate analysis → Risk of bias	2b-

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4. AG Chirurgische Therapie

4.1. Frage III.1. Sicherheitsabstände bei Primärexzision – De-novo-Recherche

Frage III.1. Welche Sicherheitsabstände sollen bei radikaler Exzision des Primärtumors eingehalten werden?

4.1.1. PICO, Suchwörter

Suchwörter		
Stichwort	melanoma	therapy, treatment, management, surgery, surgical procedures, excision
Synonyme	melanoma	safety margin, excision margin, surgical margin, narrow, wide
Ober-/Unterbegriffe, Mesh Term	s. Suchsstrategie	

4.1.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	"melanoma"[tiab] AND ("therapy"[all fields] OR "treatment"[all fields] OR "management"[all fields] OR "surgery"[all fields] OR "surgical"[all fields] OR "surgical procedures, operative"[mesh] OR "excision"[all fields]) AND ("safety margin"[all fields] OR "excision margin"[all fields] OR "surgical margin"[all fields] OR "narrow"[all fields] OR "wide"[all fields])	26.01.2012	1235
Cochrane Library	(melanoma and (therapy or treatment or management or surgery or surgical or excision) and ("safety margin" or "excision margin" or "surgical margin" or narrow or	19.01.2012	51

Datenbank	Suchstrategie	Datum	Treffer
	wide)).ti,ab.		
Embase	(melanoma and (therapy or treatment or management or surgery or surgical or excision) and ("safety margin" or "excision margin" or "surgical margin" or narrow or wide)).ti,ab.	23.01.2012	1642

Bemerkungen:
Eine erste Literaturrecherche in Medline und und Cochrane erfolgte am 06.09.2010 bzw. für Embase am 11.05.2011. Die Update-Recherche wurde am 23.01.2012 (Embase) bzw. am 26.01.2012 für Medline und am 19.01.2012 für Cochrane durchgeführt. In der Tabelle angegeben sind die Trefferzahlen der letzten Recherche.

4.1.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	2928
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt Veröffentlichung ab 1970
Ausschlusskriterien	Case Reports (Case series included), narrative Reviews
Anzahl nach Abstractscreening	61
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	12

4.1.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Mocellin et al. (2011)	To quantify the impact of excision margins on disease-specific survival of patients with primary cutaneous melanoma	systematic review of RCT with Meta-analysis	5 eligible RCT A total of 3295 patients enrolled (1633 (49.5%) were allocated to narrow excision and 1662 (50.5%) to wide excision)	locoregional disease-free (LDFS) disease-free (DFS) disease-specific (DSS) overall survival	Narrow margins: risk of both locoregional disease recurrence (HR: 1.30, CI: 1.07—1.57; P = 0.01) and death by disease (HR: 1.28, CI: 1.07—1.53, P = 0.01). As regards DFS, the borderline disadvantage (HR: 1.13, CI: 0.995—1.28; P = 0.06) becomes significant when considering RCT that enrolled patients with thicker melanoma (HR: 1.19, CI: 1.02—1.39, P = 0.03). When death by any cause (OS) was analyzed: narrow vs. wide excision margins	The lack of DSS data from all the available RCT 4 of the 5 RCT included in systematic review of Sladden et al. 2010 (Cohn-Cedermark et al (2000), Balch et al (2001), Khayat et al (2003), Thomas et al (2004)	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(HR: 1.05, 95%CI: 0.95–1.16, P = 0.32)		
Sladden et al. (2010)	To assess the effects of different excision margins for primary cutaneous melanoma.	Systematic review of 5 randomised controlled trials (RCTs) of surgical excision of melanoma comparing different width excision margins	1633 participants in the narrow excision margin group and 1664 in the wide excision margin group	<p>Primary outcomes:</p> <ol style="list-style-type: none"> 1. Time to death (any cause) 2. Time to combined endpoint of death (any cause) or recurrence (local, in transit, regional, distant) <p>Secondary outcomes:</p> <ol style="list-style-type: none"> 1. Quality of Life 2. Adverse events/outcomes 	<p>No significant difference in overall survival when comparing narrow with wide excision</p> <p>Overall survival wide excision: Hazard Ratio 1.04 compared with narrow excision; not significant</p> <p>Recurrence-free survival wide excision: Hazard Ratio 1.13 compared with narrow excision; not significant</p>	<p>Limited RCT data assessing treatment of thin melanomas < 1 mm and thick melanomas ≥ 4 mm.</p> <p>Melanomas in specific body sites not sufficiently investigated</p>	1a
Gillgren et al. (2011)	to test whether survival was different for a wide local excision margin of 2 cm	randomised, multicentre trial	936 patients with cutaneous melanoma thicker than 2 mm, at clinical stage IIA–C	Overall survival	5-year overall survival was 65% (95% CI 60–69) in the 2-cm group and 65% (60–70) in		1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	compared with a 4-cm excision margin		(465 were randomly allocated to treatment with a 2-cm resection margin, 471 to receive treatment with a 4-cm resection margin)		the 4-cm group (p=0.69)		
Subtopic: Margins in special localizations							
Jahn et al. (2006)	To define prognostic factors for melanoma of the ear and to evaluate surgical strategies for excision margins, histological evaluation and sentinel lymph node biopsy (SLNB) in order to achieve better cosmetic and functional results.	Prognostic study	161 patients with stage I and II melanoma of the external ear.	Recurrence-free and disease-specific survival	<p>Recurrence-free survival rate 83% over 3 years and 79% over 5 years</p> <p>Tumour thickness and Clark invasion level were the only significant risk factors for disease-specific survival in Kaplan-Meier univariate analysis.</p>	<p>Prospective study design</p> <p>Patients not randomized between groups with different excision margins; recommendations for excision margins were reduced during the observation period (1976 - 2004); confounding by other historical factors possible.</p>	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						For details on recurrence-free survival in relation to surgical margin, see Fig. 2 in full-text of the article.	
Hazan et al. (2008)	To review clinical and histologic features of lentigo maligna (LM) and lentigo maligna melanoma (LMM) and determine surgical margin necessary for complete excision.	Cross-sectional study	117 patients	Required surgical margin and number of stages for complete excision of LM and LMM	Mean total surgical margin required for excision of LM: 7.1 mm and 10.3 mm for LMM Mean number of stages required to completely excise a lesion: 1.67	Small number of invasive melanoma No data about recurrence rates	3b
Furukawa et al. (2007)	To evaluate how amputation level and cutaneous margin affects prognosis and reconstructive choice.	Prognostic study	15 patients (6 men, 9 women) with melanoma of the thumb between	Disease-free survival	Significant prognostic factors: stage and thickness Level of amputation and excision margin not significant	Small patient sample	3b
Mohrle et al. (2003)	To evaluate clinical parameters and	Prognostic study	368 patients with facial melanoma	Overall survival (5 years)	Significant predictors for	Patients not randomized	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	surgical strategies influencing the prognosis of patients with facial melanoma.	<p>Survival and history of 3960 patients in stages I and II were prospectively recorded between 1980 and 1999. Of these, 368 melanomas were localized in the face, 140 on the capillitium and 76 on the neck.</p> <p>Surgical margins were successively reduced during the observation period, starting from 5 cm in 1980.</p> <p>For functional and aesthetic reasons, recommendations for surgical margins could not always be followed in the head and neck regions.</p>		Recurrence-free survival (5 years)	survival: tumour thickness, Clark level and ulceration, surgery with 3D histology and histological tumour subtype	between groups with different excision margins; recommendations for excision margins were reduced during the observation period (1976 – 2004); confounding by other historical factors possible.	
Pockaj et al. (2003)	To evaluate the	Prognostic study,	84 patients with	Lymph node	Local recurrence in	Retrospective	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	prognostic variables and clinical ramifications of melanoma of the ear.	retrospective design	invasive melanoma of the external ear	involvement Local, regional and systemic recurrence	13% Recurrence of melanoma in the lymph nodes in 12% Systemic metastases in 22% Type of resection did not influence systemic recurrence (P=0.41)	design Patient numbers not sufficient for an evaluation of the influence of different surgical procedures on recurrences	
Tseng et al. (1997)	The purpose of the study was to investigate the surgical management of cutaneous melanomas of the hands and feet.	Prognostic study	116 patients with melanomas of the hands (n = 26) and feet (n = 90)	Recurrence rate	In melanomas <1.5 mm thickness, no local recurrences Metastases developed in 5% No local recurrence or metastasis in patients with < 1.5 mm acral-lentiginous melanoma Of 79 patients with	No control groups Data on elective lymph node dissection biased (decision about ELND was left to the surgeon) and not sufficient (small numbers of patients)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>melanoma \geq 1.5 mm, 15 (19%) presented with regional node disease</p> <p>All 13 patients with subungual melanomas had lesions \geq1.5 mm in thickness; 6 (46%) of 13 had evidence of nodal disease at the time of presentation or at ELND or had regional node metastases develop within 1 year of initial diagnosis</p> <p>In patients with ALM, 71% presented with lesions \geq1.5-mm thick and were treated with wide excision or amputation; local recurrence in two</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(6%) of these patients, but nodal metastases or systemic disease or both in 19 (56%) of 34 patients		
Hudson et Krige (1995)	To analyse the outcome of local treatment and patient survival using a 3 cm local excision margin and split skin grafting	Prognostic study	16 men and 3 women	Overall survival Time to progression	12 patients with stage I disease: mean Breslow depth 2.7 mm All 12 had local excision of the primary lesion with 3 cm margins and skin grafts applied to the galea; 6 developed regional lymph node metastases, 3 developed systemic metastases (all of whom died) One patient presented with stage II disease and developed local recurrence	Very small patient numbers No control group	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					5 patients in stage III disease were treated by wide local excision and therapeutic lymph node dissection; all died after a mean of 9.6 months (range 3 – 22 months)		
Then et al. (2009)	To report early cure rates for periocular melanoma using Slow-Mohs surgery with en-face margin sectioning.	Retrospective, multicenter, noncomparative case series	14 patients with periocular MM	Number of stages needed for complete excision Recurrence rate	most common site: lower eyelid (8/14, 57.1%). Breslow thickness ranged from 0.27 to 1.70 mm, with four cases less than 0.76mm and one case greater than 1.5mm. Five cases were a Clark level II or greater. Complete excision was achieved with one level (6 cases) or two or three levels (8 cases), with 2- to 3-mm margins at each	Very low LoE (case series, retrospective design)	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					level in all but one case. With median follow-up of 36 months, there were two local recurrences (2/14, 14.3%).		
Subtopic: Vertical margins							
Kenady et al. (1982)	To determine whether the presence or absence of muscle fasciae in patients with stages 0 and I malignant melanoma correlates with prognosis.	Retrospective prognostic study	202 patients with primary melanoma of the trunk and proximal limbs	Recurrence rate Survival rate	Sites of first recurrence or survival not significantly affected by the excision of fasciae	AJCC 1978 staging system used retrospectively Possible confounding by the fact that the control group is historical (other potential changes in melanoma management in the meantime)	2b

4.1.5. Literatur

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4.2. Frage III.2. Prophylaktische Lymphadenektomie - Adaptation

Frage III.2. In welchen Fällen ist eine elektive (prophylaktische) LAD indiziert?

4.2.1. Synopse Quellleitlinien (kurz)

Thema/Fragestellung	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
In welchen Fällen ist die adjuvante (prophylaktische) LAD indiziert?	Nicht empfohlen (I)	Keine Angaben	Prophylaktische LAD bringt keinen Vorteil (A)	(nur relevant für medikamentöse Therapien)

4.2.2. Empfehlung, Hintergrundtext und Literatur Australische Quell Leitlinie

(mit Seitenangaben der Quellleitlinie)

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
Schlüsselempfehlungen	keine	keine	S. 42

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
			Standard Le curage prophylactique systématique est contre- indiqué. <i>Standard</i> <i>Die prophylaktische LAD ist</i> <i>kontraindiziert.</i>
Hintergrundtexte	S. 83 A systematic review of randomised controlled trials comparing elective lymph node dissection with surgery delayed until the time of clinical recurrence showed no significant overall survival benefit for patients undergoing elective lymph node dissection. [12] Therefore, except in rare circumstances, elective lymph node dissection is not recommended for melanoma patients. S. 84 Evidence summary Elective lymph node dissection is not recommended, regardless of the Breslow thickness of the primary tumour	S. 93 Lymph node clearance One systematic review found no statistically significant advantage in terms of overall mortality arising from elective lymph node dissection compared to delayed lymph node dissection at the onset of clinical symptoms. One RCT of elective versus delayed regional lymph node dissection in patients with melanoma found that the routine use of immediate node dissection had no significant impact on survival, while the status of regional nodes significantly predicted survival. S. 232 – 234 (NICE Guideline Evidence Review)	S. 30 – 31 Curage ganglionnaire prophylactique systématique DESCRIPTION DES ÉTUDES La méta-analyse de Lens <i>et al.</i> a évalué l'impact sur la survie globale du curage ganglionnaire prophylactique chez les patients porteurs d'un mélanome sans métastases ganglionnaires cliniquement décelables [84]. Quatre essais randomisés ont été inclus, soit un total de 1 704 patients [84-89]. L'un de ces essais n'a pas pu être utilisé pour l'analyse quantitative, car les données

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
	<p>LoE: I References: 7, 12</p>	<p>Summary of the supporting evidence for the recommendations Observational study evidence suggests that the status of the regional node basin is a strong predictor of survival, along with primary tumour characteristics such as Breslow thickness and ulceration. Systematic review and RCT evidence does not demonstrate that elective lymph node dissection carries a survival benefit over a policy of observing patients with primary melanoma after wide excision. However the systematic review by Lens et al. (2002a) suggests that some patients will benefit from elective lymph node dissection.</p> <p>Evidence based clinical guidelines from the UK recommend that in patients with melanoma, the presence of disease in one node indicates radical lymph node dissection but that elective lymph node dissection in the absence of lymph node disease should not be performed. Observational study evidence suggests that the prevalence of lymphoedema</p>	<p>disponibles dans la publication, et après vérification auprès des auteurs, étaient insuffisantes [87].</p> <p>SURVIE GLOBALE Aucun des quatre essais randomisés n'a montré de bénéfice en faveur du curage [85-89] (<i>Tableau IX</i>). La méta-analyse n'a retrouvé aucune différence de survie à 5 ans entre le curage ganglionnaire et l'absence de curage ganglionnaire (odd ratio = 0,86 [IC95 : 0,68-1,09]) [84] (<i>Tableau X</i>).</p> <p>COMPLICATIONS Aucune information concernant les complications n'est disponible dans la méta-analyse. Ce type de curage a toujours une certaine morbidité, plus importante pour le membre inférieur que pour le membre supérieur. La fréquence des</p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		<p>amongst patients who have undergone complete level I-III axillary lymph node dissection for melanoma is 10%, and 53% after additional axillary radiotherapy.</p> <ul style="list-style-type: none"> The systematic review by Lens et al. (2002a), calculated a pooled odds ratio for overall mortality as 0.86 in favour of elective lymph node dissection over delayed lymph node dissection at the onset of clinical symptoms (95% CI 0.68-1.09). The authors concluded that although the result was not statistically significant and although the primary studies had flaws, the possibility exists that some subgroups of patients with melanoma will benefit from elective lymph node dissection. The RCT by Cascinelli et al. (1998) compared elective versus delayed regional lymph node dissection in patients with melanoma and found that the routine use of immediate node dissection had no impact on survival (hazard ratio 0.72, 95% CI 0.5-1.02), whilst the status of regional nodes affected survival significantly. The authors concluded that regional node dissection offers 	<p>complications précoces est de 10 à 15 % dans les meilleures séries lors de curages inguinaux [90, 91]. Le taux de lymphoedèmes tardifs varie de 6 à 15 % au membre inférieur, 6 % au membre supérieur [90, 92].</p> <p>COMMENTAIRES MÉTHODOLOGIQUES ET CLINIQUES</p> <p>La validité clinique des essais randomisés inclus dans la méta-analyse est critiquable, en raison de la réalisation du curage ganglionnaire sur la seule base de l'examen clinique.</p> <p>L'intérêt du curage prophylactique reste controversé et le curage ganglionnaire ne peut s'envisager que dans les localisations où il existe une voie de drainage unique, soit essentiellement les lésions des membres.</p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		<p>increased survival in patients with node metastases only.</p> <ul style="list-style-type: none"> · The retrospective, case series study by Kretschmer et al. (2005) found that overall survival at 5 years in patients who underwent delayed lymph node dissection following initial wide excision of melanoma was 37.4%. Disease free survival in this group of patients was 11.6%. · Evidence based guidelines produced by Roberts et al. (2002) on behalf of the British Association of Dermatologists state that elective lymph node dissection is not indicated in patients with melanoma and clinically negative lymph nodes. · Evidence based guidelines produced by the Scottish Intercollegiate Guidelines Network (2003) recommend that in patients with melanoma, the presence of disease in one node indicates radical lymph node dissection but that elective lymph node dissection in the absence of lymph node disease should not be performed. 	<p>CONCLUSION DE LA LITTÉRATURE</p> <p>Aucun bénéfice du curage ganglionnaire prophylactique après exérèse de mélanome n'a été démontré. Le curage ganglionnaire prophylactique systématique n'améliore pas la survie globale par rapport au curage ganglionnaire retardé ou à l'absence de curage ganglionnaire chez les patients atteints d'un mélanome cutané cliniquement NO (niveau de preuve A).</p> <p><i>S. 30 - 31</i></p> <p><i>Systematische prophylaktische Lymphadenektomie (LAD)</i></p> <p><i>BESCHREIBUNG DER STUDIEN</i></p> <p><i>Die Metaanalyse von Lens et al. hat den Einfluss der prophylaktischen LAD auf das Gesamtüberleben bei Patienten mit Melanom ohne klinisch nachweisbare Lymphknotenmetastasen ausgewertet [84].</i></p>

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			<p><i>Vier randomisierte Studien mit einer Gesamtzahl von 1 704 Patienten sind dabei eingeschlossen worden [84-89]. Eine dieser Studien konnte nicht für die quantitative Analyse verwendet werden, da die Daten in der Publikation auch nach Verifikation bei den Autoren insuffizient waren [87].</i></p> <p>GESAMTÜBERLEBEN <i>Keine der vier randomisierten Studien konnte einen Vorteil der LAD zeigen [85-89] (Tabelle IX). Die Metaanalyse ergab keinen Unterschied in der 5-Jahres-Überlebensrate zwischen Durchführung und Nicht-Durchführung der elektiven LAD (Odds-Ratio = 0,86 [IC95 : 0,68-1,09]) [84] (Tabelle X).</i></p> <p>KOMPLIKATIONEN <i>In der Metaanalyse sind keine Informationen über Komplikationen verfügbar. Diese Art der LAD geht immer mit einer gewissen Morbidität</i></p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
			<p><i>einher, an der unteren Extremität ausgeprägter als an der oberen Extremität. Die Häufigkeit der Frühkomplikationen reicht von 10 bis 15% in den besseren Serien der inguinalen Lymphadenektomien [90, 91]. Die Rate der späten Lymphödeme reicht von 6 bis 15% an den unteren Extremitäten und beträgt ca. 6% an den oberen Extremitäten [90, 92].</i></p> <p>METHODOLOGISCHE UND KLINISCHE KOMMENTARE <i>Die klinische Validität der in die Meta-Analyse eingeschlossenen randomisierten Studien ist fragwürdig, da die Durchführung der LAD allein mit dem Ergebnis der klinischen Untersuchung begründet wurde. Die Frage der prophylaktischen LAD bleibt kontrovers. Sie kann zudem nur bei Tumorlokalisationen in Betracht</i></p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
			<p><i>gezogen werden, an denen nur ein lymphatischer Abflussweg existiert, d.h. im Wesentlichen bei Läsionen an den Extremitäten.</i></p> <p>SCHLUSSFOLGERUNG AUS DER LITERATUR <i>Es konnte nach Exzision des Melanoms kein Vorteil der prophylaktischen LAD gezeigt werden. Sie verbessert im Vergleich zur späten LAD oder zum Verzicht auf LAD nicht das Überleben bei Patienten mit malignem Melanom im klinischen Stadium N0 (Evidenzlevel A).</i></p>
Bemerkungen		<p>Diese Leitlinie bezieht sich auf MM und auf NMSC.</p> <p>Referenzen und ausführliche Evidenztabellen dieser Leitlinie werden wegen ihres Umfangs als separates Dokument zur Verfügung gestellt: GB NICE Guideline Evidence Review, S. 232 bis 238.</p>	<p>Im Volltext der Leitlinie tabellarische Darstellung der einbezogenen Studien (S. 30).</p>

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4.3. Frage III.3. Therapeutische Lymphadenektomie – De-novo-Recherche

Frage III.3. In welchen Fällen ist die therapeutische LAD indiziert?

4.3.1. PICO-Unterfragen

- Hat die therapeutische LAD bei Patienten mit klinisch feststellbaren LK-Metastasen einen Einfluss auf das Überleben?
- Hat die therapeutische LAD bei Patienten mit klinisch feststellbaren LK-Metastasen einen Einfluss auf die rezidivfreie Zeit?
- Hat die therapeutische LAD bei Patienten mit klinisch feststellbaren LK-Metastasen einen Einfluss auf die Lebensqualität?

Suchwörter

Stichwort, Synonyme, Ober-/Unterbegriffe, Mesh Term

s. Suchsstrategie

4.3.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	melanoma AND ("lymph node excision"[MeSH Terms] OR ("lymph"[All Fields] AND "node"[All Fields] AND "excision"[All Fields]) OR "lymph node excision"[All Fields] OR "lymphadenectomy"[All Fields] OR "lymph node dissection"[All Fields] OR "lymphonodectomy"[All Fields])	08.03.2011	3408
Medline Update-Recherche	melanoma AND ("lymph node	11.01.2011	3754

Datenbank	Suchstrategie	Datum	Treffer
	excision"[MeSH Terms] OR ("lymph"[All Fields] AND "node"[All Fields] AND "excision"[All Fields]) OR "lymph node excision"[All Fields] OR "lymphadenectomy"[All Fields] OR "lymph node dissection"[All Fields] OR "lymphonodectomy"[All Fields])		
Cochrane Library	(melanoma and ((lymph and node and excision) or lymphadenectomy or "lymph node dissection" or lymphonodectomy)).ti,ab.	08.03.2011	93
Embase	(melanoma and ((lymph and node and excision) or lymphadenectomy or "lymph node dissection" or lymphonodectomy)).ti,ab.	11.05.2011	2148
2. Suche/Ergänzungen			
<p>Bemerkungen: Eine erste Literaturrecherche in Medline und und Cochrane erfolgte am 08.03.2010 bzw. für Embase am 11.05.2011. Zweite Medline-Recherche (Update-Recherche) erfolgte am 11.01.2011. Da die Frage III.3. letztendlich konsensbasiert beantwortet wurde (s.3.3.3.), wurde auf eine Update-Recherche Anfang 2012 verzichtet.</p>			

4.3.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	5995
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews
Anzahl nach Abstractscreening	61
Anzahl ausgewählter und bewerteter Volltexte, vorgesehen für Bewertung	27
Bemerkungen: Aufgrund des Fehlens von Studien, die das Outcome von Patienten, die eine therapeutische LAD erhalten haben, mit dem von Patienten vergleicht, die diese LAD trotz bestehender LK-Metastasen nicht erhalten haben, entschieden sich die Experten der AG chirurgische Therapie für eine konsensbasierte statt evidenzbasierte Beantwortung der Frage.	

4.3.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Pilko et al. (2011)	To compare the overall survival of different groups of stage III cutaneous melanoma patients	Prognostic study Cohort study	325 patients with stage III melanoma	Overall survival (OS) Disease-free survival (DFS)	The mean follow-up was 44 months (range 1 - 168 months). The 5-year DFS for the whole group was 36.6%, 5-year OS was 52.6%.	Retrospective design (prospective database) Short follow-up in some patients No control group (comparison of	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					On multivariate analysis, age, Breslow thickness, presence of ulceration, number of involved lymph nodes, type of lymph node dissection and size of SN metastasis were independent prognostic factors for OS.	lymph node dissection vs. no lymph node dissection not possible)	
Pasquali et al. (2010)	To investigate whether patients with melanoma who undergo lymphadenectomy after a positive sentinel lymph node (SN) biopsy (SNB) have a better prognosis compared with patients who are treated for clinically evident disease.	Systematic review	The included 6 studies encompassed 2633 patients who had AJCC stage III melanoma.	Overall survival	Hazard ratio for overall survival (TLND vs. CLND): Summary measure 1.602	Study included here for the data on therapeutic node dissection (not completion node dissection after SNB) Systematic review and original data, but different objective of the study (therapeutic vs. completion node dissection, not therapeutic vs.	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						control group), therefore lower level of evidence concerning the question of indication for therapeutic node dissection	
Rutkowski et al. (2010)	To compare outcomes of patients with clinical nodal melanoma metastases without a detectable primary tumor (MUP) with those with a known primary site (KPM).	Prognostic study Cohort study	459 consecutive melanoma patients, stages IIIB and IIIC	Overall survival Disease-free survival Recurrence rates	3-year and 5-year OS rates: 48.0% and 41.4%, respectively, for the MUP group (median 36.2 months) and 42.0% and 36.0%, respectively, for the KPM group (median 25.7 months). 3-year and 5-year DFS rates: 47.0% and 44.0%, respectively, for the MUP group (median 14.9 months) and 31.1% and 28.3%, respectively, for	Retrospective design No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>the KPM group (median 11.7 months).</p> <p>Disease recurrences: in the MUP group 31 patients; 52.5%, in the KPM group 299 cases; 74.8%</p>		
Allan et al. (2008)	To review the experience of routine ilioinguinal dissection for all patients presenting with palpable metastatic melanoma in the groin.	<p>prognostic and diagnostic study</p> <p>Cohort study</p>	72 patients	<p>Disease-free interval</p> <p>Disease-free survival</p> <p>Overall survival</p> <p>Pelvic lymph node status</p> <p>Diagnostic value of preoperative CT</p> <p>Complication rate (lymphoedema)</p>	<p>22 (30.6%) of 72 patients with histologically involved pelvic lymph nodes.</p> <p>Preoperative CT accuracy for pelvic lymph node involvement: sensitivity 60.0%, specificity 100.0%, PPV 100.0%, NPV 86.2%.</p> <p>Median time to first recurrence: 8.7 months (0.8–69.7 months). Regional</p>	<p>Retrospective design</p> <p>Small patient cohort</p> <p>No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)</p> <p>Confounder: adjuvant therapy</p>	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>recurrence in 6 (8.3%) of 72 patients (at a median of 4.9 months (0.9–32.0 months)).</p> <p>Extranodal spread adversely associated with disease-free survival.</p> <p>5-year DFS: 38% (95% CI 26–50), OS 47% (95% CI 33–60).</p> <p>Lymphoedema was reported in 32 (44.4%) of 72 patients.</p>		
Lee et al. (2008)	Clinical outcomes of patients with MUP and known primary melanoma (MKP) with regional nodal metastases were compared to investigate the	Prognostic study Cohort study	1,571 patients who underwent therapeutic regional lymphadenectomy (262: MUP, 1,309: MKP)	Overall survival Disease-free survival	significant factors on multivariate analysis: age, sex, nodal tumor burden, decade of diagnosis, status of primary.	Retrospective design No control group (comparison of lymph node dissection vs. no lymph node	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	prognostic significance of MUP.				<p>Greater risk was associated with age \geq 60 years, male sex, increased number of tumor-involved nodes (>1), and MKP. The risk of death was 40% lower in the MUP group than the MKP group (HR = 1.507).</p> <p>5-year and 10-year rates of OS for patients with MUP versus patients with MKP were 58% \pm 7% versus 40% \pm 7%, respectively, and 52% \pm 7% versus 36% \pm 7%, respectively.</p> <p>Median OS was also significantly longer in the MUP group than the MKP group (165 months vs. 34</p>	dissection not possible)	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months).		
Van Akkooi et al. (2007)	To evaluate morbidity and mortality following TLND, and disease-free (DFS) and overall survival (OS) following TLND.	Prognostic study Cohort study	236 melanoma patients who underwent TLND	Overall survival Disease-free survival Regional control rate Complication rate	mean follow-up after TLND: 29 months (range 0 - 280 months). estimated 5-year DFS and OS for the 236 patients after TLND: 19% and 26%. estimated 5-year regional control rate after TLND: 79%. Median time to disease progression: 7 months. estimated 5-year DFS according to site of tumor: 23% (extremities) and 9% (central tumors) estimated 5-year DFS for different	Retrospective design No follow-up in some patients No control group (comparison of lymph node dissection vs. no lymph node dissection not possible) For data on complications, see original article	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>categories of nodal status (N1, N2, N3): 31%, 15% and 10%, respectively.</p> <p>significant different estimated 5-year OS rate for different intervals of diagnosis until TLND.</p>		
Young et al. (2006)	To investigate rates of long-term survival for patients with regional (nodal) melanoma.	Prognostic study Cohort study	1422 patients with stage III melanoma who received complete lymphadenectomy	Overall survival Melanoma-specific survival	<p>maximum follow-up: 386 months (32 years)</p> <p>rates of 15-, 20- and 25-year melanoma-specific survival: 36% ± 1%, 35% ± 1%, and 35% ± 1%, respectively.</p> <p>Median melanoma-specific OS: 28.1 months in the palpable and 90 months in the non-palpable group.</p> <p>When stratified by</p>	<p>Retrospective design</p> <p>Long follow-up</p> <p>No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					clinical status of regional nodes, survival rates were significantly lower if nodes were palpable.		
Pienkowski et al. (2005)	to perform a single-institution analysis of factors influencing the clinical outcomes of cutaneous melanoma (CM) patients undergoing therapeutic lymphadenectomy (LND).	Cohort study	353 consecutive melanoma patients with metastases to regional lymph nodes	Overall survival Disease-free survival	Estimated 5-year overall survival ratio: 44% 5-year disease free survival rate: 35% independent predictors of poor OS (multivariate analysis): - extracapsular melanoma invasion (p < 3mm (p = 0.007) - male sex (p=0.011) - CM site in head/neck region (p = 0.05) negative factors for DFS: - nodal	Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					extracapsular melanoma extension (p < 0.0001) - male sex (p < 0.0001).		
Serpell et al. (2003)	To review regional disease control and morbidity in a series of lymphadenectomies	Cohort study	64 melanoma patients have undergone 73 RLND for metastatic regional melanoma	Overall survival Recurrence rate Complication rate	median time to diagnosis of regional lymph node disease: 11.2 (interquartile range 2–48) months. regional control: 92% local recurrences (LR): 8% LR all occurred within 12 months of lymphadenectomy, all but 1 patient with LR have died within 12 months. rate of LR local recurrence was similar with or without	Retrospective design Small patient cohort No control group (comparison of lymph node dissection vs. no lymph node dissection not possible) For data on complications, see original article	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>postoperative radiotherapy.</p> <p>34/64 patients died, median time to death=12 months (range 2-35 months).</p>		
Fisher (2002)	To evaluate the effects on survival, disease-free interval, and recurrence patterns for patients undergoing elective, therapeutic, and delayed lymph node dissection for malignant melanoma of the head and neck.	Cohort study	<p>1444 melanoma patients:</p> <ul style="list-style-type: none"> - 219 patients with ELND, histologically proven negative lymph nodes - 27 patients with ELND, histologically proven positive lymph nodes - 106 patients with DLND for regional lymph node recurrence - 112 patients with TLND for clinically positive lymph nodes 	<p>Disease-free survival</p> <p>Overall survival</p>	<p>overall rate of nodal recurrence for all patients: 129/1045 patients 12%.</p> <p>significant improvement in survival for DLND when compared with patients undergoing ELNDQ or TLND (P=0.01).</p> <p>Five-year survival after DLND and TLND was 56% and 36%, respectively.</p>	<p>Retrospective design</p> <p>Study included here for data on delayed lymph node dissection (DLND); for further data on ELND and TLND see original article</p> <p>No control group for DLND (comparison of lymph node dissection vs. no lymph node dissection not possible)</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Pathak et al. (2002)	To determine the rates of regional recurrence for node-positive melanoma after neck dissection alone.	Cohort study	31 patients who underwent neck dissection for node-positive melanoma	Recurrence rate Mean time to recurrence Overall survival	mean follow-up: 45.3 months with a SD of 35.3 months and a range of 1 to 108 months. regional recurrence rate at 5 years for melanoma: 31%. mean time to recurrence: 78 months (95% CI: 63 to 93 months). mean survival for patients undergoing neck dissection: 61 months.	Small patient cohort Very short follow-up in some patients (recurrence rate may be underestimated) No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b
White et al. (2002)	To examine the long-term outcomes of patients with melanoma metastatic to regional lymph nodes.	Cohort study	2,505 patients	Overall survival Recurrence-free survival	For regional lymph node metastases: median overall survival: 3.4 years, median recurrence-free survival: 1.5 years. Estimated overall	Retrospective design Missing data led to exclusion of patients No control group (comparison of lymph node	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>survival rates(95% CI) at 5, 10, 15, 20, and 25 years: 43% (41–45%), 35% (33– 37%), 28% (25–30%), 23% (20–26%), and 19% (13–24%), respectively.</p> <p>Estimated recurrence-free survival rates at 5, 10, 15, and 20 years: 33% (31–35%), 28% (26–30%), 25% (23–27%), and 22% (18–26%) respectively,</p> <p>Both curves appeared to plateau at approximately 20%, no first recurrences after 21 years.</p>	dissection vs. no lymph node dissection not possible)	
Hughes et al. (2000)	to identify disease- and treatment-related factors that influence the	132 patients With clinically detectable LN-metastases		Morbidity Overall survival	no difference in postoperative morbidity or major lymphoedema	Retrospective study	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	outcome of patients undergoing therapeutic groin dissection for clinically detectable melanoma lymph node metastases	60 patients: superficial inguinal lymph node dissection (SLND) 72 patients: combined superficial inguinal and pelvic lymph node dissection (CLND)		Recurrence rate	between SLND and CLND overall 5-year-survival-rate: - 34% 5-year-survival-rate: -pelvic lymph node metastases (CLND): 19% - no pelvis lymph node metastases (CLND): 17% (P = 0.015) Factors with significant impact on survival (univariate analysis): - age (P = 0.003) - number of involved superficial lymph nodes (P = 0.001) - presence of extracapsular spread (P = 0.003)		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>Systemic recurrence rate: 62%</p> <p>Median time to systemic recurrence: 9 months</p> <p>.</p>		
Cascinelli et al. (1998)	To evaluate the efficacy of immediate node dissection in patients with melanoma of the trunk and without clinical evidence of regional node and distant metastases.	Randomized controlled trial	<p>Of 240 patients</p> <p>122: wide excision and immediate node dissection</p> <p>118: wide excision and dissection delayed until the time of appearance of clinically detectable node metastases.</p>	<p>Time to first recurrence</p> <p>Overall survival</p>	<p>36/118 patients (30.5%) developed regional node metastases</p> <p>median lag between excision of primary tumour and the diagnosis of regional node metastases: 8.3 months (interquartile range 3.7-16.2). minimum delay: 0.43 months, maximum 55.0 months</p> <p>"Delayed" patients</p>	<p>Study included here for the data on delayed node dissection (not immediate node dissection)</p> <p>Prospective, randomized design, but different objective of the study (elective vs. therapeutic node dissection, not therapeutic vs. control group), therefore lower level of evidence concerning the</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					had a survival rate at 5 years of 51.3% (95% CI 41.7–60.1).	question of indication for therapeutic node dissection	
Jonk et al. (1998)	To identify prognostic factors determining overall survival in patients with surgically treated neck node metastases of cutaneous melanoma	Cohort study	70 surgically treated with curative intent for cervical lymph node metastasis - radical neck dissection: 64 patient - - modified radical neck dissection: 4 patients - postero-lateral neck dissection: 2 patients.	Overall survival	overall survivals after 5 and 10 years: 23% and 20%, respectively. Median survival: 22 months. Following a therapeutic neck dissection, 5-year survival rate: 22% following elective dissection, 5-year survival rate: 29% (difference not significant).	Retrospective design Small patient cohort Patients predominantly male No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b
Karakousis and Driscoll (1996)	To report the experience with groin dissection for melanoma	Cohort study	205 patients who underwent groin dissection	Overall survival Disease-free survival Complication rate	Estimated-overall 5-year survival and disease-free survival rates for patients with histologically proven negative	Retrospective design No control group (comparison of lymph node dissection vs. no	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>nodes: 73% and 67% respectively, rates for those with positive nodes: 39% and 29%, respectively. 10-year survival rate for patients with negative nodes was 63% and for those with positive nodes 33%.</p> <p>median length of survival for patients with clinically positive nodes: 29 months, for the 40 with negative nodes: 52 months. 5- and 10-year survival rates: in the former group: 37% and 32% respectively, in the latter group: 43% and 35%.</p> <p>For patients with positive nodes only</p>	lymph node dissection not possible)	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					in the inguinal region: 5-year overall and disease-free survival rates were 43% and 35% respectively; for patients with positive nodes in both the inguinal and deep node groups: 34% and 21%. Estimated 10-year survival rate for the former group: 39%. for the latter group: 25% at 92 months.		
Karakousis et al. (1994)						Patient cohort is a subset of Karakousis and Driscoll (1994); see above	
Gadd and Coit (1992)	To analyze the patterns of initial recurrence and outcome of patients with recurrence of	Cohort study	403 patients with recurrences after lymphadenectomy;	Disease-free interval survival	The median disease-free interval: 11.2 months, range from 1 to 157 months.	Retrospective design Missing tumor characteristics for circa half of the	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma following axillary or inguinal lymphadenectomy				<p>Median survival of patients with:</p> <ul style="list-style-type: none"> - single-site recurrence: 11 months, with a 5-year survival rate of 10% - multiple sites: 3 months, no 5-year survivors - nonvisceral single-site recurrence: 18.5 months with a 5-year-survival rate of 14% - single visceral recurrence: 6 months with a 5-year-survival rate of 3% - surgical resection of single-site recurrences: 17 months with a 5- 	<p>patient population; also missing treatment information in some patients</p> <p>No separate analysis for elective and therapeutic dissections</p> <p>Comparison between surgical and nonsurgical therapy, but groups not randomized</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>year survival rate of 14% (Complete resection: median survival: 19 months, partial resection: 6 months)</p> <p>- nonsurgical therapy: 5 months with a 5-year survival rate of 2%</p> <p>- surgical resection of multiple site recurrences: 7 months</p> <p>- nonsurgical therapy of multiple site recurrences: 3 months</p>		
Morton et al. (1991)	To evaluate the importance of various prognostic features after lymphadenectomy.	Cohort study	<p>1134 patients with lymph node metastases</p> <p>737 patients in whom complete information was</p>	Overall survival	<p>5-, 10- and 15-year survival: 46%, 41%, and 38%, respectively.</p> <p>Multivariate analysis:the</p>	<p>Missing information in many patients, who were excluded from the analysis</p> <p>Retrospective</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			available		number of involved nodes ($p = 0.001$), the location on an extremity ($p = 0.0059$), the depth of the primary ($p = 0.0334$), the patient's sex ($p = 0.0627$), and clinical stage ($p = 0.0942$) were significantly correlated with survival.	design No control group (comparison of lymph node dissection vs. no lymph node dissection not possible) For mathematical model of prognosis, see original article	
Karakousis et al. (1990)	To report on results and complications of axillary node dissection in melanoma	Cohort study	133 melanoma patients who underwent axillary node dissection	Overall survival Disease-free survival Complication rate	estimated 5-year disease-free survival rate for patients with: - histologically negative nodes: 80% - histologically positive nodes: 23%. - palpable nodes: 13%	For data on complications, see original article Retrospective design No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>- clinically negative nodes: 60%.</p> <p>In patients with clinically & histologically involved nodes: the greater the number of involved nodes, the shorter was the disease-free survival time after node dissection.</p> <p>Considering all patients with elective and therapeutic node dissections: recurrence in 53 patients (40%), 74% of them within 2 years.</p>		
Karakousis et al. (1986)						Patient cohort is a subset of Karakousis and Driscoll (1994); see above	
Finck et al. (1982)	To review the	Cohort study	82 melanoma	Disease-free	Significant	Retrospective	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	results of ilioinguinal dissection and to compare results for patients with inguinal and iliac node involvement with those with only inguinal involvement.		patients with inguinal lymph node metastases.	interval Overall survival	<p>difference in disease-free interval for patients with inguinal and iliac node metastases and patients who had only inguinal involvement. ($p < 0.01$).</p> <p>Disease recurrence: - 20/24 (83.3%) patients with positive iliac nodes - 32/58 (55.2%) patients with negative iliac nodes.</p> <p>Median disease-free interval: - 5.8 months for patients with iliac metastases - 25.6 months for patients without iliac nodal involvement.</p>	<p>design</p> <p>Small patient cohort</p> <p>Missing information on primary tumour characteristics in many patient files</p> <p>No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Median survival: - for patients with iliac metastases: 20.0 months - for patients with negative iliac nodes: 52,1 months		
Veronesi et al. (1982)	To investigate whether regional lymph nodes should or should not be removed in stage I melanoma patients (elective dissection).	Randomized controlled trial	553 stage I melanoma patients	Overall survival	The type of treatment given did not modify the chances of cure for the patients, even if adjusted by single significant factors or by all of them. 5-year overall survival rates for delayed dissection: 57.9% for males 76.5% for females 10-year overall survival rates for delayed dissection: 48.7% for males 62.0% for females	Prospective design Study included here for the data on therapeutic node dissection (not elective dissection) Different objective of the study (therapeutic vs. completion node dissection, not therapeutic vs. control group), therefore lower level of evidence concerning the question of indication for therapeutic node dissection	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Predominantly women in study group	
Sandeman (1966)	To review the results of radical surgery and other methods in the treatment of regionally advanced melanoma	Cohort study	113 patients with malignant melanoma in stages I-III	Overall survival	<p>5-year OS survival for patients who originally presented in stage I, depending on treatment method: Surgery 27% Irradiation 23% Combined 67%</p> <p>5-year overall survival for patients who originally presented in stage II, depending on treatment method: Surgery 27% Irradiation 33% Combined 0/4</p> <p>Stage III: 5-year survival for irradiation 33%</p> <p>Insufficient data</p>	<p>Retrospective design</p> <p>Insufficient control group of patients who did not receive treatment</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					for “no treatment” group and stage III with other treatment modalities		
Price and Duval (1963)	To determine whether or not prognosis in malignant melanoma is affected by regional lymph node excision	Cohort study	50 patients with malignant melanoma arising on an extremity	Overall survival	<p>27 of 50 patients had clinically positive nodes on presentation. Of these 2 refused treatment (0% survivors) and</p> <p>27/25 patients with clinical positive nodes received regional lymph node dissection: 20% survivors</p> <p>14/23 patients with had clinically negative nodes; received regional lymph node dissection: 43% survivors</p>	<p>Retrospective design</p> <p>Small patient cohort</p> <p>Very old patient cohort (1931 – 1956), questionable transferability to current situation</p> <p>Very small, probably biased control group (2 patients with clinically involved nodes who refused treatment)</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bowsher et al. (1986)	To evaluate short and long term postoperative morbidity, mortality and local recurrence rate after regional node dissection for melanoma	Cohort study	86 patients who received regional node dissection for melanoma (28% prophylactic, 72% therapeutic)	Recurrence rate	Local recurrence after dissection: - cervical: 33% - axillary: 13% - inguinal: 9% - axillary for trunk lesions: 21% - axillary for arm lesions: 6%	Retrospective design Small patient cohort No control group (comparison of lymph node dissection vs. no lymph node dissection not possible) For data on prophylactic RND and complications, see original article	3b-
Fortner et al. (1964)	To present results of groin dissection in malignant melanoma	Cohort study	220 patients who had undergone a groin dissection for malignant melanoma	Overall survival Recurrence rate Complication rate	5-year-survival-rate of patients with dissection: - unilateral groin dissection: 33,5% - histologically positive nodes: 23,3 % - histological negative nodes: 78,8% -radical groin	Very old patient cohort (1931 – 1956), questionable transferability to current situation No control group (comparison of lymph node dissection vs. no lymph node	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>dissection: 31,6% - nodal involvement by metastatic cancer confined to the superficial groin: 41,6% - positive nodes in both superficial and deep groups: 8,7%</p> <p>Complication-rate - during operation: 3% - postoperative: Approximately 60%</p> <p>Mortality rate within 30 days after operation: <0,5%</p> <p>Morbidity rate (relative to other than wound problems: 19,4%)</p> <p>Recurrence rate total for first year: 55,8%</p>	<p>dissection not possible)</p> <p>For further prognostic data see original article</p>	

4.3.5. Literatur

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4.4. Frage III.7. Operative Therapie bei Fernmetastasen – De-novo-Recherche

Frage III.7. Wann ist bei Fernmetastasen eine operative Therapie indiziert?

4.4.1. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	("melanoma"[tiab] AND ("neoplasm metastasis"[MeSH Terms] OR ("metastasis"[tiab])) AND ("surgery"[All Fields] OR "metastasectomy"[All Fields]))	26.01.2012	3878
2. Suche/Ergänzungsrecherche			
Medline	("melanoma"[tiab] AND ("neoplasm metastases"[MeSH Terms] OR ("metastases"[tiab]) OR ("metastatic"[tiab])) AND ("surgery"[All Fields] OR "metastasectomy"[All Fields]))	26.01.2012	4137
Cochrane Library	(melanoma and (metastasis or metastases) and (surgery or metastasectomy)).ti,ab.	19.01.2012	89
Embase	(melanoma and metastasis and (surgery or metastasectomy)).ti,ab. (melanoma and metastases and (surgery or metastasectomy)).ti,ab.	23.01.2012	806 1342

Bemerkungen: Eine erste Literaturrecherche in Medline und und Cochrane erfolgte am 26.04.2011 bzw. für Embase am 11.05.2011. Eine Ergänzungsrecherche in Medline erfolgte am 08.12.2011. Die Update-Recherche wurde am 23.01.2012 (Embase) bzw. am 26.01.2012 (Medline) und am 19.01.2012 (Cochrane) durchgeführt. In der Tabelle angegeben sind die Trefferzahlen der letzten Recherche.

4.4.2. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer inkl. Dupletten	10252
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt, ab Erscheinungsjahr 1978 population \geq 20 patients
Ausschlusskriterien	narrative Reviews, Case Reports, gemischte Kollektive mit anderen Krebsarten, Studien ausschließlich zu Gehirn-Metastasen (andere AG)
Anzahl nach Abstractscreening	93
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	31

4.4.3. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Subtopic Pulmonary Metastases							
Petersen et al. (2007)	to discriminate predictors of survival for patients with pulmonary metastatic	Cohort study	1720 patients with metastatic pulmonary melanoma 318 patients	Survival 1-, 2- and 5-year- survival	OS (n=1720) - 1 year: 34% - 2-year: 14% - 5 years: 6%. median survival:	Retrospective design complete follow-up on all patients	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma.		underwent resection (with curative intent)		<p>7.3 months.</p> <p>complete vs incomplete pathologic resection:</p> <ul style="list-style-type: none"> - median survival: 19 vs. 11 months - 5-year survival: 21 vs. 3% (P<0.0001). <p>single vs. repeated metastasectomy:</p> <ul style="list-style-type: none"> - median survival: 17 vs. 15 months (P<0.9). <p>Significant predictors of survival (multivariate model):</p> <ul style="list-style-type: none"> - nodular histologic type (P=0.033) - disease-free interval (P<0.001) - number of pulmonary metastases 	<p>large sample</p> <p>data collection during a span of 35 years.</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>(P=0.012)</p> <ul style="list-style-type: none"> - presence of extrathoracic metastasis (P<0.001) - performance of pulmonary metastasectomy (P<0.001). <p>disease-free interval after surgery > 5 years: Survival: 19 months (vs 7 months, P<0.01)</p> <p>Patients without extrathoracic metastasis: 18 (vs 8 months, P<0.01).</p>		
Leo et al (2000)	To evaluate the long-term results of lung metastasectomy for melanoma and to define a subset of patients with better	Cohort study	<p>328 patients who underwent lung metastasectomy</p> <p>Surgical patients underwent resection with</p>	<p>Overall survival</p> <p>Mortality</p> <p>Prognostic factors of survival</p>	<p>5-year-survival: 18% 10-year-survival: 14% median survival 17 months.</p> <p>R0-resection:</p>	<p>Retrospective design</p> <p>Old patient cohort (1945-1995) /questionable</p>	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	prognosis.		curative intent only		<p>5- and 10-year survival: 22% and 16%(median survival 19 months)</p> <p>R1/R2-resection: 5-year-survival: 0% (median survival 11 months).</p> <p>Long- term survival according to the radicality of metastasectomy (16% vs 0% at 10 years, $P < 0.01$)</p> <p>independent unfavourable prognostic factors:</p> <ul style="list-style-type: none"> - time to pulmonary metastases (TPM) <36 months - presence of multiple metastases <p>Patients without these risk factors:</p>	<p>transferability to current situation</p> <p>Bias: chemo- /radiotherapy</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					5-year-survival rate:29% Patients with 1 risk factors: 5-year-survival rate:20% Patients with 2 risk factors or incomplete resection: 5-year-survival rate:7% - mortality rate 67% - in the R0 group: 65% - in the R1-2 group: 80%). 5-year-survival inpatients with intrathoracic recurrence and further surgery: 19%		
Harpole et al. (1992)	To analyse patients from a melanoma data base	Cohort study	945 patients withpulmonary metases.	1-, 3- and 5-year survival-rates	1-, 3- and 5-year survival-rates: 30%, 9% and 4%	Retrospective analysis	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<ul style="list-style-type: none"> - overall risk of pulmonary metastatic disease? - pulmonary resection as a primary therapy for metastases? - multivariate risk factors for survival? 			survival	<p>Multivariate predictors of improved survival ($p < 0,001$):</p> <ul style="list-style-type: none"> -complete resection of pulmonary disease - longer time for formation of metastases -treatment with chemotherapy -1 or 2 pulmonary nodules - lymph nodes negative for metastases ($p < 0,005$) -histologic type ($p < 0,04$) <p>curative resection for a solitary nodule (n=84) vs. no operation (n=142): 2-year and 5-year survival: 42% versus 20% ($p < 0,001$)</p>	No information about follow up	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Neuman et al. (2007)	to evaluate the natural history of stage-IV melanoma metastatic to the lung and identify factors predictive of survival.	Cohort study	122 patients with stage-IV melanoma and pulmonary metastases	factors predictive of survival survival time to recurrence 5-year-survival	Median survival: 14 months 5-year survival: 8% Factors independently predictive of survival: - solitary pulmonary metastasis (HR 2.7, CI 1.6-4.4, p<0.0005) - absence of extra-pulmonary disease (HR 1.9, CI 1.2-3.1, P=0.01). - metastasectomy (HR 0.42, CI 0.21-0.87, P = 0.02). median survival of patients with metastasectomy vs. no surgical treatment: - 40 vs. 13 months Median time to recurrence: 5 months	Retrospective design No information about staging Small number of patients who received metastasectomy (n=26) Patients with pulmonary metastases and concurrent skin/subcutaneous /distant nodal disease were included Bias: systemic therapy	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>estimated 5-year survival of patients undergoing metastasectomy: 29%.</p> <p>Patient who were followed up 3 and/or 5 years: 3-year- survival: 50% 5-year- survival: 23%</p>		
Andrew et al.(2006)	To describe the experience with pulmonary metastasectomy	cohort study	<p>86 patients 1-4 pulmonary metastases.</p> <p>(10 patients with unknown primary site)</p>	<p>relapse-free survival</p> <p>overall-survival</p> <p>5-year-survival</p>	<p>overall median time to relapse: 8.4 months</p> <p>median survival: 35 months.</p> <p>5-year survival rate: 33%</p> <p>48/86 patients died (median survival time = 24 months),</p> <p>16% of patients</p>	<p>Retrospective design</p> <p>Short follow-up</p> <p>Patients received different postsurgical therapies</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>were relapse-free at a median follow-up of 35 months.</p> <p>median survival of patients with a solitary vs. multiple lesions: 41 vs. 25 months ($P = .05$)</p>		
Schuhan et al. (2011)	to determine the clinical course, outcome and prognostic factors in a subset of patients recently treated by metastasectomy.	Cohort study	<p>30 patients with pulmonary metastases from malignant melanoma who underwent pulmonary resection</p> <p>Complete pulmonary resection in 27 patients</p>	<p>5-year survival rate</p> <p>Median survival</p> <p>prognostic parameter for OS</p>	<p>Cumulative 5-year survival rate after pulmonary resection: 35.1%, median survival: 18.3 months.</p> <p>patients with complete pulmonary vs. patients with incomplete resection: median survival: 20.5 months vs. 13.0 months</p> <p>completeness of resection=no statistically</p>	Small patient cohort	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>prognostic factor for survival.</p> <p>Multivariate analysis: only significant prognostic parameter for overall survival: gender (9.4 months vs. 25.0 months for the female and male group, respectively (P = 0.022)).</p>		
Delaunay et al. (1991)	to assess the value of surgery in terms of survival and to delimit its indications	cohort study	38 patients with pulmonary metastases of malignant melanoma	<p>Overall-survival</p> <p>Disease-free survival</p> <p>5-year survival rate</p>	<p>median survival: 15 months (range 2-144 months).</p> <p>5-year-survival: 20%</p> <p>median disease-free-survival: 10,5 months.</p> <p>Statistical significance in survival (incomplete vs.</p>	<p>Retrospective multicenter study</p> <p>No information about follow-up/recruitment period</p> <p>10 patients received neo-adjuvant treatment</p>	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					radical surgery: p<0,0001)		
Pogrebniak et al. (1988)	To update and reexamine the efficacy of excision of pulmonary melanoma metastases	Cohort study	49 patients with resection of presumed pulmonary metastases from malignant melanoma	survival	Benign disease (n=13), metastatic disease (n=32), lung cancer (n=1) Survival (benign vs. malignant disease): 169 vs. 22 months Median survival after thoracotomy (malignant disease): 13 months. No difference in survival after complete vs. incomplete resection. 2-year-survival for patients with 1 vs. >1 nodule resected: 30% vs. 10%	retrospective study screening methods out of use, questionable transferability to current situation	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Mathisen et al (1979)	To determine the efficacy of resection of pulmonary metastases from malignant melanoma	Cohort study	33 patients who underwent thoracotomy for resection of suspected pulmonary metastases from malignant melanoma	survival	11 patients: non-malignant disease 10 unresectable disease: median survival: 10,5 months (3-20) 12 were rendered disease-free, median survival: 12 months (3-35). 5-year survival: 0%	Retrospective study Small population Population not described Old patient cohort (1957-1978) questionable transferability to current data 10 patients received postoperative chemotherapy	3b-
Subtopic Abdominal/ retroperitoneal metastases							
Sanki et al. (2009)	To assess survival, morbidity and mortality following therapeutic or palliative resection of gastrointestinal (GI) tract melanoma metastases	retrospective prognostic cohort study	117 patients who underwent operations for acute and/or sub-acute symptoms or for imminently symptomatic GI metastases	Mortality Postoperative complications survival	Mortality rate after GI resection: 1.4% post-operative complications-rate: 2,5% 1-, 2- and 5-year		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			detected radiologically		<p>survival rates:</p> <ul style="list-style-type: none"> - for all patients: 57%, 39% and 27% - for patients having palliative resections: 34%, 19% and 0%. <p>The median survival:</p> <ul style="list-style-type: none"> - after surgical resection: 16.4 mo. - after resection with curative intent: 22.6 mo. - following palliative resection: 7.7 mo. <p>significant prognostic indicators of survival (on multivariate analysis):</p> <ul style="list-style-type: none"> - presence of residual intraabdominal disease - presence of non- 		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					GI metastases at the time of surgery or after surgery were the		
Ollila et al. (1996)	To evaluate the role of surgery in the survival of patients with melanoma metastatic to the gastrointestinal (GI) tract	Retrospective prognostic cohort study	124 patients with metastatic melanoma in the stomach, small intestine, colon, or rectum	Operative morbidity and mortality relief of symptoms median and 5-year survival	median DFI: 23.2 (range, 1-154) months. 1 operative death 1 major operative complication After surgery relief of symptoms in 97% median survival in patients with curative resection vs. palliative procedures and nonsurgical interventions: 48.9 vs 5.4 and 5.7 months, respectively prognostic factors for long-term		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>survival (multivariate analysis):</p> <ul style="list-style-type: none"> - complete resection of GI tract metastases - GI tract as the initial site of distant metastases. 		
Hodgson et al. (2007)	To determine the role of resectional surgery in metastatic melanoma of the abdomen	Cohort study	<p>25 patients</p> <p>(5 patients had occult tumours)</p>	<p>Survival</p> <p>morbidity</p> <p>mortality</p>	<p>median survival after abdominal resection: 8.3 (range 0.4-41.1) months.</p> <p>1-year survival: 36%</p> <p>1-year-survival after surgery with curative vs. palliative intend: 89 vs 10%, P < 0.0001)</p> <p>Superior survival in patients with ≤ 2 metastases compared with ≥ 2</p>	<p>Retrospective study</p> <p>Small population</p> <p>No information about follow-up</p>	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>(P = 0.0001)</p> <p>Intent of surgery (curative vs palliative) was the only factor significant on multivariate analysis (P = 0.001).</p> <p>Relief of preoperative symptoms: 87%</p> <p>Operative morbidity: 12%</p> <p>30-day mortality: 4%.</p>		
Mittendorf et al. (2008)	to determine the natural history of melanoma metastasis to the adrenal gland and the appropriate role for surgical intervention	Cohort study	<p>154 patients with adrenal metastasis</p> <p>22 patients underwent surgical resection</p>	surgical treatment survival	<p>median OS: 6.4 months (range 0,2-97 months).</p> <p>median OS for patients with:</p> <ul style="list-style-type: none"> - synchronous metastatic disease: 6.6 months - isolated adrenal 	<p>Retrospective design</p> <p>Small population</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>metastasis: 18.7 months (p<0,0001)</p> <p>median OS for patients with a disease-free interval of: - <1 year: 7 months - >1 year: 11 months (P=0,35).</p> <p>After a median follow-up of 12.6 months, 9/22 (41%) Patients who underwent surgical resection were alive, incl. 7 without recurrence.</p> <p>Survival of patients who underwent surgery vs. those managed nonoperatively (p<0,0001).</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Pawlik et al. (2006)	To evaluate the efficacy of hepatic resection in patients with metastatic ocular and cutaneous melanoma and to assess factors that could affect survival after resection	Cohort study	40 patients with metastatic melanoma involving the liver who were treated with hepatic resection with curative intent	Survival 5-year-survival Time to recurrence	<p>median time to recurrence: 8.3 months</p> <p>median survival: 28.2 months (range, 4.6–93.7 months)</p> <p>5-year survival rate: 10.9%.</p> <p>5-year survival rate for patients with a primary ocular melanoma: 20.5%.</p> <p>5-year survival rate for patients with cutaneous melanoma (P=0.03).</p> <p>No clinicopathologic factors predictive of survival after hepatic resection</p>	<p>Retrospective design</p> <p>Patients with ocular melanoma included</p> <p>Some patients had other metastatic sites (not only liver) which were not operated</p> <p>Bias: 17 patients (70.8%) received some form of systemic therapy</p>	3b
Ricaniadia et al. (1995)	to investigate the role of surgical	Cohort study	68 patients with clinical indications	Complication rate	median survival for patients unsuitable	Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	intervention in patient with GI metastasis and to define the group of patients who would benefit surgical resection.		of involvement of the gastrointestinal (GI) tract with metastatic melanoma 47 patients underwent abdominal surgery	Survival 5-year-survival	for surgery: 2.9 months. Relief of preoperative symptoms after surgery: 73% Postoperative complications: 29% Death within 30 days of surgery: 11% median survival: - after surgery vs. no surgery: 5.66 vs. 2.9 months (P=0.0035) - after complete resection and no other disease vs. resection and other metastasis present: 27,6 vs. 5.1 months - after by-pass procedure: 1,9 months		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					5-year survival: - after complete resection and no other evidence of disease: 28.3% (the other groups had only 1-year survivors)		
Szynglarewicz et al. (2012)	To assess the role of colorectal surgery in the treatment of metastatic melanoma and to identify patients who can most benefit from surgical resection.	Cohort study	34 consecutive patients with skin melanoma who underwent surgical resection of large bowel metastasis 9 patients: emergency surgery for obstruction, 25 patients had an elective procedure. Intent of surgery: curative in 14 patients, palliative in 20 patients	Mortality Morbidity Median survival 1-, 2-, and 5-year survival rates Prognostic factors	postoperative mortality: 0% postoperative morbidity: 9%. Median survival following surgery: 11.5 (4-68) months. 1-, 2-, and 5-year survival rates: 50%, 32%, and 17% respectively. Median survival significantly increased in patients without extra-abdominal metastases, with no evidence of	Small patient cohort No information about R1-Status	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>non-large bowel metastases, if the DFI >24 months and when curative resection was performed.</p> <p>most important prognostic factors on multivariate analysis: apparently complete or palliative resection and the absence or presence of extraabdominal metastases</p>		
de Wilt et al. (2003)	To analyse indications for surgery, complications, and overall survival with the aim of clarifying the indications for surgical treatment in such patients	Cohort study	<p>15 patients who underwent surgical treatment of metastases</p> <p>98 patients were treated conservatively</p> <p>.</p>	<p>Postoperative morbidity</p> <p>Overall survival</p> <p>1-year-survival rate</p> <p>2-year-survival rate</p>	<p>patients with splenectomy: median OS: 11 months 1-year survival rate: 35%, 2-year-survival-rate 21%</p> <p>patients with single splenic lesion and splenectomy:</p>	<p>retrospective design</p> <p>Small patient number</p> <p>Medical/conservative treatment not described in detail, 4 patients who underwent splenectomy were</p>	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>median OS: 23 months. 1-year survival rate: 70%, 2-year-survival-rate: 50%</p> <p>conservatively treated patients: median OS: 4 months. 1-year survival rate: 13%, 2-year-survival-rate 3%</p> <p>survival of patients with splenic metastases treated surgically vs. conservatively: P=0.02</p> <p>Survival after splenectomy with palliative vs. curative intent: P=0,07</p>	<p>included in clinical trials.</p> <p>No information about follow-up</p>	
Berger et al. (1999)	To determine whether surgery influences outcomes	Retrospective cohort study	Fifty patients with melanoma metastatic to the GI tract	Mortality rate survival	operative mortality rate: 2.5% mean survival		3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>times for the unexplored and unresected groups: 4.1 months</p> <p>significantly increased survival:</p> <ul style="list-style-type: none"> - in the partial-resection group (8.9 months) compared with the unresectable group (P<0. 001). - in the complete-resection group (23.5 months) than in the less than complete resection-group (P<0.0001). 		
Khadra et al. (1990)	To examine if a surgical approach of metastases in the GIT is justified.	Cohort study	<p>56 patients with symptomatic melanoma of the gastrointestinal tract (GIT) treated surgically</p> <p>(13 occult primary)</p>	<p>complication rate</p> <p>postoperative survival</p> <p>overall survival</p> <p>time to recurrence</p>	<p>relief of symptoms in 44 patients postoperatively.</p> <p>postoperative complications: 8/56 patients (2 died)</p>	<p>Retrospective design</p> <p>Methods of follow-up not described</p> <p>No information about metastases other than in GIT-</p>	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>mean postoperative OS after 1st vs. 2nd metastases: 11.7 (range 1-60) vs. 3,6 months (range 0-12 months)</p> <p>median time of recurrence: 12 months (range 3-47 months)</p> <p>mean OS for ulcerated vs. non-ulcerated tumor: 46,6 vs. 84,9 months.</p> <p>mean OS when primary tumor <1,5 mm vs. >1,5 mm: 11,7 vs. 9,5 months.</p>	tract Bias: Adjuvant therapy (chemotherapy in 26 patients, radiotherapy in 1 patients, immunotherapy in 4 patients)	
Chua et al. (2010)	To evaluate the efficacy of surgical metastasectomy on survival outcomes.	Retrospective cohort study	23 patients with visceral metastases from melanoma (15 underwent surgical resection)	disease-free interval Overall survival	DFI: 49 (range, 5 to 559) months Median OS: 9 months. 1- and 3-year survival: 39%	Small patient cohort	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>and 30%, respectively.</p> <p>Survival was influenced by - the number of metastases ($P = 0.05$) and the treatment received ($P = 0.03$).</p> <p>After metastasectomy: DFI and OS: 14 and 21 months, respectively. 1- and 3-year survival: 60% and 40%, respectively.</p> <p>Significant longer survival for patients with single site vs. >1 site of metastasis ($P = 0.005$)</p>		
Branum et al. (1991)	To evaluate the role of resection in the management of melanoma	Retrospective cohort study	28 patients with melanoma metastatic to the adrenal gland	Survival 5-year-survival	Mean survival in the group that underwent resection for cure:		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastatic to the adrenal gland				59 months (3 to 112 months) survival in the group with unresectable tumors: 15 months (1.5 to 132 months). 5-year-survival: - 4/8 patients who underwent resection for cure 1/14 patients with unresectable tumors		
Subtopic different metastatic sites							
Wasif et. (2011)	to study the impact of metastasectomy on survival in these patients.	Prognostic factors	4229 patients with stage IV melanoma patients were subdivided into M1a disease (cutaneous metastases) and Mbc disease (visceral	Median survival 5-year-survival	median survival of the study population: 7 months. Patients who underwent metastasectomy (33.6%) vs. patients without	Those who had metastasectomy performed were compared with patients that did not.	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			metastases).		<p>metastasectomy: median OS: 12 months vs 5 months 5-years OS: 16% vs. 7% (P < 0.001).</p> <p>In patients with M1a disease (n = 1,994): median survival of 14 months vs. 6 months, 5-year OS: 20% vs. 9% (P < 0.001).</p> <p>Younger age and diagnosis from 2001 to 2006 were predictors of metastasectomy. Metastasectomy was an independent and significant predictor of survival for the entire cohort (HR 0.59, 95% CI 0.55-0.63).</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Essner et al (2004)	to evaluate the outcome of patients with advanced-stage melanoma treated by surgical resection with curative intent.	Cohort study	4426 patients stage IV melanoma, 1574 (35%) underwent surgical resection with curative intent;	5-year-survival rate predictive factors on survival	5-year survival rate: patients who underwent surgical resection vs. nonsurgical treatment: mean±SD, 23%±2% vs. 6%±5% (P<0.001) 5-year survival rate: patients with a solitary vs. ≥4 metastases: 29%±2% vs. 11%±3% (P<0.001) median survival is slightly higher for patients with skin or subcutaneous sites (alone) than for LN, GIT or lung sites, no significant differences in the estimated 5-year survival rate (P=0.29)	retrospective study No information about adjuvant therapies	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>predictive factors on multivariate analyses:</p> <ul style="list-style-type: none"> - earlier primary tumor stage (I vs II) ($P < 0.001$) - absence of intervening stage III metastases ($P = 0.02$) - solitary metastasis ($P < 0.001$) - disease-free interval > 36 months from AJCC stage I or II to stage IV ($P = 0.005$) 		
Brand et al. (1997)	to identify important prognostic factors associated with Stage IV melanoma.	Retrospective prognostic cohort study	<p>3258 melanoma patients</p> <p>442 melanoma patients with distant metastases</p>	<p>Overall survival</p> <p>Prognostic factors</p>	<p>median survival time: 7 months</p> <p>2-year, 5-year, and 10-year survival rates: 11.9%, 6.7%, and 4.7%, respectively.</p> <p>Of the modalities of therapy given, only surgery was</p>		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>associated with prolonged survival (P< 0.0001)</p> <p>Factors significantly related to short term survival:</p> <ul style="list-style-type: none"> - primary metastasis to the skin (P = 0.006) - the brain (P = 0.015) - >1 metastatic site (P = 0.002) - Karnofsky performance status <80 (P = 0.0035) - subsequent >/=2 new metastatic sites (P = 0.0025) 		
Tauceri et al (2009)	to agree on the role of surgery in patients with metastatic melanoma	cohort study	84 consecutive patients operated on for stage IV melanoma	<p>survival</p> <p>1-, 3- and 5-year-survival rate</p> <p>Mortality</p> <p>morbidity</p>	<p>postoperative mortality: 0</p> <p>overall morbidity: 15%.</p> <p>minimal and maximal survival:</p>	<p>retrospective design</p> <p>bias: 90.5% underwent adjuvant therapies</p>	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>1.5 and 142.5 months, respectively.</p> <p>mean OS: 56.7 months (1 year: 72.1%, 3 years: 46.5%, 5 years: 23.16%).</p> <p>survival of reiterative surgery vs. single surgery: 62.7 vs 42.4 months, median 50.9 vs 16.0, p=0.03.</p> <p>Reiterative surgery was shown as an independent prognostic factor (p<0.05).</p>		
Ollila et al. (1999)	To examine whether a 2 nd metastasectomy could prolong the survival of patients with recurrent stage IV melanoma.	Retrospective cohort study	131 patients who developed recurrent stage IV diseases	DFI to recurrence Survival 5-year-survival	<p>Median DFI: 8 (range 0.6–91.8) months.</p> <p>Median survival: 18.2 months after complete</p>	<p>Possibly overlapping population/ Ollila et al. 1996</p> <p>2 gynecologic</p>	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>metastasectomy vs. 12.5 months or 5.9 months after palliative surgical procedure or nonsurgical management, respectively.</p> <p>5-year survival: 20.0% after complete surgical metastasectomy vs. 7.0% and 2.1% after palliative surgical and nonsurgical intervention, respectively.</p> <p>prognostic factors for survival: - prolonged DFI (P=0,0001) - complete surgical metastasectomy (P=0,0001)</p>	tumor sites included	
Gohl et al. (1996)	To examine the value of surgical treatment of	Cohort study	In 174 cases surgery was performed, in 70	Survival	Median survival - after R0 (curative surgery): 13	Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	distant metastases of malignant melanoma		patients with curative intent. 15 patients with occult melanoma.		<p>months</p> <ul style="list-style-type: none"> - R1/R2: 6 months. - Patients without treatment: 3 months <p>statistically significant difference in 1-year-survival for patients who underwent curative surgery vs.palliative surgery.</p> <p>5-year-survival and 10-year-survival after curative surgery: 24% and 7% respectively</p>	<p>No information about adjuvant therapy</p> <p>Staging of patients not described</p>	
Karakousis CP et al. (1994)	To evaluate surgical treatment during the management of patients with a small number of resectable lesions in an effort to prolong their life	Cohort study	114 with disseminated melanoma amenable to surgical resection	<p>Survival</p> <p>Estimated 5-year-survival</p> <p>5-year-survival rate</p>	<p>Median survival after metastasectomy: 19 months</p> <p>estimated 5-year survival rate: 22%.</p> <p>5-year survival rate</p>	<p>Retrospective design</p> <p>bilateral nodal metastasis or spread from one groin to the contralateral groin was considered</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>for those with:</p> <ul style="list-style-type: none"> -distant subcutaneous metastases: 33% - distant LN metastases: 22% - pulmonary metastases: 74% (P=0.72). <p>5-year survival rate for :</p> <ul style="list-style-type: none"> - combined group of s.c. and nodal metastases: 28% - pulmonary and visceral sites: 17% <p>Significant prognostic parameters:</p> <ul style="list-style-type: none"> - thickness of the primary melanoma (p=0.05) - number of metastatic lesions (p=0.03) - prior disease-free interval (p=0.05) . 	<p>likely to be regional spread and these patients were excluded</p> <p>93% underwent chemotherapy, 27% radiotherapy, 5% no further therapy</p>	
Overett et al.	To review	Cohort study	176 patients who	Survival	estimated 2- and	Retrospective	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(1985)	clinicopathologic factors that determine the successful resection of tumor, survival, and quality of life		underwent surgical intervention for distant metastases of	2- and 5-year-survival-rate Mortality Relapse rate	5-year survival rate: 21% and 13%, respectively median survival time: 8.5 months. Estimated 2-year and 5-year survival-rate after complete resection of single-site- vs. multiple-site lesions: 47% and 33% vs. 17% and 9%, respectively (P < 0.01). Operative mortality Rate: 1.4% relapse-rate: 66% Median interval to relapse in case of incomplete vs. complete resection: 3 vs. 9 months (P = 0.07). 5-years survival	design Old patient cohort (1965-1979), questionable transferability to current situation	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>after repeated resection: 20%</p> <p>median survival in case of repeated resection vs. incomplete resection of new disease: 26 vs. 8 months (P<0.0005)</p>		
Garbe (1996)	to identify patients with prolonged survival in stage IV disease and to analyse the possible impact of therapy on the course of the disease.	Retrospective review	<p>263 patients having stage IV melanoma</p> <p>111 patients: surgery and/or radiation therapy. (17 surgery alone)</p> <p>89 patients: systemic treatment</p> <p>48 patients: both systemic and local therapy.</p> <p>111 patients: no treatment.</p>	Survival	<p>22 patients treated with multimodality survived > 24 months (median Survival: 33 months)</p> <p>16: both systemic treatment and surgery and/or radiation, 3: systemic drug therapy, 3: only local treatment.</p> <p>12/22 patients became tumour free after initial surgery or radiation.</p>	Confounder adjuvant therapy	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					2-year-survival for patients without treatment:0%		
Karakousis et al. (1983)	to identify, or confirm, favorable characteristics that may improve palliation	Cohort study	79 consecutive patients with resectable, recurrent malignant melanoma were treated with surgical excision	Survival	<p>significant survival difference between Stage IV survivors (36 months) and those who manifested disease progression (12 months) (P < 0.02).</p> <p>Characteristic of those patients who remain disease free:</p> <ul style="list-style-type: none"> - initial presence </=3 metastatic lesions - long prior disease-free interval 	<p>Retrospective design</p> <p>Small population</p> <p>No information about staging</p> <p>Poor information about follow-up</p>	3b-
Wornom et al. (1983)	To examine the efficacy of surgery as palliative treatment in 65 patients with distant metastatic	Cohort study	65 patients with distant metastatic melanoma amenable to surgical	Survival mortality	<p>overall operative mortality: 11%</p> <p>Relief of symptoms after excision of:</p> <ul style="list-style-type: none"> - 77% of brain 	<p>Retrospective design</p> <p>Most patients received chemotherapy</p>	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma amenable to surgical excision				<p>metastases, - 100% of lung metastases - 88% of distant LN and s.c. metastases - 100% of abdominal metastases</p> <p>Median survival after excision of: - brain metastases: 8 months - lung metastases: 9 months - abdominal metastases 8 months - distant s.c., LN metastases: 15 months.</p> <p>median survival of patients with - combined visceral and resected superficial metastases: 14 months, 5-year</p>	<p>No information about staging</p> <p>No detailed information about population</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>survival: 0% - resection of superficial metastases and no detectable evidence of visceral metastasis: 17 months. 5-year survival: 14%</p> <p>2-year survival: 29% for both groups.</p>		
Feun et al. (1982)	To discuss the natural history of Stage IVA melanoma and the role of adjuvant therapy	Cohort study	102 patients with malignant melanoma who had distant metastases surgically resected and were judged to be clinically free of disease	<p>survival</p> <p>disease-free-survival</p>	<p>median survival: 18 months.</p> <p>survival depending on site of resected metastases: - brain: 15 months - lung: 16 months - intraabdominal 18 months - skin and/or LN 23 months</p> <p>Disease-free interval not influenced by site</p>	<p>Retrospective design</p> <p>35 patients who had surgery vs. 67 patients who received adjuvant therapy</p>	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>Similar survival of patients who had metastases resected from several organs at the same time and patients with one resected site</p> <p>group treated with surgery only vs. adjuvant group: median disease-free interval and survival: 6 and 16 months vs. 6 and 21 months, respectively</p>		

4.4.4. Literatur

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5. AG Adjuvante Therapie

5.1. Frage IV.1. Adjuvante Chemotherapie - Adaptation

5.1.1. Synopse Quelleitlinien

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
Beeinflusst eine adjuvante Chemotherapie das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?	Nein Kein zytotoxisches Medikament hat eine Überlegenheit gegenüber Beobachtung gezeigt	Nein Keine Evidenz für adjuvante Chemotherapie nach erfolgter chirurgischer Therapie	Nein Dacarbazin verbessert nicht das Überleben in adjuvanter Situation	Nein Keine Verbesserung des Gesamtüberlebens durch adjuvante Chemotherapie
Zugrunde liegende Evidenz	S. 93, keine Verknüpfung mit zugrundeliegender Evidenz	Manual: S. 81, keine Verknüpfung mit zugrundeliegender Evidenz Evidenz Review: S. 537 („keine Rolle im adjuvanen Setting“) 10 Studien zitiert	Niveau A 5 randomisierte Studien wurden untersucht + Bezug auf Cancer Care Ontario 2002	Ergebnis aus 9 random. Studien

Update Recherche am 11.01.2011

Suchstrategie Medline: (melanoma[tiab] OR melanoma[MeSH]) AND (chemotherapy[tiab] OR vindesine[tiab] OR dacarbazine[tiab] AND adjuvant[tiab])

Treffer: 483, Auswahl: Eigentler et al. 2008, Retsas et al. 1994

Literatur:

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5.1.2. Empfehlung und Hintergrundtext französische Quell Leitlinie
Quelleitlinie: Recommandations pour la Pratique Clinique : Standards, Options et Recommandations 2005

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.39)	Übersetzung
<p>DESCRIPTION DES ÉTUDES Au total, 5 essais randomisés ont été retenus pour l'analyse critique. Aucun nouvel essai randomisé n'a été retrouvé dans le cadre de la mise à jour 2005. Deux essais ont comparé l'administration de dacarbazine versus observation *114, 130+, un essai a comparé la dacarbazine versus placebo [127] et 1 essai a évalué l'association de dacarbazine à d'autres substances versus observation *131+. Un seul essai a étudié le méthyl-CCNU [116]. Le CCOPGI a révisé en 2002 la synthèse méthodique avec analyse quantitative initialement publiée en 1997 [12].</p> <p>SURVIE GLOBALE Aucune des 4 études qui ont évalué la dacarbazine (DITC) n'a rapporté de différence significative en termes de survie globale [114, 117, 127, 130, 131]. L'analyse poolée des données réalisée par le CCOPGI sur 7 essais randomisés n'a pas retrouvé de différence significative sur la survie globale à 3 ans (odds ratio = 1,03 [IC95 : 0,74-1,43] [12]. L'étude de Fisher et al. qui a comparé méthyl-CCNU versus observation n'a pas retrouvé de différence significative entre les deux bras comparés [116].</p> <p>COMMENTAIRES MÉTHODOLOGIQUES ET CLINIQUES La dacarbazine est la molécule qui a été la plus étudiée, seule ou association avec le BCG. Un seul essai randomisé a étudié l'efficacité du méthyl-CCNU sur une population de 136 patients, ce qui limite la portée des conclusions qui pourront être établies concernant cette molécule.</p> <p>CONCLUSIONS DE LA LITTÉRATURE La dacarbazine en situation adjuvante n'améliore pas la survie des patients porteurs d'un mélanome cutané opéré (niveau de preuve A). Les données disponibles sont insuffisantes pour conclure sur le bénéfice/risque du méthyl-CCNU en situation adjuvante chez les patients porteurs d'un mélanome cutané.</p> <p>Standards, Options et Recommandations Les traitements adjuvants systémiques à base de levamisole, BCG ou dacarbazine ne sont pas recommandés en dehors d'essais thérapeutiques.</p>	<p>Beschreibung der Studien Insgesamt wurden 5 randomisierte Studien für eine kritische Analyse ausgewählt. Im Rahmen des Update 2005 wurde keine neue randomisierte Studie gefunden. Zwei Studien haben Dacarbazin versus Beobachtung verglichen [114,130], eine Studie hat Dacarbazin gegen Placebo verglichen [127] und 1 Studie hat Dacarbazin in Kombination mit anderen Substanzen versus Beobachtung evaluiert. [131] Nur eine Studie untersuchte Methyl-CCNU [116]. Die CCOPGI hat 2002 ein systematisches Review von 1997 mit Metaanalyse überarbeitet [12].</p> <p>Gesamtüberleben Keine der 4 Studien, die Dacarbazin untersucht haben, haben einen signifikanten Unterschied in Bezug auf das Gesamtüberleben gezeigt [114, 117, 127, 130, 131]. Die gepoolte Analyse der Daten, die durch die CCOPGI aus 7 randomisierten Studien durchgeführt wurde, fand keinen signifikanten Unterschied bezogen auf das Gesamtüberleben nach 3 Jahren (odds ratio = 1,03 [IC95: 0,74-1,43] [12]. Die Studie von Fisher et al., die Methyl-CCNU versus Beobachtung verglichen hat, fand keinen signifikanten Unterschied zwischen den Vergleichsarmen [116].</p> <p>Methodologische und Klinische Kommentare Dacarbazin ist die am meisten untersuchte Substanz, allein oder zusammen mit BCG. Nur eine randomisierte Studie überprüfte die Wirksamkeit von Methyl-CCNU an einer Population von 136 Patienten, dies beschränkt die Aussagekraft dieser Substanz.</p> <p>Schlussfolgerungen aus der Literatur Dacarbazin verbessert nicht das Überleben von Patienten mit operiertem kutanem Melanom in adjuvanter Situation (Level A). Die Daten für Methyl-CCNU sind insuffizient um über Benefit/Risiko in adjuvanter Situation bei Patienten mit kutanem Melanom zu entscheiden.</p> <p>Standard, Optionen und Empfehlungen Eine adjuvante systemische Therapie mit Levamisole, BCG oder Dacarbazin wird ausserhalb von Therapiestudien nicht empfohlen.</p>

Literatur:

12. CCOPGI, (Cancer Care Ontario Practice Guidelines Initiative). Systemic adjuvant therapy for patients at high risk for recurrent melanoma. Practice Guideline Report No 8-1 [online]. 2002. Available: URL: http://www.cancercare.on.ca/index_practiceGuidelinesandEvidencesummaries.htm#list
131. Randomized controlled trial of adjuvant chemoimmunotherapy with DTIC and BCG after complete excision of primary melanoma with a poor prognosis or melanoma metastases. *Can Med Assoc J* 1983;128:929-933
116. Fisher RI, Terry WD, Hodes RJ, et al. Adjuvant immunotherapy or chemotherapy for malignant melanoma. Preliminary report of the National Cancer Institute randomized clinical trial. *Surg Clin North Am* 1981;61:1267-1277
130. Hill GJ, 2nd, Moss SE, Golomb FM, et al. DTIC and combination therapy for melanoma: III. DTIC (NSC 45388) Surgical Adjuvant Study COG PROTOCOL 7040. *Cancer* 1981;47:2556-2562
127. Lejeune F, Macher E, Kleeberg UR, Rumke P, Prade M, Thomas D, et al. An assessment of DTIC versus levamisole or placebo in the treatment of high risk stage I patients after removal of a primary melanoma of the skin: a phase III adjuvant study (EORTC protocol 18761). *Eur J Cancer* 1988;24:S81-90.
114. Veronesi U, Adamus J, Aubert C, et al. A randomized trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. *N Engl J Med* 1982;307:913-916

5.1.3. Empfehlung und Hintergrundtext kanadische Quell Leitlinie

Quellleitlinie: Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma: Updated Guideline Recommendations (Cancer Care Ontario) 2009

KEY EVIDENCE Chemotherapy

Data from randomized controlled trials do not suggest an improvement in OS with adjuvant chemotherapy alone for patients with resected high-risk melanoma (10 trials).

OUTCOMES Chemotherapy

Ten trials of chemotherapy are summarized in Table 9 (33,41,45-52). None of the trials were limited to high-risk patients. Two trials compared dacarbazine with observation (45,46), one compared dacarbazine with placebo (33), and five trials evaluated dacarbazine in combination with other agents (including immunomodulatory agents such as BCG) that are not commonly used at present, against observation alone (47-51). There was also a trial of methyl lomustine (methyl-CCNU) versus control (41) and a trial of carmustine (BCNU) combined with actinomycin-D and vincristine versus control (52). In the largest study of chemotherapy (46), 47% of patients treated with dacarbazine were alive after three years compared with 42% of control ($p=0.64$). Only the study by Hansson et al (49) reported a statistically significant survival benefit for patients who received chemotherapy as adjuvant treatment ($p<0.025$). That was the smallest of the chemotherapy trials, with only 26 patients randomized to three treatment groups. Data from the two active-treatment arms (da-carbazine alone and dacarbazine in combination with CCNU and vincristine) were combined and compared with results for nine patients in the control group, but that trial is far too small to permit any conclusions. Three-year mortality rates, from the text or from survival curves in the published reports from seven studies, were pooled and are presented in Figure 3. Three studies were not included in the meta-analysis because the number of deaths at three years could not be

ascertained (45,51) or because no survival data were reported (47). The mortality risk ratio from the pooled analysis (0.94; 95% CI, 0.84 to 1.06; p=0.3) does not demonstrate any difference between chemotherapy and control. No heterogeneity was found among the results from these studies (p=0.52). Because response rates to chemotherapy in advanced disease have been unsatisfactory, there is no current interest in pursuing chemotherapy alone in the adjuvant setting.

Literatur:

48. Randomized controlled trial of adjuvant chemoimmunotherapy with DTIC and BCG after complete excision of primary melanoma with a poor prognosis or melanoma metastases. *Can Med Assoc J* 1983;128:929-933
41. Fisher RI, Terry WD, Hodes RJ, et al. Adjuvant immunotherapy or chemotherapy for malignant melanoma. Preliminary report of the National Cancer Institute randomized clinical trial. *Surg Clin North Am* 1981;61:1267-1277
49. Hansson J, Ringborg U, Lagerlof B, et al. Adjuvant chemotherapy of malignant melanoma. A pilot study. *Am J Clin Oncol* 1985;8:47-50
45. Hill GJ, 2nd, Moss SE, Golomb FM, et al. DTIC and combination therapy for melanoma: III. DTIC (NSC 45388) Surgical Adjuvant Study COG PROTOCOL 7040. *Cancer* 1981;47:2556-2562
47. Jacquillat C, Banzet P, Maral J. Clinical trials of chemotherapy and chemoimmunotherapy in primary malignant melanoma. *Recent Results Cancer Res* 1982;80:254-258
52. Karakousis C, Blumenson L. Adjuvant chemotherapy with a nitrosourea-based protocol in advanced malignant melanoma. *Eur J Cancer* 1993;29A:1831-1835
50. Karakousis CP, Emrich LJ. Adjuvant treatment of malignant melanoma with DTIC + estracyt or BCG. *J Surg Oncol* 1987;36:235-238
33. Lejeune FJ, Macher E, Kleeberg U, Rumke P, Prade M, Thomas D, et al. An assessment of DTIC versus levamisole or placebo in the treatment of high risk stage I patients after surgical removal of a primary melanoma of the skin. *Eur J Cancer Clin Oncol*. 1988;24 Suppl 2:S81-S90.
46. Veronesi U, Adamus J, Aubert C, et al. A randomized trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. *N Engl J Med* 1982;307:913-916

5.2. Frage IV.2. Adjuvante Vakzinierung – Adaptation

5.2.1. Synopse Quellleitlinien

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
Beeinflusst eine adjuvante Vakzinationstherapie das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?	Nein Keine Überlegenheit von Vakzinierungen gegenüber Beobachtung	Nein Verwendung von Impfstoffen ist experimentell	Nein Aucun des procédés de vaccination utilisés jusqu'à ce jour n'a mis en évidence une différence significative sur la survie	Nein

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
			<p>sans récurrence ou sur la survie globale des patients atteints d'un mélanome cutané réséqué avec ou sans envahissement ganglionnaire et dont l'épaisseur est supérieure à 1,5 mm (niveau de preuve B1). Keine Vakzinierung hat einen signifikanten Unterschied zwischen rezidivfreiem Überleben oder Gesamtüberleben zeigen können (Td >1,5 N0 und N+)</p> <p>Niveau B1 Entspricht in etwa Level of Evidence nach Oxford 1b</p>	
Schlüsselempfehlung	Zur Vakzinierung keine Schlüsselempfehlung	Zur Vakzinierung keine Schlüsselempfehlung	<p>Les procédés de vaccination ne sont pas indiqués dans le traitement adjuvant des patients opérés d'un mélanome cutané en dehors d'essais thérapeutiques. Recommandation: Option</p>	Zur Vakzinierung keine Schlüsselempfehlung

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
			Vakzinierungstherapien sind als adjuvante Behandlung bei Patienten nach Operation eines kutanen Melanoms ausserhalb von klinischen Studien nicht indiziert.	
Zugrunde liegende Evidenz	S. 93, keine Verknüpfung mit zugrundeliegender Evidenz	Manual: S. 81, keine Verknüpfung mit zugrundeliegender Evidenz Evidenz Review: S.538, kein verbessertes OS, manche zeigen verbessertes rezidivfreies Überleben, Vakzinierung wichtiges Forschungsfeld 7 Studien	Diskutiert werden Studien mit:BCG, GMK, Melanomzell-Lysat (VMCL), Melanom Oncolysat (VMO), allogenes Melanomvakzin, polyvalentes Melanomvakzin, GM2-KLH, TIL	9 randomisierte Studien wurden zusammengefasst (virales Oncolysat, Ganglioside, polyvalentes Vakzin, Melanomzell-Lysat, „whole-cell“Vakzin) aufgrund der Heterogenität der Studien wurden die Daten nicht gepoolt. Keine Studie konnte ein verbessertes Überleben zeigen. Eine Subgruppenanalyse SWOG 9035 zeigte einen Überlebensbenefit für HLA-A2 und/oder HLA-C3 positive Patienten der Vakzin-Gruppe, dazu wurde jedoch keine klinische Empfehlung abgeleitet Im Update 10 Studien: EORTC18961, signifikant

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
				schlechteres Gesamtüberleben für GM2- KLH21 Arm

5.2.2. Empfehlung und Hintergrundtext französische Quell Leitlinie

Quelleitlinie: *Recommandations pour la Pratique Clinique : Standards, Options et Recommandations 2005*

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.36)	Übersetzung
<p>VACCINATION</p> <p><i>BCG thérapie</i></p> <ul style="list-style-type: none"> · Description des études <p>Deux essais randomisés ont été retenus et ont comparé l'administration de BCG <i>versus</i> observation d'une part, et BCG <i>versus</i> l'association BCG et dacarbazine (<i>Tableau XV</i>) [114, 115]. L'étude de L'OMS a concerné 761 patients randomisés en 4 bras (observation <i>versus</i> BCG seul <i>versus</i> dacarbazine seule <i>versus</i> association BCG et dacarbazine) [114] L'étude de Agarwala <i>et al.</i> présente les résultats à long terme d'un essai sur 734 patients mené entre 1974 et 1978 [115]. Les patients ont été randomisés selon 4 bras constituant 2 cohortes. La première cohorte a comparé BCG <i>versus</i> observation et la seconde BCG et dacarbazine <i>versus</i> BCG seul.</p> <ul style="list-style-type: none"> · Survie globale <p>Aucun des 2 essais n'a mis en évidence une différence significative en termes de survie globale dans les différents bras comparés [114, 115]. Dans une analyse en sous-groupe, l'étude de l'OMS a observé une différence</p>	<p>Vakzinierung</p> <p><i>BCG Therapie</i></p> <ul style="list-style-type: none"> · Beschreibung der Studien <p>Zwei randomisierte Studien wurden ausgewählt und haben die Gabe von BCG <i>versus</i> Beobachtung einerseits und BCG <i>versus</i> gemeinsame Gabe von BCG und Dacarbazin verglichen (Tab. XV) [114, 115]. Die Studie der WHO betraf 761 randomisierte Patienten in 4 Armen (Beobachtung <i>versus</i> BCG allein <i>versus</i> DTIC allein <i>versus</i> BCG plus DTIC) [114]. Die Studie von Agarwala <i>et al.</i> präsentierte die Langzeitergebnisse einer Studie an 734 Patienten, die zwischen 1974 und 1978 durchgeführt wurde [115]. Die Patienten wurden in 4 Arme randomisiert die Teil zweier Kohorten waren. Die erste Kohorte verglich BCG <i>versus</i> Beobachtung, die zweite BCG plus DTIC <i>versus</i> BCG allein.</p> <ul style="list-style-type: none"> · Gesamtüberleben <p>Keine der zwei Studien hat einen signifikanten Unterschied in Bezug auf das Gesamtüberleben in den Vergleichsarmen gezeigt [114, 115]. In einer</p>

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.36)

significative sur la survie globale en faveur du traitement par BCG pour les patients présentant 2 à 3 ganglions envahis (45 % *versus* 31,7 % à 3 ans ; p = 0,01).

- Survie sans récurrence

Aucun des 3 essais n'a mis en évidence une différence significative en termes de survie globale dans les différents bras comparés [114-116].

- Toxicité

Les résultats de toxicité ont été rapportés dans les 2 études [114, 115], mais seule l'étude de Agarwala *et al.* a présenté des résultats détaillés. Aucune toxicité létale n'a été rapportée. Des adénopathies régionales et des réactions systémiques corrélées au traitement par le BCG ont été observées dans 10 à 13 % des cas [115].

- Commentaires cliniques et méthodologiques

Les résultats de l'analyse en sous-groupes réalisée dans l'étude de l'OMS sont méthodologiquement très critiquables [114]. D'une part, l'analyse en sous-groupe n'était pas prévue initialement dans le protocole et, d'autre part, l'existence de ce résultat isolé n'a pas de cohérence clinique, puisque la différence de survie n'est significative que pour le sous-groupe de patients avec 2 ou 3 ganglions envahis, ce qui rend ces résultats difficilement interprétables.

Vaccins mélaniques

- Description des études

Quatre essais randomisés sont disponibles :

- 2 essais ont comparé un vaccin mélanique versus observation [117-119] (Tableau XVI),
- 2 essais ont comparé l'administration d'un vaccin mélanique versus placebo [120-122] (Tableau XVII).

Au total, 1 677 patients ont été randomisés dont 1 230 évaluables. Aucune des 4 études n'a inclus de patients porteurs d'un mélanome dont l'épaisseur était inférieure à 1,5 mm. Les interventions évaluées dans les 4 essais randomisés ont été :

Übersetzung

Subgruppenanalyse fand sich in der Studie der WHO einen signifikanten Unterschied für das Gesamtüberleben zugunsten einer Behandlung mit BCG für Patienten mit 2-3 positiven Lymphknoten. (45 % *versus* 31,7 % nach 3 Jahren ; p = 0,01).

- Rezidivfreies Überleben

Keine der drei Studie zeigte einen signifikanten Unterschied in Bezug auf das Gesamtüberleben in den unterschiedlichen Vergleichsarmen [114-116].

- Toxizität

Ergebnisse zur Toxizität wurden in beiden Studien berichtet [114, 115], aber nur die Studie von Agarwala *et al.* präsentiert detaillierte Ergebnisse. Keine letale Toxizität wurde berichtet. Regionale Adenopathien und Systemreaktionen wurden korrelierten in 10 bis 13% mit einer Behandlung mit BCG [115].

- Klinische und Methodische Kommentare

Die Ergebnisse der Subgruppenanalyse die in der Studie der WHO durchgeführt wurde sind methodisch sehr kritisierbar [114]. Zum einen war die Subgruppenanalyse ursprünglich nicht im Protokoll vorgesehen und, zum anderen hat dieses isolierte Ergebnis keinen klinischen Zusammenhang, da der Unterschied im Überleben nur für die Subgruppe mit 2 oder 3 positiven Lymphknoten signifikant war, wodurch diese Ergebnisse schwierig zu interpretieren sind.

Melanom Impfstoffe

- Beschreibung der Studien

Vier randomisierte Studien stehen zur Verfügung:

- Zwei Studien haben einen Melanom Impfstoff versus Beobachtung verglichen observation [117-119] (Tab. XVI),
- Zwei Studien haben die Gabe eines Melanom Impfstoffes versus Placebo verglichen [120-122] (Tab. XVII).

Insgesamt wurden 1 677 Patienten randomisiert, von denen 1 230 auswertbar waren. Keine der vier Studien hat Melanompatienten mit einer Tumordicke von weniger als 1,5mm eingeschlossen. Die untersuchten Interventionen in

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.36)

- lysat cellulaire de vaccin mélanique (VMCL) [117],
- lysat de cellules tumorales irradiées (Melacine®) provenant de deux lignées allogéniques + un adjuvant [118, 119],
- vaccin issu de quatre lignées allogéniques + virus de la variole atténué [120, 121],
- vaccin issu de trois lignées allogéniques et une lignée xénogénique + un adjuvant (aluminium) [122]

· **Survie globale**

Trois des 4 essais randomisés disponibles ont évalué l'impact sur la survie d'un vaccin mélanique versus placebo ou observation [117, 120-122]. La survie globale était le critère de jugement secondaire pour ces études. Aucune différence de survie globale n'a été mise en évidence après un suivi médian variable selon les études compris entre 2,5 ans et 8 ans. Dans le quatrième essai, le suivi n'a pas été suffisant pour permettre l'analyse de la survie globale [118, 119].

· **Survie sans récurrence**

Les 4 essais randomisés disponibles ont évalué l'impact sur la survie sans rechute d'un vaccin mélanique versus placebo ou observation. La survie sans rechute était le critère de jugement principal pour 3 études ; le critère de jugement principal n'était pas précisé pour la quatrième étude. Aucune différence significative de survie sans rechute n'a été retrouvée. Des analyses en sous-groupes ont été proposées dans certaines études. L'étude SOGT-9035 a notamment évalué l'interaction entre antigènes HLA et la survie sans récurrence [119]. La survie sans récurrence a été augmentée dans le groupe vaccin chez les patients qui exprimaient 2 ou plus de 5 antigènes de classe I (97 patients traités par vaccin versus 78 patients dans le groupe observation ; p = 0,0002). Avec les antigènes HLA A2 et C3, la survie sans rechute a été de 77

Übersetzung

den vier randomisierten Studien waren:
 Zelllysate Impfstoff (VMCL) [117]
 Lysat aus bestrahlten Tumorzellen (Melacine®) aus zwei allogenen Linien plus ein Adjuvant [118, 119],
 Impfstoff aus vier allogenen Linien plus abgeschwächtes Varizellen Virus [120,121],
 Impfstoff aus drei allogenen Linien und einer xenogenen Linie plus ein Adjuvant (Aluminium) [122]

· **Gesamtüberleben**

Drei der vier randomisierten verfügbaren Studien haben den Einfluss auf das Überleben eines Melanom Impfstoffes versus Placebo oder Beobachtung untersucht [117, 120-122]. Das Gesamtüberleben war der sekundäre Endpunkt dieser Studien. Einen Unterschied im Gesamtüberleben konnte in keiner der Studien nachgewiesen werden, die ein medianes Follow up zwischen 2,5 und 8 Jahren hatten. In der vierten Studie war das Follow up für eine Analyse des Gesamtüberlebens nicht ausreichend. [118, 119].

· **Rezidivfreies Überleben**

Die vier verfügbaren randomisierten Studien haben den Einfluss auf das rezidivfreie Überleben eines Melanom Impfstoffes versus Placebo oder Beobachtung untersucht. Das rezidivfreie Überleben war der primäre Endpunkt in Drei Studien, für die vierte Studie war der primäre Endpunkt nicht klar. Es wurde kein signifikanter Unterschied im rezidivfreien Überleben gefunden. In einigen Studien wurden Subgruppenanalysen vorgeschlagen. Die Studie SOGT-9035 beinhaltet eine Untersuchung der Interaktion zwischen HLA Antigenen und rezidivfreiem Überleben [119]. Ein verlängertes rezidivfreies Überleben wurde in der Impfstoff Gruppe unter den Patienten die 2 oder mehr als 5 Antigene der Klasse I exprimierten, beobachtet (97 mit Impfstoff behandelte Patienten versus 78 Patienten im Beobachtungsbereich; p = 0,0002). Mit den Antigenen HLA A2 und C3 war das rezidivfreie Überleben

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.36)

% dans le groupe vaccin versus 64 % dans le groupe observation (p = 0,004).

· Toxicité

La toxicité a été évaluée dans les 4 études [117, 118, 121, 122]. Les données de toxicité sont clairement présentées dans 2 des 4 études. Globalement, peu d'effets indésirables ont été observés. Dans l'étude de Sondak et al., 9 % des patients ont présenté une toxicité de grade 3 (réactions locales sévères, malaises et fatigue, troubles visuels, fièvre, diarrhées, thrombopénies et éruptions cutanées), 64 % ont présenté des toxicités de grade 2 et 23 % ont présenté des toxicités de grade 1 [118]. L'équipe de Hersey *et al.* a essentiellement observé des toxicités de grade 2 (érythèmes et ulcération au site d'injection chez 47 % des patients ; lymphopénie pour 33 % d'entre eux) et de grade 1 (malaises et fièvre respectivement chez 35 % et 20 % des patients).

· Commentaires méthodologiques et cliniques

Toutes les études ont réalisé les analyses en intention de traiter. Trois des 4 études présentent clairement le calcul du nombre de patients *a priori* (sur la survie sans rechute) [117-119, 122]. L'étude de Bystryn *et al.* a été arrêtée prématurément et n'a porté que sur 38 patients au lieu des 210 patients initialement prévus. De ce fait, le suivi n'a pas été suffisant (inférieur à 2 ans pour la majorité des patients) et n'a pas permis l'analyse de la survie globale [122]. Pour 3 des 4 études, les populations étudiées peuvent être appliquées à la pratique courante [117-119, 122]. En revanche, dans l'étude de Wallack *et al.* la population traitée est un peu complexe et hétérogène par rapport à la pratique courante bien que correspondant à des types cliniques définis et reconnus par la classification AJCC. Toutes les variables pertinentes n'ont pas été prises en compte lors de la randomisation, puisque seul le nombre de ganglions envahis a été considéré [120-121].

Übersetzung

77% in der Impfstoff Gruppe versus 64% im Beobachtungsarm (p = 0,004).

· Toxizität

Die Toxizität wurde in allen vier Studien untersucht [117, 118, 121, 122]. Daten zur Toxizität sind in zwei der vier Studien klar dargestellt. Insgesamt wurden nur wenig Nebenwirkungen beobachtet. In der Studie von Sondak et al. zeigten 9% der Patienten eine Grad 3 Toxizität (schwere Lokalreaktion, Unwohlsein und Fatigue, visuelle Probleme, Fieber, Durchfälle, Thrombopenien und Hautausschläge), 64% zeigten eine Grad 2 Toxizität und 23% eine Grad 1 Toxizität [118]. Das Team von Hersey et al. beobachtete im Wesentlichen Grad 2 Toxizitäten (Erytheme und Ulzerationen am Injektionsort bei 47% der Patienten; Lymphopenie bei 33%) und Grad 1 Toxizitäten (Unwohlsein und Fieber bei 35% und 20% der Patienten)

· Klinische und Methodische Kommentare

Alle Studien haben eine Intent to treat (ITT) Analyse durchgeführt. Drei der vier Studien präsentieren eine klare Fallzahlberechnung a priori für das rezidivfreie Überleben [117-119, 122]. Die Studie von Bystryn et al. wurde vorzeitig beendet und wurde nur an 38 statt der 210 ursprünglich geplanten Patienten durchgeführt. Aus diesem Grund war die Dauer der Nachbeobachtung nicht ausreichend (weniger als 2 Jahre für die Mehrheit der Patienten) und erlaubt keine Analyse des Gesamtüberlebens [122]. In drei der vier Studien wurden Populationen untersucht, die auf die derzeitige Praxis übertragen werden können [117-119, 122]. Demgegenüber ist die in der Studie von Wallack et al. behandelte Patientenpopulation recht komplex und heterogen im Vergleich zur derzeitigen Praxis obwohl die klinischen Stadien durch die AJCC Klassifikation angegeben wurden. Für die Randomisierung wurden nicht alle Variablen sondern nur die Anzahl der beteiligten Lymphknoten berücksichtigt wurde [120-121].

IFNa versus *GMK*

· Beschreibung der Studien

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.36)*IFN alpha versus GMK*

· Description des études

Une seule étude randomisée est disponible [123] (*Tableau XVIII*). Cette étude a comparé l'IFN alpha 2b hautes doses *versus* vaccine GMK (ganglioside GM2 conjugué avec de l'hémocyanine (KLH) combinée à une molécule adjuvante QS-21). Cette étude a porté sur des patients atteints d'un mélanome de stades IIB ou III résequés.

· Survie globale

La survie globale a été évaluée après un suivi médian de 16 mois. Une différence statistiquement significative a été mise en évidence en faveur des patients traités par l'IFN alpha 2b. La survie globale à 2 ans a été de 78 % dans le bras IFN α 2b *versus* 73 % dans le bras GMK ($p = 0,035$) [123].

· Survie sans récurrence

La survie sans récurrence a été évaluée après un suivi médian de 16 mois. Une différence statistiquement significative a été mise en évidence en faveur des patients traités par l'IFN alpha 2b. La survie sans récurrence à 2 ans a été de 62 % dans le bras IFN alpha 2b *versus* 49 % dans le bras GMK ($p = 0,027$) [123].

· Toxicité

Les toxicités les plus fréquemment observées dans le bras IFN alpha 2b ont été des toxicités de grade 3 de type fatigue, cytopénies, élévation du taux des enzymes du foie et symptômes neurologiques. Quarante-cinq pour cent des patients traités par l'IFN alpha 2b ont arrêté le traitement en raison des effets indésirables. Les toxicités ont été globalement moins fréquentes dans le bras GMK. La toxicité la plus rapportée chez les patients traités par GMK a été une réaction locale au niveau du site d'injection. Aucun décès toxique n'a été rapporté.

· Commentaires méthodologiques et cliniques

Les analyses ont toutes été réalisées en intention de traiter. Les auteurs se sont basés sur les résultats positifs de l'étude ECOG1684 pour définir le protocole de leur essai définissant ainsi l'interféron-alpha à haute dose

Übersetzung

Eine einzige randomisierte Studie ist verfügbar [123]. Diese Studie hat Hochdosis IFN α 2b versus GMK Vakzin (Ganglioside GM2 konjugiert mit KLH kombiniert mit einem adjuvanten Molekül QS-21) verglichen. Diese Studie wurde an Melanom Patienten im resezierten Stadium IIB oder III durchgeführt.

· Gesamtüberleben

Das Gesamtüberleben wurde nach einer medianen Nachbeobachtung von 16 Monaten evaluiert. Ein statistisch signifikanter Unterschied wurde für die mit IFN alpha 2b behandelten Patienten gesehen. Das Gesamtüberleben nach 2 Jahren war 78% im IFN alpha 2b Arm versus 73% im GMK Arm ($p = 0,035$) [123].

· Rezidivfreies Überleben

Das rezidivfreie Überleben wurde nach einer medianen Nachbeobachtung von 16 Monaten evaluiert. Ein statistisch signifikanter Unterschied wurde für die mit IFN alpha 2b behandelten Patienten gesehen. Das rezidivfreie Überleben nach 2 Jahren war 62% im IFN α 2b Arm versus 49% im GMK Arm ($p = 0,027$) [123].

· Toxizität

Die am häufigsten beobachteten Toxizitäten im IFN alpha 2b Arm waren Grad 3 Toxizitäten vom Typ Fatigue, Zytopenie, Anstieg der Leberenzyme und neurologische Symptome. 45% der Patienten im IFN alpha 2b Arm haben die Therapie aufgrund von Nebenwirkungen gestoppt. Die Nebenwirkungen waren insgesamt weniger häufig im GMK Arm. Die am häufigsten berichtete Nebenwirkung im GMK Arm waren Lokalreaktionen am Injektionsort. Es wurde keine tödliche Nebenwirkung berichtet.

· Klinische und Methodische Kommentare

Alle Analysen wurden als Intent to treat Analyse durchgeführt. Die Autoren haben sich auf die positiven Ergebnisse der Studie ECO1684 gestützt, um die Hochdosis Interferon-alpha Therapie in ihrem Protokoll als Kontrollarm zu definieren [104], obwohl sich diese Ergebnisse nachträglich nicht bestätigt haben. Da dadurch ein echter Kontrollarm fehlt, ist es nicht möglich gültige Schlussfolgerungen zu ziehen. Die untersuchte Population ist gemischt (77%

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.36)

comme contrôle [104], bien que ces résultats n'aient pas été confirmés par la suite. De ce fait, l'absence de vrai bras contrôle invalide considérablement les conclusions. La population étudiée est mixte (77 % de patients présentaient un envahissement ganglionnaire) et la stadification NO (23 %) est hétérogène (45 % des patients ont été évalués cliniquement et 46 % ont eu une évaluation histologique). L'interprétation des résultats est donc rendue plus complexe, puisque dans les autres études, la proportion de patients sans envahissement est généralement majoritaire. Par ailleurs, le suivi médian n'étant que de 16 mois, l'évaluation de la survie doit être interprétée avec précaution.

Tumor infiltrating lymphocytes (TIL)

· Description des études

Une étude est disponible [124, 125] (Tableau XIX). Il s'agit d'une étude prospective randomisée comparant un traitement par TIL+ IL-2 versus IL-2 seule chez 88 patients porteurs d'un mélanome de stade III (AJCC) après curage ganglionnaire. Le suivi médian a été de 46,9 mois.

· Survie globale, survie sans récurrence

Aucune différence significative en termes de survie globale et de survie sans récurrence n'a été mise en évidence entre les 2 groupes. Néanmoins, une différence significative a été observée entre les deux bras de traitement dans un sous groupe de patients (avec un seul ganglion envahi, mais pas de précision sur la rupture capsulaire), notamment sur la survie globale et le taux de rechute.

· Toxicité

Globalement, le traitement par TIL a été très bien toléré. Aucune toxicité de grades 3 ou 4 n'a été observée. Les principaux effets indésirables ont été une inflammation au site de l'injection et une asthénie.

· Commentaires méthodologiques et cliniques

Übersetzung

der Patienten haben eine Lymphknotenbeteiligung) und die Stadieneinteilung NO (23%) ist heterogen (45% der Patienten wurden klinisch klassifiziert und 46% der Patienten wurden histologisch klassifiziert). Die Interpretation der Ergebnisse ist daher komplex, da in anderen Studien die Mehrzahl der Patienten keine Lymphknotenbeteiligung hat. Da auch die Nachbeobachtungszeit nur 16 Monate betrug, müssen die Überlebenszeitanalysen mit Vorsicht interpretiert werden.

Tumor infiltrating lymphocytes (TIL)

· Beschreibung der Studien

Eine Studie steht zur Verfügung [124, 125]. Es ist eine prospektive randomisierte Studie die eine Therapie mit TIL+IL-2 versus IL-2 allein bei 88 Melanom Patienten im Stadium III (AJCC) nach einer Lymphknotenausräumung vergleicht. Die mediane Nachbeobachtungszeit betrug 46,9 Monate.

· Gesamtüberleben, Rezidivfreies Überleben

In Bezug auf das Gesamtüberleben und das rezidivfreie Überleben wurde kein signifikanter Unterschied zwischen den 2 Gruppen beobachtet. Dennoch wurde bei einer Subgruppe (bei Beteiligung nur eines Lymphknoten aber ohne Angaben zur Kapselüberschreitung) zwischen den Behandlungsarmen ein signifikanter Unterschied bezogen auf Gesamt- und rezidivfreies Überleben gesehen.

· Toxizität

Insgesamt wurde die Behandlung mit TIL sehr gut toleriert. Keine Grad 3 oder 4 Toxizitäten wurden beobachtet. Die hauptsächlichsten Nebenwirkungen waren Entzündungen am Injektionsort und Asthenie.

· Klinische und Methodische Kommentare

Die Methode der Randomisation wurde im Artikel nicht berichtet und das Fehlen eines echten Kontrollarms machen es schwierig gültige Schlussfolgerungen zu ziehen. Nachträglich durchgeführte Subgruppenanalysen (die zum Zeitpunkt der Randomisierung nicht

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.36)	Übersetzung
<p>La méthode de randomisation n'est pas décrite dans les articles et l'absence de réel bras contrôle limite considérablement la portée des conclusions qui pourront être établies. Les analyses en sous-groupes conduites <i>a posteriori</i> (non prévues initialement lors de la randomisation) ne permettent pas d'extrapoler des conclusions sur les critères de jugement. Il est également important de relever les contraintes techniques liées à ce procédé dont le succès est conditionné, dans un premier temps, par la production de TIL chez les patients concernés.</p> <p><i>Conclusions de la littérature</i> Aucun des procédés de vaccination utilisés jusqu'à ce jour n'a mis en évidence une différence significative sur la survie sans récurrence ou sur la survie globale des patients atteints d'un mélanome cutané réséqué avec ou sans envahissement ganglionnaire et dont l'épaisseur est supérieure à 1,5 mm (niveau de preuve B1).</p>	<p>vorgesehen waren) machen Schlussfolgerungen aus den Ergebnissen nicht möglich. Es ist auch wichtig die technischen Zwänge zu bedenken, da in einem ersten Schritt die Produktion von TIL bei den betroffenen Patienten erfolgen muss.</p> <p>Schlussfolgerung aus der Literatur Keine der Impfverfahren die bis heute verwendet wurden haben einen signifikanten Unterschied für das Gesamtüberleben oder rezidivfreie überleben bei Patienten mit reseziertem Melanom, oder ohne Lymphknotenbeteiligung und mit einer Tumordicke grösser als 1,5mm erbracht (niveau de preuve B1). <i>Entspricht in etwa Level of Evidence nach Oxford 1b</i></p>

5.2.3. Empfehlung und Hintergrundtext kanadische Quell Leitlinie

Quelleitlinie: Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma: Updated Guideline Recommendations (Cancer Care Ontario) 2009

Nine randomized trials of vaccines are summarized in Table 8, one of a viral oncolysate, one of a ganglioside, one of a polyvalent vaccine, one of vaccinia melanoma cell lysate, and five of whole-cell vaccines. Six RCTs compared vaccine with observation, while three trials were double-blind. Seven of the nine trials were confined to patients with nodal involvement, and the majority of patients in one of the other trials were node positive. None of the reported trials have shown a statistically significant improvement in overall survival for patients treated with vaccines, an observation confirmed in a recent update of the SWOG 9035 trial. However, in that study, the subset analysis of patients who were positive for human leukemic antigen (HLA)-A2 and/or HLA-C3 demonstrated a significant five-year

overall survival benefit of 93% for vaccine patients compared with 74% for patients in the observation group ($p=0.009$). This clearly hypothesis-generating observation cannot be used to direct clinical decisions. For obvious reasons attesting to heterogeneity of the studies and vaccines employed, we have elected not to pool those data in our analysis.

Literatur:

LL Frankreich French National Authority for Health 2005)

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117. Hersey P, Coates AS, McCarthy WH, et al. Adjuvant immunotherapy of patients with high-risk melanoma using vaccinia viral lysates of melanoma: results of a randomized trial. *J Clin Oncol* 2002;20:4181-4190
123. Kirkwood JM, Ibrahim JG, Sosman JA, et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol* 2001;19:2370-2380
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118. Sondak VK, Liu PY, Tuthill RJ, et al. Adjuvant immunotherapy of resected, intermediate-thickness, node-negative melanoma with an allogeneic tumor vaccine: overall results of a randomized trial of the Southwest Oncology Group. *J Clin Oncol* 2002;20:2058-2066
119. Sosman JA, Unger JM, Liu PY, et al. Adjuvant immunotherapy of resected, intermediate-thickness, node-negative melanoma with an allogeneic tumor vaccine: impact of HLA class I antigen expression on outcome. *J Clin Oncol* 2002;20:2067-2075
114. Veronesi U, Adamus J, Aubert C, et al. A randomized trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. *N Engl J Med* 1982;307:913-916
120. Wallack MK, Sivanandham M, Ditaranto K, et al. Increased survival of patients treated with a vaccinia melanoma oncolysate vaccine: second interim analysis of data from a phase III, multi-institutional trial. *Ann Surg* 1997;226:198-206
121. Wallack MK, Sivanandham M, Whooley B, et al. Favorable clinical responses in subsets of patients from a randomized, multi-institutional melanoma vaccine trial. *Ann Surg Oncol* 1996;3:110-117

LL Kanada Cancer Care Ontario 2007

Eggermont AM, Suci S, Ruka W, Marsden J, Testori A, Corrie P. EORTC 18961: Post-operative adjuvant ganglioside GM2-KLH21 vaccination treatment vs observation in stage II (T3-T4N0M0) melanoma: 2nd interim analysis led to an early disclosure of the results. *J Clin Oncol*. 2008;26(May 20 suppl):9004.

5.3. Frage IV.3. Adjuvante Extremitätenperfusion - Adaptation

5.3.1. Synopse Quellleitlinien

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
Beeinflusst eine adjuvante Extremitätenperfusion das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?	Adjuvant regional drug therapy improves disease free interval but does not improve overall survival Level II	-	La perfusion de melphalan sur membre isolé ne semble pas améliorer la survie globale des patients atteints d'un mélanome cutané Niveau de preuve C <i>Eine adjuvante Extremitätenperfusion mit Melphalan scheint das Gesamtüberleben von Melanompatienten nicht zu verbessern. Niveau C</i>	-
Schlüsselempfehlung	Prophylactic isolated limb perfusion (ILP) is not recommended Grade A	-	La perfusion de membre isolé n'est pas recommandée en dehors d'essais thérapeutiques et doit être réalisée par des équipes entraînées. Recommandation: Option <i>Eine Extremitätenperfusion wird ausserhalb klinischer Studien nicht empfohlen und soll durch erfahrene Teams durchgeführt werden.</i>	-
Zugrunde liegende Evidenz	1 Studie Koops, H.S. et al. 1998	-	2 Studien Koops, H.S. et al. 1998 Ghussen, F. et al. 1989	-

5.3.2. Empfehlung und Hintergrundtext französische Quell Leitlinie

Quellleitlinie: Recommandations pour la Pratique Clinique : Standards, Options et Recommandations 2005

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.40)	Übersetzung
<p>Perfusion de melphalan sur membre isolé</p> <p>DESCRIPTION DES ÉTUDES Deux études randomisées ont étudié l'effet d'une perfusion sur membre isolé de melphalan après exérèse d'un melanoma primitif isolé [134, 135] (Tableau XXI). Les 2 essais ont évalué respectivement 107 et 832 patients dont l'épaisseur de la tumeur était supérieure à 1,5 mm. Dans l'étude de Ghussen et al. la perfusion de melphalan a été associée à une hyperthermie.</p> <p>SURVIE GLOBALE, SURVIE SANS RÉCIDIVE Seule une des deux études randomisées a montré un avantage en termes de contrôle local et de survie globale en faveur du traitement sur membre isolé par une association hyperthermie-melphalan après exérèse d'un melanoma primitif isolé [134]. L'étude de Koops et al. n'a pas montré de différence significative en termes de survie globale [135]. Une analyse en sous-groupe a cependant mis en évidence une survie sans récurrence plus élevée chez les patients qui ont eu un curage ganglionnaire (RR = 0,75 [IC95 : 0,55-0,98]) et plus particulièrement chez les patients dont la tumeur était inférieure à 3 mm (RR = 0,56 [IC95 : 0,36-0,88]) [135]. Aucune différence en termes de survie globale n'a été observée dans les analyses en sous-groupes.</p> <p>TOXICITÉ Les toxicités ont été principalement de grade 1 et globalement plus importantes dans les groupes de patients perfusés [134, 135]. Les toxicités les plus fréquentes ont été la douleur et les infections du membre, souvent localisées au niveau du site de la perfusion. La plupart des complications ont cependant été réversibles.</p>	<p>Isolierte Extremitätenperfusion mit Melphalan</p> <ul style="list-style-type: none"> · Beschreibung der Studien Zwei randomisierte Studien haben den Effekt einer isolierten Extremitätenperfusion mit Melphalan nach Exzision des Primärmelanoms untersucht. Die beiden Studien haben 107 und 832 Patienten mit einer Tumordicke ab 1,5 mm eingeschlossen. In der Studie von Ghussen et al. war die Perfusion mit Melphalan mit Hyperthermie kombiniert. · Gesamtüberleben, Rezidivfreies Überleben Nur eine der beiden Studien zeigte einen Vorteil in Bezug auf lokale Kontrolle und Gesamtüberleben zugunsten einer Therapie mit isolierter Extremitätenperfusion mit Hyperthermie-Melphalan nach Exzision eines Primärmelanoms. Die Studie von Koops et al. zeigte keinen signifikanten Unterschied in Bezug auf das Gesamtüberleben. Eine Subgruppenanalyse zeigte jedoch ein verlängertes rezidivfreies Überleben bei Patienten mit Lymphknotendisektion (RR = 0,75 [IC95 : 0,55-0,98]) <i>[Kommentar: in der Originalarbeit bezieht sich das verlängerte rezidivfreie Überleben auf Patienten OHNE Lymphknotendisektion: "...The difference was significant for patients who did not undergo elective lymph node dissection (ELND)."]</i> und besonders bei Patienten mit einem Tumordicke unter 3mm (RR = 0,56 [IC95 : 0,36-0,88]). Die Subgruppenanalysen ergaben keine Unterschiede in Bezug auf das Gesamtüberleben. · Toxizität Toxizitäten waren hauptsächlich Grad 1 und insgesamt am wichtigsten in den Gruppen der perfundierten Patienten. Die häufigsten Toxizitäten waren

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.40)	Übersetzung
<p>COMMENTAIRES MÉTHODOLOGIQUES ET CLINIQUES L'étude de Ghussen et al. a été arrêtée prématurément en raison d'une analyse intermédiaire qui a montré l'existence d'un bénéfice évident en termes de survie sans récurrence en faveur des patients qui ont reçu une perfusion hyperthermique de melphalan ($p < 0,001$). Au total, 115 patients ont été inclus, dont 107 évaluables. Le calcul a priori du nombre de sujets nécessaires n'étant pas présenté, la puissance de l'étude ne peut être recalculée et la fiabilité des résultats est limitée. Les analyses en sous-groupes définies a posteriori ne permettent pas d'établir de conclusions fiables en regard de ces résultats. Les populations des 2 études ne sont pas comparables. À noter également que près de 10 ans séparent les 2 études et que les protocoles de traitement ont été différents (hyperthermie dans l'étude de Ghussen et al.).</p> <p>CONCLUSIONS DE LA LITTÉRATURE La perfusion de melphalan sur membre isolé ne semble pas améliorer la survie globale des patients atteints d'un mélanome cutané (niveau de preuve C).</p>	<p>Schmerzen und Infektionen in der Extremität, häufig am Ort der Infusion. Die meisten Komplikationen waren jedoch reversibel.</p> <ul style="list-style-type: none"> · Klinische und Methodische Kommentare Die Studie von Ghussen et al. wurde vorzeitig beendet, da eine Zwischenanalyse einen Benefit in Bezug auf das rezidivfreie Überleben zugunsten einer hyperthermen Perfusion mit Melphalan gezeigt hat ($p < 0,001$). Insgesamt wurden 115 Patienten eingeschlossen, davon waren 107 auswertbar. Die erforderliche Fallzahlberechnung wurde nicht dargestellt, die Power der Studie konnte nicht berechnet werden und die Verlässlichkeit der Daten ist limitiert. Die nachträglich definierten Subgruppenanalysen lassen keine verlässlichen Schlussfolgerungen aus den Ergebnissen zu. Die Populationen aus den beiden Studien sind nicht vergleichbar. Es ist zu beachten, dass fast 10 Jahre zwischen den beiden Studien lag und die Behandlungsprotokolle unterschiedlich waren (Hyperthermie in der Studie von Ghussen et al.) · Schlussfolgerung aus der Literatur Eine adjuvante Extremitätenperfusion mit Melphalan scheint das Gesamtüberleben von Melanompatienten nicht zu verbessern. (Niveau de preuve C)

Literatur:

Ghussen F, Kruger I, Smalley RV, et al. Hyperthermic perfusion with chemotherapy for melanoma of the extremities. World J Surg 1989;13:598-602
 Koops HS, Vaglini M, Suci S, et al. Prophylactic isolated limb perfusion for localized, high-risk limb melanoma: results of a multicenter randomized phase III trial. European Organization for Research and Treatment of Cancer Malignant Melanoma Cooperative Group Protocol 18832, the World Health Organization Melanoma Program Trial 15, and the North American Perfusion Group Southwest Oncology Group-8593. J Clin Oncol 1998;16:2906-2912

5.4. Frage IV.4. Adjuvante Immunstimulation - Adaptation

5.4.1. Synopse Quelleitlinien

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
Beeinflusst eine unspezifische Immunstimulation (BCG, Levamisol) das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?	-	-	<p>Le levamisole en situation adjuvante n'améliore pas la survie des patients porteurs d'un mélanome cutané opéré (niveau de preuve A).</p> <p><i>Eine adjuvante Therapie mit Levamisole verbessert nicht das Überleben von Melanompatienten. (Niveau de preuve A)</i></p>	<p>After the review of the available information with respect to levamisole, we have concluded that, if levamisole has an impact on the clinical course of malignant melanoma when given in the adjuvant setting, that effect is marginal</p> <p>(BCG wurde nicht in die Literatursuche eingeschlossen)</p>
Schlüsselempfehlung	-	-	<p>Les traitements adjuvants systémiques à base de levamisole, BCG ou dacarbazine ne sont pas recommandés en dehors d'essais thérapeutiques.</p> <p><i>Adjuvante systemische Therapien mit Levamisol, BCG oder Dacarbazine werden ausserhalb von klinischen</i></p>	Keine Empfehlung zu Levamisole enthalten

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
			<i>Studien nicht empfohlen.</i>	
Zugrunde liegende Evidenz	-	-	4 Studien, 1 Metaanalyse aus der kanadischen LL 2002 Loutfi et al 1987, Lejeune et al. 1988, Quirt et al 1991, Spitler et al. 1991, Cancer Care Ontario Practice Guidelines Initiative 2002	4 Studien Spitler et al 1980, Loutfi et al 1987, Lejeune et al. 1988, Quirt et al 1991, Spitler et al. 1991

Update Recherche am 07.03.2011

Suchstrategie Medline: melanoma [tiab] AND levamisole [tiab], Treffer: 50, Darunter seit 2005 keine neuen randomisierten Studien zu Levamisol

5.4.2. Empfehlung und Hintergrundtext französische Quell Leitlinie

Quellleitlinie: Recommandations pour la Pratique Clinique : Standards, Options et Recommandations 2005

Originaltext (Evidenztabelle siehe Quell LL ab S.38)	Übersetzung
<p>LEVAMISOLE</p> <p>· Description des études Quatre essais randomisés ont évalué l'efficacité du levamisole (immunomodulateur) en situation adjuvante chez les patients porteurs d'un mélanome cutané opéré [126-129]. Aucun nouvel essai randomisé n'a été retrouvé dans le cadre de la mise à jour 2005. Trois essais ont comparé levamisole versus placebo [126, 127, 129] et 1 essai a évalué levamisole versus observation [128].</p> <p>· Survie globale Aucun des 3 essais contre placebo n'a rapporté de différence significative en termes de survie globale [126, 127, 129]. L'étude du NCIC a observé une différence significative de la survie à 5 ans en faveur des patients traités par levamisole par rapport à l'absence de traitement (78 % versus 62 % ; p = 0,027) [128]. L'analyse poolée des données réalisée par le CCOPGI n'a pas retrouvé de différence significative (odd ratio = 0,90 [IC95 : 0,63-1,30]) [12].</p> <p>· Commentaires méthodologiques et cliniques Les doses de levamisole administrées dans les 4 études sont très hétérogènes, ce qui ne permet pas d'établir de conclusions concernant la relation effet-dose. La population incluse dans l'étude du NCIC est hétérogène (seuls 50 % des patients sont des patients à haut risque de récidence).</p>	<p>LEVAMISOLE</p> <p>· Beschreibung der Studien Vier randomisierte Studien haben den Effekt von Levamisole (Immunmodulator) bei Patienten in der adjuvanten Situation nach Exzision eines kutanen Melanoms untersucht[126-129]. Keine neue randomisierte Studie wurde im Rahmen der Aktualisierung 2005 gefunden. Drei Studien haben Levamisole gegen Placebo verglichen [126, 127, 129] und eine Studie hat Levamisole gegen Beobachtung untersucht [128].</p> <p>· Gesamtüberleben Keine der drei Studien versus Placebo berichtete einen signifikanten Unterschied in Bezug auf das Gesamtüberleben [126, 127, 129]. Die Studie der NCIC (National Cancer Institute of Canada Clinical Trials Group) hat einen signifikanten Unterschied des Überlebens nach 5 Jahren für Pataienten die mit Levamisole behandelt wurden im Vergleich zu unbehandelten Patienten gezeigt. Die Metaanalyse durch die CCOPGI hat keinen signifikanten Unterschied gezeigt. (odd ratio = 0,90 [IC95 : 0,63-1,30]) [12].</p> <p>· Klinische und Methodische Kommentare Die in den vier Studien verabreichten Dosierungen von Levamisole waren sehr heterogen, daher lassen sich keine Schlussfolgerungen zur dosisabhängigen Wirkung ziehen. Die eingeschlossene Population in der NCIC Studien ist sehr heterogen (nur 50% der Patienten sind Hochrisikopatienten)</p>

Originaltext (Evidenztabelle siehe Quell LL ab S.38)	Übersetzung
<p>· Conclusions de la littérature Le levamisole en situation adjuvante n'améliore pas la survie des patients porteurs d'un mélanome cutané opéré (niveau de preuve A).</p>	<p>· Schlussfolgerung aus der Literatur Eine adjuvante Therapie mit Levamisole verbessert nicht das Überleben von Melanompatienten. (Niveau de preuve A)</p>

Literatur:

12. CCOPGI, (Cancer Care Ontario Practice Guidelines Initiative). Systemic adjuvant therapy for patients at high risk for recurrent melanoma. Practice Guideline Report No 8-1 [online]. 2002. Available: URL: http://www.cancercare.on.ca/index_practiceGuidelinesandEvidencesummaries.htm#list.
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128. Quirt IC, Shelley WE, Pater JL, et al. Improved survival in patients with poor-prognosis malignant melanoma treated with adjuvant levamisole: a phase III study by the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1991;9:729-735
129. Spitler LE. A randomized trial of levamisole versus placebo as adjuvant therapy in malignant melanoma. J Clin Oncol 1991;9:736-740

5.4.3. Empfehlung und Hintergrundtext kanadische Quell Leitlinie

Quelleitlinie: Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma: Updated Guideline Recommendations (Cancer Care Ontario) 2009

Levamisole is an anti-helminthic with disputed immunostimulatory properties in vitro. On the basis of that activity, levamisole has been investigated as adjuvant therapy in a number of cancers. Apart from results as adjuvant therapy in colon cancer when combined with a cytotoxic agent, the trials in other cancers have been negative.

There are four randomized controlled trials of levamisole in melanoma, of which three are placebo-controlled (30-33). The (NCIC) study (34) enrolled a heterogeneous group of patients with 50% being at high risk of recurrence (personal communication, B. Zee). The total dose of levamisole used in this level I study was 800 mg over a two-week period for an 80 kg individual. Three smaller trials evaluated total doses of 450 mg (31,31), 600 mg (32), and 600 to 1000 mg (33) over a two-week period. Whether those differences in dose are substantive is difficult to know in the absence of any data that demonstrate a dose-response relationship for levamisole with any measure of activity.

Although the initial report by Spitler et al (31) described a survival trend in favour of levamisole compared with placebo in the subgroup of patients without lymph node disease ($p=0.07$, two-sided), there was no survival difference between treatments for the total study population. That lack of benefit was confirmed by a subsequent report of long-term follow-up (30). Loutfi et al (32) and Lejeune et al (33) concluded that

there was no meaningful impact on survival with levamisole compared with placebo. The only study in which levamisole had an impact, albeit a marginal one, was the study from the NCIC (34) in which there was a statistically significant difference in the survival rate in favour of levamisole when the five-year point estimates of overall survival were assessed (78% for levamisole versus 62% for control, $p=0.027$, 2-sided). However, when the whole survival experience was compared between the groups, the difference in survival was not significant ($p=0.08$, two-sided). That difference represented a risk reduction in mortality of 29% and was observed in all risk groups, including the group to which this systematic review is directed.

Without an intermediate marker of activity for levamisole, it is impossible to categorically state whether or not there are substantive differences in the regimens used in those four trials. This systematic review is directed at a specific segment of the population involved in those trials. While a meta-analysis restricted to data from the high-risk subgroup might help to reconcile the seemingly disparate findings, survival results are not reported separately for that patient subgroup, and data for individual cases are generally not available. However, it is our belief that the regimens evaluated are unlikely to be substantially different in their clinical activity and that the impact of levamisole does not differ across risk groups. A meta-analysis of five-year death rates (Figure 2), abstracted from survival curves in published reports, yields a risk ratio of 0.94 (95% CI, 0.75 to 1.20; $p=0.6$). No heterogeneity was found among the results from these studies ($p=0.19$).

After the review of the available information with respect to levamisole, we have concluded that, if levamisole has an impact on the clinical course of malignant melanoma when given in the adjuvant setting, that effect is marginal.

Adverse effects

Morbidity from levamisole is generally mild, although it was severe enough to result in discontinuation of therapy in 41% of patients in the NCIC study (34), 44% in the Loutfi et al study (compared with 16% in the placebo group) (32), and 17% in the Lejeune et al study (compared with no patients in the placebo group) (33). Data on toxicity was reported for two of the placebo-controlled trials (32,33). In the study by Loutfi et al, 22% of patients on levamisole reported a flu-like syndrome (compared with 3% on placebo), 14% reported nausea and vomiting (compared with 8% on placebo), and 14% reported musculoskeletal symptoms (compared with no patients on placebo) (32). The most commonly reported adverse events in the Lejeune et al study were nausea and vomiting (27% with levamisole versus 10% with placebo), weakness (27% versus 14%), and anorexia (22% versus 8%) (33). Hematologic abnormalities were noted for 7% of patients on levamisole and none of the placebo group in the Loutfi et al study (32), and for 16% and 5%, respectively, of those groups in the Lejeune et al study (33). No treatment-related mortality has been observed in the four levamisole studies summarized here.

Literatur:

33. Lejeune FJ, Macher E, Kleeberg U, Rumke P, Prade M, Thomas D, et al. An assessment of DTIC versus levamisole or placebo in the treatment of high risk stage I patients after surgical removal of a primary melanoma of the skin. *Eur J Cancer Clin Oncol*. 1988;24 Suppl 2:S81-S90.
32. Loutfi A, Shahr A, Jerry M, et al. Double blind randomized prospective trial of levamisole/placebo in stage I cutaneous malignant melanoma. *Clin Invest Med* 1987;10:325-328

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30. Spitler LE. A randomized trial of levamisole versus placebo as adjuvant therapy in malignant melanoma. *J Clin Oncol* 1991;9:736-740
31. Spitler LE, Sagebiel R. A randomized trial of levamisole versus placebo as adjuvant therapy in malignant melanoma. *N Engl J Med* 1980;303:1143-1147

5.5. Frage IV.5. und IV.6. Adjuvante Interferon alpha Therapie – De novo Recherche

Frage IV.5. Beeinflusst eine Therapie mit IFN-alpha das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?

Frage IV.6. Welche Patientengruppe profitiert von einer Interferon-alpha-Therapie?

5.5.1. PICO, Suchwörter

PICO - Schema

Population	Intervention	Comparison	Outcome
Melanoma patients, clinical stage II and III	IFN-alpha treatment	Observation	OS, PFS

Suchwörter

Stichwort	melanoma	Interferon-alpha	adjuvant	
Synonyme		Interferon alpha, Interferon alpha, IFN- α , IFN-alpha		
Ober-/Unterbegriffe		interferon-alpha-2b, interferon-alpha-2a, multiferon		
Mesh Term	melanoma	Interferon-alpha		

5.5.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (Interferon-alpha[tiab] OR Interferon-alpha[MeSH] OR "Interferon alpha"[tiab] OR IFN-alpha [tiab] OR IFN-alpha[tiab] OR interferon-alpha-2b[tiab] OR interferon-alpha-2a[tiab] OR multiferon[tiab]) AND (adjuvant[tiab])	12.04.11	404 (25)
Cochrane Library	(melanoma and interferon alpha and adjuvant).mp.	12.04.11	46 (8, davon 7 Dubletten, 1 Studie dazu Rudolf Z 1994)
Embase	(melanoma and (Interferon alpha or IFN alpha or interferon alpha 2b or interferon alpha 2a or multiferon) and (adjuvant)).ti,ab.	11.05.11	301 (nach Dublettenelimination 0 dazu)
Update Suche			
Medline	s.o.	30.01.12	427 (2 dazu: Petrella, Eggermont)
Cochrane Library	s.o.	30.01.12	47 (0 dazu)
Embase	s.o.	23.01.12	308 (0 dazu)

5.5.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	782
Einschlusskriterien	system. Reviews, klinische Studien zu adjuvanter Therapie mit Interferon alpha bei Patienten mit Rezidivrisiko, tumorfreies Stadium I-III Intervention: IFN alpha Monotherapie, Vergleichsgruppe: Beobachtung Sprachen: e,dt
Ausschlusskriterien	Nicht systematische Reviews Kohorten Studien, Case Reports Kombinationstherapien Vergleichsgruppe Chemotherapie, andere Systemtherapien Therapiestudien mit Interferon alpha im Stadium IV Kollektive mit gemischten Tumorentitäten
Anzahl ausgewählter Studien (8 Reviews, 16 RCTs, <i>davon 2 nur als Abstract vorliegend</i>)	24
Anzahl in Reviews zusätzlich berücksichtigter Studien (E2696+E1694 kein Obs Arm, Kokoschka, Rusciani mangelnde Qualität)	4
Anzahl der ausgeschlossenen Studien nach Bewertung (Rudolf)	1

5.5.4. Evidenztabelle - Kurzfassung

RCT	No. of patients	OS	p	RFS	p	LoE
Low Dose						
Pehamberger, AMCG, 1998	311	no benefit, HR n.r.	-	benefit, HR n.r.	<0.2	1b
Garbe, DeCOG, 2008	444	HR = 0.62	0.0045	HR = 0.69	0.018	1b
Kleeberg, EORTC 18871, 2004	484	HR = 0.96	0.72	HR = 1.04	0.71	1b
Hancock, UKCCCR, 2004	674	OR = 0.94	0.6	OR = 0.91	0.3	1b
Cascinelli, WHO, 2001	444	no benefit, HR n.r.	0.72	no benefit, HR n.r.	0.5	1b
Cameron, SMG, 2001	95	no benefit, HR n.r.	>0.2	no benefit, HR n.r.	-	1b
Kirkwood, E1690, 2000	642	HR = 1.04 ^s	0.813	HR = 1.19 ^s	0.171	1b
Grob, FCGM, 1998	489	no benefit, HR n.r.	0.059	benefit, HR n.r.	0.035	1b
Intermediate Dose						
Hansson, Nordic trial, 2011	855	HR = 0.91	0.642	HR = 0.80	0.030	1b
Eggermont, EORTC 18952, 2005	832 835	HR = 1.00* HR = 0.85*	0.96 0.11	HR = 0.95* HR = 0.83*	0.59 0.05	1b
High Dose						
Agarwala, E1697, 2011	1150	no benefit, HR n.r.	-	no benefit, HR n.r.	-	
McMasters, Sunbelt Trial, 2008	218	HR = 1.07	0.79	HR = 0.82	0.46	
Kirkwood, E1690, 2000	642	HR = 1.0 ^s	0.995	HR = 1.28 ^s	0.054	1b

RCT	No. of patients	OS	p	RFS	p	LoE
Kirkwood, E1684, 1996/2004	287	Upd.: HR = 1.22 [§] benefit, HR n.r.	0.18 0.0237	Upd.: HR = 1.38 [§] benefit, HR n.r.	0.02 0.0023	1b
Creagan, NCCTG, 1995	262	HR = 0.9	0.53	HR = 0.83	0.37	1b
Pegylated						
Eggermont, EORTC 18991, 2008	1256	HR = 0.98	0.78	HR = 0.82	0.01	1b

*13 month, 25 month interferon; DMFS not RFS was calculated, § HR relates to proportion alive and proportion relapsfree (> 1 = Favour IFN)

Agarwala 2011, Mc Masters 2008: only abstract available

5.5.5. Hochdosis versus Niedrigdosis Interferon alpha

Randomisierte Studie HDI versus LDI versus Beobachtung: kein signifikanter Unterschied

RCT	No. of patients	OS	p	RFS	p	LoE
Kirkwood et al. 2000	HDI n=215, HDI vs. Obs LDI n=215, LDI vs. Obs HDI vs. LDI*	HR = 1.0 [§] HR = 1.04 [§] RR = 1.02* [§] Favour LDI, n.s.	n.s. n.s. 0.92*	HR = 1.28 [§] HR = 1.19 [§] RR = 0.93* [§] , Favour HDI, n.s.	n.s. n.s. 0.50*	1b

* Data not reported, calculated based on event data $RR = (\text{events}/\text{group A}) / (\text{events}/\text{group B})$, p value: Fisher's exact test; [§]HR relates to proportion alive and proportion relapsfree

Subgruppenvergleich Metaanalyse Mocellin et al. 2010: 6 HDI Studien versus 7 LDI und IDI Studien, kein signifikanter Unterschied

Study	No. of trials / patients	OS HR (95% CI)	No. of trials / patients	PFS HR (95% CI)	No. of trials / patients	OS HR (95% CI)	No. of trials / patients	PFS HR (95% CI)	Subgroup comparison	LoE
Mocellin et al. 2010	HDI			LDI or IDI					OS p=0.99 PFS p=0.05	2b
	5/3114	0.89 (0.77 - 1.02)	6/3221	0.75 (0.68 - 0.83)	7/4590	0.89 (0.81 - 0.98)	8/4901	0.85 (0.78 - 0.93)		

Vergleich Hochdosis versus Niedrigdosis Interferon alpha Studien im Stadium der lokoregionären Metastasierung (AJCC 2009: St. III)

RCT Low Dose	Anteil Patienten mit lokoreg. Met.	OS	p	RFS	p	RCT High Dose	Anteil Patienten mit lokoreg. Met.	OS	p	RFS	p
Cascinelli, WHO, 2001	97%	no benefit, HR n.r.	0.72	no benefit, HR n.r.	0.5	Kirkwood, E1684, 2004 (Update), 1996	89%	Upd.: no benefit: HR = 1.22 ^s benefit, HR n.r.	0.18 0.0237	Upd.: HR = 1.38 ^s benefit, HR n.r.	0.02 0.0023
Hancock, UKCCCR, 2004	81%	OR = 0.94	0.6	OR = 0.91	0.3	Kirkwood, E1690, 2000	74%	HR = 1.0 ^s	0.995	HR = 1.28 ^s	0.054
Kirkwood, E1690, 2000	74%	HR = 1.04 ^s	0.813	HR = 1.19 ^s	0.171	Creagan, NCCTG, 1995	61%	HR = 0.9	0.53	HR = 0.83	0.37
Garbe, DeCOG, 2008	61%	HR = 0.62	0.0045	HR = 0.69	0.018						

RCT Low Dose	Anteil Patienten mit lokoreg. Met.	OS	p	RFS	p	RCT High Dose	Anteil Patienten mit lokoreg. Met.	OS	p	RFS	p
Kleeberg, EORTC 18871, 2004	60%	HR = 0.96	0.72	HR = 1.04	0.71						
Cameron, SMG, 2001	St II + III Anteil n.r.	no benefit, HR n.r.	>0.2	no benefit, HR n.r.	-						
Pehamberger, AMCG, 1998	0%	no benefit, HR n.r.	-	benefit, HR n.r.	<0.2						
Grob, FCGM, 1998	0%	no benefit, HR n.r.	0.059	benefit, HR n.r.	0.035						

^sHR relates to proportion alive and proportion relapsfree

5.5.6. Evidenztabellen – Langfassung

5.5.6.1. Evidenztabelle – Systematische Reviews and Metaanalysen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Petrella et al. 2012	To conduct another update of the evidence and recommendations. This report summarises the	Systematic review (Update) adjuvant treatment for stage AJCC stage IIB, IIC and	7 new RCTs: EORTC 18991 Sunbelt Trial Pectasides et al. 2009	OS DFS	HDI vs. Obs: no sign. benefit Hazard Ratio: 0.93 [0.78,1.12] HDI vs. Obs: sign.	most LDI studies not included Conflict of Interest: The first author received consulting	1a-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	evidence published between July 2005 and June 2010 that informed the development of revised recommendations for adjuvant interferon therapy by the Melanoma DSG.	III.	EORTC 18952 Stadler et al. 2006 DeCOG 2008 DeCOG 2010 Metaanalyses: Mocellin et al. Wheatley et al.		Benefit Hazard Ratio: 0.77 [0.65, 0.92] P = 0.004; 9% absolute risk reduction at 5 years	fees or honoraria greater than \$5000 from Schering-Plough in the past 2 years.	
Eggermont et al. 2011	To present a meta-analysis of the two largest adjuvant IFN/PEG-IFN randomised trials in a combined total of 2644 patients with high-risk melanoma (stage IIb/III)	Metaanalysis of 2 studies	EORTC 18991 EORTC 18952 2644 patients with high-risk melanoma stage IIb/III	OS RFS DMFS	IDI+peg IFN vs. Obs: no sign. benefit Hazard Ratio: 0.94 [0.80, 1.11] sign. benefit Hazard Ratio: 0.85 [0.76, 0.95] p=0.004 sign. benefit Hazard Ratio: 0.89 [0.79, 1.00] p=0.36	Conflict of Interest: Alexander M.M. Eggermont: Consultant in advisory boards for melanoma for Merck, BMS, Roche, GSK. Poulam Patel: Ad hoc advisory boards for Schering-Plough Research Institute – honoraria paid.	1a-
Garbe et al. 2011	to present the success of current treatments and the	Systematic review adjuvant and	Interferon alpha: 11 RCTs	Metaanalysis Overall survival	12 RCTs Significant	Number needed to treat not reported	1a- (SR with heterogeneity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	promise of those still in clinical development that may yield incremental improvements in the treatment of advanced, metastatic melanoma	palliative treatments	NCCTG ECOG 1684 ECOG 1690 EORTC 18952 SMG WHO DeCOG FCGM UKCCCR AMCG EORTC 18991	(OS) Disease free survival (DFS)	improvement odds ratio = 0.88, 95% CI = 0.79– 0.99, p<0.03 Significant improvement odds ratio = 0.83, 95% CI = 0.75–0.92 p<0.0001	No quality assessment of studies updated data of E1684 (Kirkwood 2004) and EORTC 18871 (Kleeberg 2004) not included Conflict of Interest: Claus Garbe: Consultant/advisory role: Roche Pharma, MSD, Bristol-Myers Squibb, Swedish Orphan, Genta, GlaxoSmithKline; Research funding/contracted research: Roche Pharma, MSD, Bristol-Myers Squibb, Swedish Orphan, Genta, GlaxoSmithKline; Axel Hauschild: Consultant/advisory role: Abraxis Oncology, Bayer	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Schering, Bristol-Myers Squibb, Essex Pharma/Schering-Plough; Honoraria: GlaxoSmithKline, Merck, Onyx Pharmaceuticals, Pfizer, Roche Pharma, Synta Pharmaceuticals Corp.; John M. Kirkwood: Consultant/advisory role: Schering (for FDA review of PegIFN), GlaxoSmithKline (for chairmanship of vaccine steering committee).	
Mocellin et al. 2010	to examine the effect of IFN-alpha on DFS and OS in patients with high-risk cutaneous melanoma	Systematic review Adjuvant treatment with interferon alpha	14 RCTs (published 1990 – 2008) 8122 patients NCCTG ECOG 1684 AMCG FCGM	OS	Significant improvement HR for death = 0.89, 95% CI = 0.83–0.96; P=.002 Number needed to treat 29 patients	absolute risk reduction not reported Reported hazard ratio were used for meta-analysis	1a- (SR with heterogeneity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			ECOG 1690 SMG WHO ECOG 1694 E2696 UKCCCR EORTC 18871 EORTC 18952 DeCOG EORTC 18991	DFS	Significant improvement HR for disease recurrence = 0.82, 95% CI = 0.77-0.87; p<.001	updated data of E1684 (Kirkwood 2004) not included Data of E1694 and E2696 (control vaccination arm with potentially worse outcome) were included OS benefit was observed only when trials that used low or intermediate IFN- α doses were considered Funding: no funds involved All authors declared no conflict of interest.	
Verma et al. 2006	To examine the role of systemic adjuvant therapy	Systematic review	Interferon alpha: 13 RCTs, published 1980 - 2004 Metaanalysis: E1684, E1690,	OS	Metaanalysis E1684, E1690, E1694: significant Improvement RR (2 years) 0.85, 95% CI = 0.73-	Number needed to treat not reported No quality assessment of studies	1a- (SR with heterogeneity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			E1694		0.99; P=.03 not significant after exclusion of E1694: HR 0.87, 95% CI = 0.71-1.07; P=.18	only 3 RCTs were included into metaanalysis other RCTs and published metaanalyses were reported narratively Funding: Supported by Cancer Care Ontario and the Ontario Ministry of Health and Long- Term Care.	
Pirad et al. 2004	to evaluate the effect of IFN-alpha on the relapse rate (RR) and the overall survival (OS).	Systematic review	9 RCTs 2 880 patients ECOG 1684 NCCTG ECOG 1690 Rusciani FCGM AMCG SMG Kokoschka WHO	Metaanalysis OS RR	no significant benefit OR = 0.87; 95% CI =0.74-1.02; p = 0.1029 Significant lower OR = 0.74; 95% CI = 0.64-0.86; p = 0.0001	Number needed to treat not reported No quality assessment of studies heterogeneity tests are non-significant (=homogeneous effects of studies), but studies were heterogeneous in	1a- (SR with heterogene ity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						regard to the schedules, the classification used and the median time of follow-up Funding/Conflict of interest: not mentioned	
Wheatley et al. 2003	To assess all the available evidence for adjuvant interferon-alpha	Metaanalysis	12 RCTs ECOG 1684 ECOG 1690 NCCTG E2696 EORTC 18952 WHO UKCCCR FCGM AMCG SMG Kleeberg (18871) Kleeberg (DKG-80)	Metaanalysis OS RFS	no significant benefit HR = 0.93; 95% CI 0.85-1.02; p=0.1 significant benefit HR = 0.83; 95% CI 0.77-0.90; p=0.000003	Number needed to treat not reported few studies were used without existing publication, data of EORTC 18871 + DKG-80 were not reproducible within the later publication (Kleeberg et al. 2004) Funding/Conflict of interest: not mentioned	1a- (SR with heterogeneity)
Lens et al. 2002	to assess the benefit of IFN	Systematic review	9 RCTs, 8 RCTs included, 3 178	OS	analysis on available data for 2	High quality SR	1a- (SR with

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	alpha therapy in malignant melanoma		patients AMCG FCGM ECOG 1684 ECOG 1690 NCCTG SMG UKCCCR WHO	RFS	771 patients from 6 trials no study with benefit ECOG 1684: significant benefit, not confirmed analysis on available data for 2 020 patients from 4 trials 1 study with benefit ECOG 1684 significant benefit, confirmed ECOG 1690: significant benefit, not confirmed	Number needed to treat reported for each individual trial no metaanalysis due to heterogeneity of studies, the authors state that any recommendation should be made on the basis of an evaluation of the individual studies. Funding: Center for Evidence-Based Medicine, University of Oxford	heterogeneity)

5.5.6.2. Evidenztabelle – Niedrigdosis IFN alpha

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Garbe et al. 2008 DeCOG	to improve disease-free survival (DFS) and overall survival (OS) with interferon (IFN) α 2a with or without dacarbazine (DTIC) compared with observation alone	RCT Treatment groups LDI (LDI plus DTIC) OBS	444 patients, resected Stage III n=148 (n=148) n=148	OS DFS	LDI vs OBS significant benefit HR 0.62; 97.5% CI: 0.42-0.89; p=0.0045; events: 65/148 vs 88/148 significant benefit HR 0.69; 97.5% CI: 0.49-0.96; p=0.018; events: 84/148 vs 102/148	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: German Cancer Aid (Deutsche Krebshilfe); German Cancer Society (Frankfurt, Germany); Hoffmann-LaRoche AG (Grenzach- Whylen, Germany).	1b
Hancock et al. 2004 UKCCCR	To evaluate low-dose extended duration interferon α 2a	RCT Treatment groups LDI OBS	674 patients, resected stage IIB and stage III n=338 n=336	OS RFS	LDI vs OBS no benefit OR 0.94; 95% CI: 0.75-1.18; p=0.6; events: 151/338 vs 156/336 no benefit OR 0.91; 95% CI: 0.75-1.10; p=0.3; events: 211/338 vs 215/336	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: The study was supported by a grant from Roche Products Ltd	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Kleeberg et al. 2004 EORTC 18871	to evaluate the efficacy and toxicity of low dose recombinant interferon-alpha 2 b (rIFN-alpha2b) (1 MU) or recombinant interferon gamma in comparison with an untreated control group	RCT Treatment groups OBS very LDI alpha (very LDI gamma)	728 patients Stage II-III n=244 n=240 (n=244)	OS RFS	LDI vs. OBS no benefit HR 1.04; 95% CI: 0.84-1.30; events: 137/240 vs 148/244 no benefit HR 0.96; 95% CI: 0.76-1.21; events: 159/240 vs 158/244	Jadad Score 2 of 5 not placebo controlled, not blinded, randomization scheme not described Funding:Essex and Boeringer- Ingelheim, grant number 3U10- CA11488-18S1 through 5U10- CA11488-33 from the National Cancer Institute	1b
Cascinelli et al. 2001 WHO	to see whether interferon alpha-2a increased survival prospects in stage III melanoma patients	RCT Treatment groups OBS LDI	444 patients with lymph node involvement n=219 n=225	OS RFS	LDI vs. OBS no benefit HR n.r., p=0.72 events: 146/225 vs 138/219 no benefit HR n.r., p=0.5; events: 162/225 vs 158/219	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: not mentioned	1b
Cameron et al. 2001	To test the possible disease-	RCT	95 patients with at least 3mm Breslow		LDI vs. OBS no benefit	Jadad Score 2 of 5 not placebo	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
SMG	free and overall survival advantage of a short, 6-month course of low-dose IFN for patients with high-risk, surgically resected, malignant melanoma.	Treatment groups OBS LDI	thickness or lymph node involvement n=49 n=46	OS RFS	HR n.r., p>0.2; events: 31/46 vs 36/49 no benefit HR n.r., p>0.1; events: 32/46 vs 35/49	controlled, not blinded, randomization scheme not described Funding: not mentioned, IFN supplied by Schering-Plough	
Kirkwood et al. 2000 E1690	To evaluate the efficacy of high-dose IFN α 2b (HDI) for 1 year and low-dose IFN α 2b (LDI) for 2 years versus OBS	RCT Treatment groups OBS (HDI) LDI	642 patients, 75% nodal involvement n=212 (n=215) n=215	OS RFS	LDI vs. OBS no benefit HR 1.04 [§] ; 95% CI: 0.78-1.38; p=0.813; events: 96/215 vs 93/212 no benefit HR 1.19 [§] ; 95% CI: 0.93-1.53; p=0.171; events: 122/215 vs 127/212	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: not reported assistance of Schering-Plough Research Institute and Schering-Plough Oncology Biotech with posttrial data collection	1b
Grob et al. 1998 FCGM	To assess the efficacy of adjuvant low dose interferon alpha	RCT	489 patients, tumor thickness > 1.5mm without clinically	OS	LDI vs. OBS no benefit HR n.r., p=0.059 events: 59/244 vs	Jadad Score 3 of 5 not placebo controlled, not blinded	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Treatment groups OBS LDI	detectable node metastases n=245 n=244	RFS	76/245 significant benefit HR n.r., p=0.035 events: 100/244 vs 119/245	Funding: grant from Hoffman-La Roche Ltd, also provided the interferon α -2a (Roferon-A).	
Pehamberger et al. 1998 AMCG	To investigate whether adjuvant IFN α 2a diminishes the occurrence of metastases and thus prolongs disease-free survival in melanoma patients	RCT Treatment groups OBS LDI	311 patients, tumor thickness > 1.5mm n=157 n=154	OS RFS	LDI vs. OBS no benefit HR n.r., events: 17/154 vs 21/157 significant benefit HR n.r., p=<0.2 events: 37/154 vs 57/157	Jadad Score 2 of 5 not placebo controlled, not blinded, randomization scheme not described Funding: in part by Hoffmann-La Roche, Vienna, Austria.	1b
Rusciani et al. 1997	<i>to study the use of recombinant interferon-alpha (IFN-alpha) as adjuvant therapy for patients with Stage I and Stage II melanoma</i>	<i>RCT Treatment groups Obs LDI</i>	<i>84+ 70 patients, stages I+II, n=70 n=84</i>	<i>DFS</i>	<i>Significant benefit events LDI vs. OBS 11/84 vs 21/70</i>	<i>Jadad Score 0 of 5 matched controls, no randomisation, not placebo controlled, not blinded, no description of dropouts Study excluded</i>	<i>2b low quality RCT study excluded</i>

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
<i>Kokoschka et al. 1990</i>	<i>To evaluate the efficacy of rIFN alpha 2b therapy in high-risk melanoma patients stage I and stage II</i>	<i>Cohort Study Treatment groups OBS LDI</i>	<i>135 patients, stages I+II n=82 n=53</i>	<i>OS DFS</i>	<i>no significant benefit</i>	<i>Cohort Study Only included in SR by Pirad et al.</i>	<i>2b study excluded</i>

[§]HR relates to proportion alive and proportion relapsfree (> 1 = Favour IFN)

5.5.6.3. Evidenztabelle - Mittlere Dosis IFN alpha

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hansson et al. 2011 Nordic IFN trial	To investigate whether adjuvant therapy with intermediate-dose interferon alfa-2b for 1 or 2 years would improve outcomes in patients with stage IIB-IIC or III resected cutaneous melanoma	RCT Treatment groups OBS IDI 12 months IDI 24 months	855 patients stage IIB-IIC n=284 n=285 n=286	OS (12 months + 24 months) PFS (12 months + 24 months)	IDI vs. OBS no benefit HR 0.91; 95% CI: 0.74-1.10; p=0.642; events: 285/571 vs 148/284 significant benefit HR 0.80; 95% CI: 0.67-0.96; p=0.030; events: 338/571 vs 183/284	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: Schering-Plough; the Radiumhemmet Research Funds, Stockholm; and the Stockholm County Council	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				24 months alone	no benefit		
Eggermont et al. 2005 EORTC 18952	to assess the effect of two regimens of interferon of intermediate dose versus observation alone	RCT Treatment groups Intermediate IFN, 13 months Intermediate IFN, 25 months OBS	1388 patients n=553 n=556 n=279	OS 13 months 25 months DFS 13 months 25 months	IDI vs. OBS no benefit HR 1.00; 95% CI: 0.79-1.25; p=0.96; HR 0.85; 95% CI: 0.67-1.07; p=0.11; events: 535/1109 vs 146/279 no benefit HR 0.97; 95% CI: 0.78-1.20; p=0.72; HR 0.83; 95% CI: 0.67-1.03; p=0.05; events: 679/1109 vs 183/279	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: not mentioned The authors declared that they have no conflict of interest.	1b

5.5.6.4. Evidenztabelle - Hochdosis IFN alpha

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Kirkwood et al. 2004/1996 Update E 1684	To update the analyses To evaluate	RCT Treatment groups OBS	287patients, stages IIb and III n=137	OS	HDI vs. OBS Update: no benefit HR 1.22; 95% CI: n.r.; p=0.18;	Jadad Score 3 of 5 not placebo controlled, not blinded	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Initial Data E1684	Interferon alfa-2b as an adjuvant therapy	HDI	n=143	RFS	Initial: significant benefit HR n.r., p=0.0237 events 81/143 vs 90/137 significant benefit Update: HR 1.38, p=0.02 Initial: HR n.r., p=0.0023 events HDI vs. OBS 90/143 vs 103/137	Funding: grants from the National Institutes of Health, Bethesda, MD. Update: Grant CA-23318, awarded by the National Cancer Institute, United States Department of Health and Human Services.	
Kirkwood et al. 2000 E1690	To evaluate the efficacy of high-dose IFNalpha2b (HDI) for 1 year and low-dose IFNalpha2b (LDI) for 2 years versus OBS	RCT Treatment groups OBS HDI (LDI)	642 patients, 75% nodal involvement n=212 n=215 (n=215)	OS RFS	HDI vs OBS no benefit HR 1.00; 95% CI: 0.75-1.33; p=0.995; events HDI vs. OBS 98/215 vs 93/212 no benefit HR 1.28; 95% CI: 1.00-1.65; p=0.054; events HDI vs. OBS 114/215 vs 127/212 events LDI vs. OBS	Jadad Score 3 of 5 not placebo controlled, not blinded Impact on RFS only significant by Cox multivariable analysis Funding: not reported assistance of Schering-Plough Research Institute and Schering-	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					122/215 vs 127/212	Plough Oncology Biotech with posttrial data collection	
Creagan et al. 1995 NCCTG	To report a prospective randomized trial designed to determine the clinical efficacy in terms of recurrence rates, time to recurrence, and patient survival following IFN-a2a given as postsurgical adjuvant therapy to selected patients with high-risk stage I and II malignant melanoma	RCT Treatment groups OBS HDI	262 patients, stages I and II n=131 n=131	OS RFS	HDI vs OBS no benefit HR 0.83; 95% CI: 0.61-1.13; p=0.24; events: 68/131 vs 72/131 no benefit HR 0.90; 95% CI: 0.64-1.25; p=0.53; events: 77/131 vs 85/131	Jadad Score 2 of 5 not placebo controlled, not blinded, randomization scheme not described Funding: supported in part by Public Health	1b
Agarwala et al. 2011 E1697	To assess the benefit of 4 weeks of HDI compared with Observation in relation to the	RCT Treatment groups OBS	1150 patients T2N0, T3N0, T4N0, T1-4N1a-2a n=596	5-year survival rate	no benefit IFN vs OBS 0.82 vs 0.85	only ASCO abstract available	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<i>RFS and OS of patients with resectable intermediate and high-risk melanoma</i>	<i>HDI 4 weeks</i>	<i>n=581</i>	<i>RFS</i>	<i>6.8 vs 7.3 years</i>		
<i>McMasters et al. 2008</i> <i>Sunbelt Trial</i>	<i>To evaluate the role of high-dose interferon alfa-2b (IFN) or completion lymph node dissection (CLND) in patients with melanoma staged by sentinel lymph node (SLN) biopsy</i>	<i>RCT</i> <i>Treatment groups</i> <i>Observation</i> <i>HDI</i>	<i>218 patients, after SLN biopsy, 1 positive node</i> <i>n=106</i> <i>n=112</i>	<i>OS</i> <i>RFS</i>	<i>no benefit</i> <i>HR 1.07; CI: 0.65-1.78; p=0.79</i> <i>no benefit</i> <i>HR 0.82; 95% CI: 0.47-1.40; p=0.46</i>	<i>only ASCO abstract available</i>	
<i>Kirkwood et al. 2001</i> <i>E 1694</i>	<i>To evaluate the efficacy of HDI for 1 year versus vaccination with GM2</i>	<i>RCT</i> <i>Treatment groups</i> <i>HDI</i> <i>vaccination</i>	<i>874 patients, stages IIB/III</i> <i>n=385</i> <i>n=389</i>	<i>OS</i> <i>RFS</i>	<i>significant benefit events IFN vs. Vacc.</i> <i>52/385 vs 81/389</i> <i>significant benefit events IFN vs. Vacc.</i> <i>98/385 vs 151/389</i>	<i>Included in SR although no OBS Arm</i> <i>Funding: Eastern Cooperative Oncology Group grant no. NIH CA 39229-16 and R03 grant no. CA75950-02.</i>	
<i>Kirkwood et al.</i>	<i>To evaluate the</i>	<i>RCT</i>	<i>107 patients,</i>	<i>RFS</i>	<i>significant benefit</i>	<i>Included in SR</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
2001 E2696	<i>toxicity and other effects of the established adjuvant high-dose IFNalpha2b regimen in relation to immune responses to GMK</i>	<i>Treatment groups Vacc+HDI day 1 Vacc+HDI day 28 Vacc</i>	<i>stages IIB, III, and IV n=36 n=36 n=35</i>	<i>no OS analysis due to short follow up</i>	<i>events IFN+Vacc vs. Vacc. 28/72 vs 19/35</i>	<i>although no OBS Arm Funding: unrestricted grant from Dr Craig Tendler of Schering Plough Research Institute, provision of the vaccine by Drs Robert Israel and Paul Maddon of Progenics, Inc.</i>	

5.5.6.5. Evidenztabelle - Pegyliertes IFN alpha

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
<p>Eggermont et al. 2008/2011</p> <p>Update EORTC 18991</p> <p>Initial Data EORTC 18991</p>	<p>To present the long-term results at 7.6-years follow up</p> <p>To determine whether pegylated interferon alfa-2b can facilitate prolonged exposure while maintaining tolerability</p>	<p>RCT</p> <p>Treatment groups</p> <p>Observation</p> <p>Peylated IFN alfa-2b</p>	<p>1256 patients, resected Stage III</p> <p>n=629</p> <p>n=627</p>	<p>OS</p> <p>RFS</p>	<p>PegIFN vs. OBS no benefit</p> <p>Update: HR 0.96; 95% CI 0.82-1.11; p=0.57</p> <p>Events: 332/627 vs 336/629</p> <p>Initial: HR 0.98; 95% CI 0.82-1.16.; p=0.78 events: 262/627 vs 263/629</p> <p>significant benefit</p> <p>Update: HR 0.87; 95% CI 0.76-1.00, p=0.05 events: 384/627 vs 406/629</p> <p>Initial: HR 0.82; 95% CI 0.71-0.96; p=0.01 events: 328/627 vs 368/629</p>	<p>Jadad Score 3 of 5 not placebo controlled, not blinded</p> <p>Funding: Schering Plough Research International.</p>	<p>1b</p>

5.5.7. Subgruppenanalysen

Subgruppenvergleich Metaanalyse Mocellin et al. 2010: Stadium II versus Stadium III, kein signifikanter Unterschied

Study	No. of trials / patients	OS HR (95% CI)	No. of trials / patients	PFS HR (95% CI)	No. of trials / patients	OS HR (95% CI)	No. of trials / patients	PFS HR (95% CI)	Subgroup comparison	LoE
Mocellin et al. 2010	Stadium II			Stadium III			OS p=0.36 PFS p=0.42			2a
	1/499	0.70 (0.50 - 0.98)	2/810	0.70 (0.55 - 0.88)	3/2144	0.87 (0.68 - 1.11)	3/2144	0.82 (0.72 - 0.93)		

Subgruppenanalysen der eingeschlossenen randomisierten Studien

Study	Subgroup / No. of patients	OS, HR	p	PFS, HR	p	LoE
Hansson et al. 2011 (Intermediate Dose)	All patients / n=855	0.91	0.642	0.80	0.030	1b
	Stage IIB-IIC / n=166	n.r.	-	Favour IFN, n.s.	0.082	3b
	Stage III, palpable nodes / n=554	n.r.	-	Favour IFN	0.015	3b
	Stage III, 1 pos. node / n=374	n.r.	-	Favour IFN, n.s.	-	3b
	Stage III, 2-3 pos. node, n=201	n.r.	-	Favour IFN, n.s.	-	3b
	Stage III, >= 4 pos. node / n=114	n.r.	-	Favour IFN	0.038	3b
	Ulzeration, n=238	1.05, Favour Obs, n.s.	0.809	1.04, Favour Obs, n.s.	0.829	3b

Study	Subgroup / No. of patients	OS, HR	p	PFS, HR	p	LoE
Eggermont et al. 2011	2 studies, all patients, n = 2644	0.94	0.36	0.85	0.004	1a-
(Intermediate Dose+ Pegylated Interferon alpha)	N1, n=1154	0.81	0.07	0.78	0.01	3b
	N2, n=1031	1.01	0.92	0.91	0.25	3b
	No Ulceration, n=1336	1.11	0.20	0.92	0.30	3b
	Ulceration, n=849	0.72	0.001	0.75	0.001	3b
	Ulceration + N1, n=484	0.58	0.0003	0.69	0.003	3b
	Ulceration + N2, n=365	0.89	0.41	0.83	0.15	3b
McMasters et al. 2010	SN-, Ulceration, n=127	n.s.		n.s.		3b
	SN+, Ulceration, n=75	n.s.			0.0169	3b
	SN+, no Ulceration, n=147	n.s.		n.s.		
Kleeberg et al. 2004	St. IIb vs. St. III	IFN benefit: similar				3b
(Low Dose)						
Hancock et al. 2004	stage, age, sex	IFN benefit: n.s. differences				3b
(Low Dose)						
Kirkwood et al. 2000	T4 N0 M0			1.46	0.20	3b
	T1-4 N1 M0			1.16	0.74	3b
(Benefit of High Dose)						

Study	Subgroup / No. of patients	OS, HR	p	PFS, HR	p	LoE
	T1-4 N1-2 M0			1.57	0.20	3b
	Recurrent N+			1.27	0.18	3b
	N0			1.46	0.19	3b
	N1			1.0	0.99	3b
	N2-3			1.92	0.02	3b
	N \geq 4			1.15	0.58	3b
Creagan et al. 1995 (High Dose)	Stage I			n.s.	0.93	3b
	Stage II			Favour IFN, n.s.	0.09	3b

5.5.8. Toxizität

Study	Treatment groups (number of patients)	Treatment related deaths	Discontinuation because of toxicity	Number of patients with Grade 3 or 4 Toxicities (%)	Fatigue Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Depression Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Neutropenia Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Hepatotoxicity Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)
Agarwala et al. 2011	OBS (n=596) HDI 4 weeks (n=581)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Eggermont et al. 2008	OBS (n=629) Peylated IFN alfa-2b (n=627)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Hansson et al. 2011	OBS (n=284)	n=0		n.r.	n=106 (37%) / n=5 (2%)	n=108 (38%) / n=1 (<1%)	n.r.	n=41 (14%) / n=2 (1%)*
Nordic IFN trial	IDI 12 months (n=285) IDI 24 months (n=286)		n=72 (25%) n=72 (25%)		n=267 (94%) / n=28 (10%) n=266 (93%) / n=32 (11%)	n=210 (74%) / n=17 (6%) n=214 (75%)		n=118 (41%) / n=2 (1%)* n=122 (43%) / n=6 (2%)* *ALAT
Kirkwood et al. 1996	OBS (n=140) HDI (n=146)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.

Study	Treatment groups (number of patients)	Treatment related deaths	Discontinuation because of toxicity	Number of patients with Grade 3 or 4 Toxicities (%)	Fatigue Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Depression Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Neutropenia Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Hepatotoxicity Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)
Eggermont et al. 2008 EORTC 18991	OBS (n=629, Tox. assessed n=613)	n.r.		n=74 (12%)	n=252 (41%) / n=7 (1%)	n=153 (25%) / n=3 (<1%)	n.r.	n=221 (36%) / n=10 (2%)*
	Peplated IFN alfa-2b (n=627, Tox. assessed n=608)		n=191 (31%)	n=278 (46%)	n=574 (94%) / n=97 (16%)	n=360 (59%) / n=39 (6%)		n=479 (79%) / n=66 (11%)* *Liver function test
Garbe et al. 2008 DeCOG	LDI (n=148) (LDI plus DTIC) OBS (n=148)	n.r.	n=20 (14%)	n=13 (9%)	n.r.	n.r.	n.r.	n.r. / n=0
Eggermont et al. 2005 EORTC 18952	Intermediate IFN, 13 months (n=553, tox. assessed n=521)	n=0	n=87 (16%) (N=539)	n.r.	n.r. / 78 (15%)	n.r. / n=62 (12%)	n.r.	n.r. / n=16 (3%)
	Intermediate IFN, 25 months (n=556, tox. assessed n=532)		n=108 (20%) (N=539)		n.r. / n=67 (13%)	n.r. / n=56 (11%)		n.r. / n=21 (4%)

Study	Treatment groups (number of patients)	Treatment related deaths	Discontinuation because of toxicity	Number of patients with Grade 3 or 4 Toxicities (%)	Fatigue Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Depression Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Neutropenia Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Hepatotoxicity Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)
	OBS (n=279, tox. assessed n= 252)				n.r. / n=5 (2%)	n.r. / n=9 (4%)		n.r. / n=1 (<1%)
Hancock et al. 2004 UKCCCR	LDI (n=338, tox. assessed range 322-327)) OBS (n=336)	n=0	n=50 (15%)	n=56 (17%)	n=265 (78%) / n=22 (7%) n=116 (38%) / n=4 (1%)	n=179 (55%) / n=11 (3%) n=94 (31%) / n=5 (2%)	n.r.	n=113 (35%) / n=7 (2%) n=65 (22%) / n=1 (<1%)
Kleeberg et al. 2004 EORTC 18871	OBS (n=244) very LDI alpha (n=240) (very LDI gamma, n=244)	n.r.	n=11 (5%)	n.r.	n.r.	n.r.	n.r.	n.r.
Cascinelli et al. 2001 WHO	OBS (n=219) LDI (n=225)	n.r.	n=0	n.r.	n.r.	n.r.	n.r.	n.r.

Study	Treatment groups (number of patients)	Treatment related deaths	Discontinuation because of toxicity	Number of patients with Grade 3 or 4 Toxicities (%)	Fatigue Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Depression Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Neutropenia Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Hepatotoxicity Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)
Cameron et al. 2001 SMG	OBS LDI	n=0	n=0	n.r.	n.r.	n.r.	n.r.	n.r.
Kirkwood et al. 2000 E1690	OBS (n=212) HDI (n=215) LDI (n=215)	n=0	n.r.	n.r.	n.r. / n=0 n.r. / n=51 (24%) n.r. / n=7 (3%)	n.r. / n=0 n.r. / n=20 (9%) n.r. / n=5 (2%)	n.r. / n=0 n.r. / n=94 (44%) n.r. / n=12 (6%)	n.r. / n=6 (3%) n.r. / n=61 (29%) n.r. / n=9 (4%)
Grob et al. 1998 FCGM	OBS (n=245) LDI (n=244)	n=0	n=35 (14%)	n.r. n=24 (10%)	n.r. n=118 (48%) / n=5 (2%)	n.r. n=40 (16%) / n=3 (1%)	n.r. n.r. / n=6 (2%)	n.r.
Pehamberger et al. 1998 AMCG	OBS (n=157) LDI (n=154)	n.r.	n=5 (3%)	n.r.	n.r.	n.r.	n.r.	n.r.
Kirkwood et al. 1996 E 1684	OBS (n=137) HDI (n=143)	n=2 (lethal hepatic toxicity)	26%	67%	n.r. n=140 (100%) / n=69 (48%)*	n.r. n=118 (83%) / n=40 (28%)*	n.r.	n.r. n=89 (62%) / n=20 (14%)

Study	Treatment groups (number of patients)	Treatment related deaths	Discontinuation because of toxicity	Number of patients with Grade 3 or 4 Toxicities (%)	Fatigue Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Depression Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Neutropenia Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	Hepatotoxicity Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)
					*constitutional symptoms including fatigue	*neurologic		
Creagan et al. 1995 NCCTG	OBS (n=131) HDI (n=131)	n.r.	n.r.	n.r.	n.r. n=117 (89%) / n=26 (20%)	n.r.	n.r.	n.r.

5.5.9. Metaanalysen

Eine Metaanalyse wurde mit 13 Studien (14 Vergleiche) unter Einschluss der in bisherigen Metaanalysen nicht erfassten Studie von Hansson et al. 2011 wurden nach den definierten Ein- und Ausschlusskriterien durchgeführt (kein Einschluss bei fehlendem Beobachtungsarm, damit Ausschluss E1694 und E2696: Vergleichsarm jew. Vakzine).

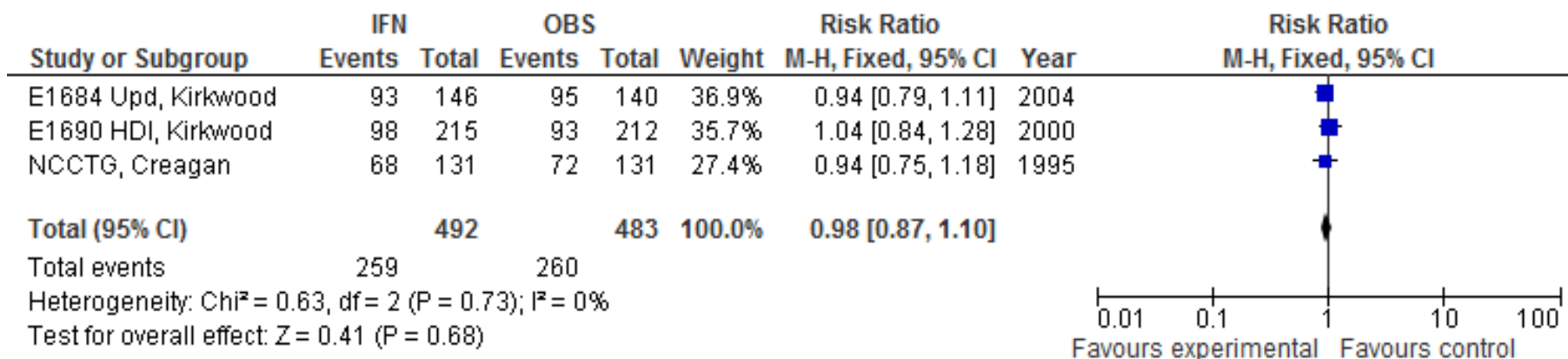
Aufgrund der Heterogenität der Studien keine Metaanalyse über alle 14 Vergleiche, sondern getrennt nach verschiedenen Dosis Schemata:

- Hochdosis Interferon alpha
- Mittlere Dosis Interferon alpha
- Niedrigdosis Interferon alpha

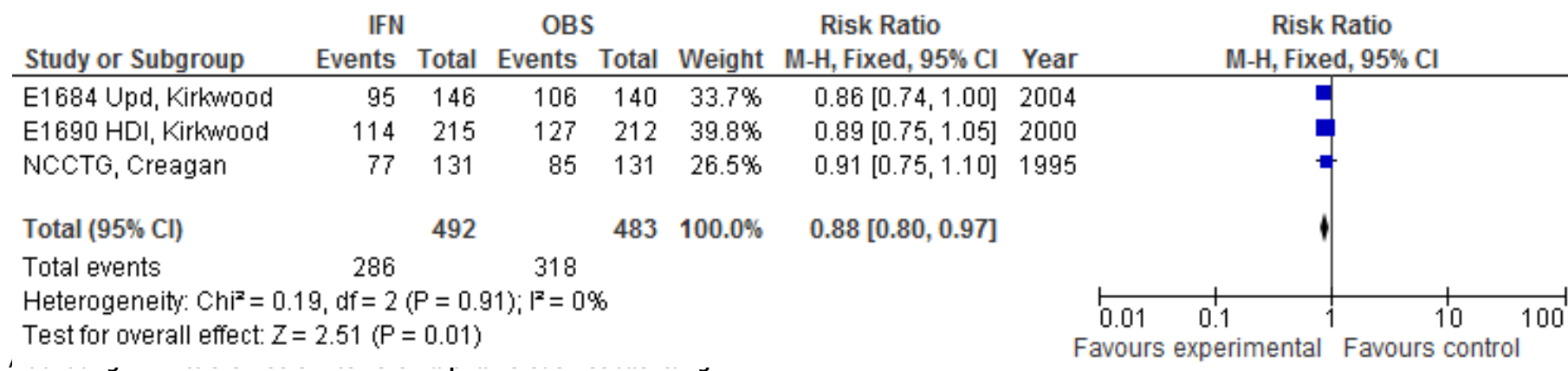
Limitation: unterschiedliche Follow up Perioden innerhalb der Studien
Auswertung durch Review Manager 5.1, The Cochrane Collaboration

Abbildung 1: Hochdosis Interferon alpha versus Beobachtung

Outcome: Mortalität Risk Ratio: 0.98 CI [0.87, 1.10] n.s

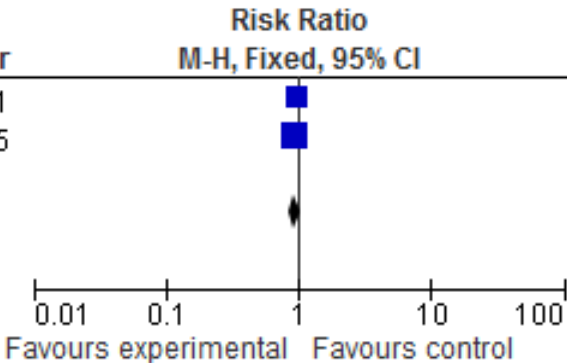


Outcome: Progression Risk Ratio: 0.88 CI [0.80, 0.97] sign.



Outcome: Mortalität Risk Ratio: 0.94 CI [0.85, 1.03] n.s

Study or Subgroup	IFN		OBS		Weight	Risk Ratio		Year
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
NordicTrial, Hansson	285	571	148	284	45.9%	0.96 [0.83, 1.10]	2011	
EORTC 18952, Eggermont	535	1109	146	279	54.1%	0.92 [0.81, 1.05]	2005	
Total (95% CI)		1680		563	100.0%	0.94 [0.85, 1.03]		
Total events	820		294					
Heterogeneity: Chi ² = 0.16, df = 1 (P = 0.69); I ² = 0%								
Test for overall effect: Z = 1.33 (P = 0.18)								



Outcome: Progression Risk Ratio: 0.93 CI [0.86, 1.00] sign.

Study or Subgroup	IFN		OBS		Weight	Risk Ratio		Year
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
NordicTrial, Hansson	338	571	183	284	45.5%	0.92 [0.82, 1.03]	2011	
EORTC 18952, Eggermont	679	1109	183	279	54.5%	0.93 [0.85, 1.03]	2005	
Total (95% CI)		1680		563	100.0%	0.93 [0.86, 1.00]		
Total events	1017		366					
Heterogeneity: Chi ² = 0.05, df = 1 (P = 0.83); I ² = 0%								
Test for overall effect: Z = 2.05 (P = 0.04)								

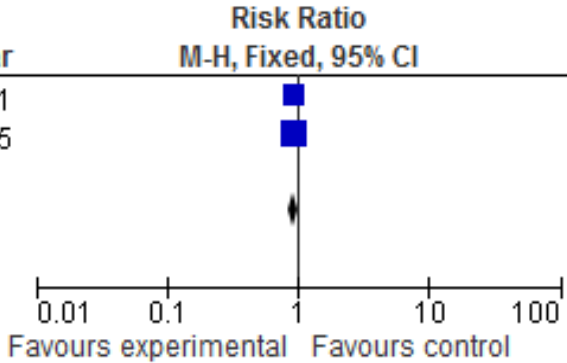
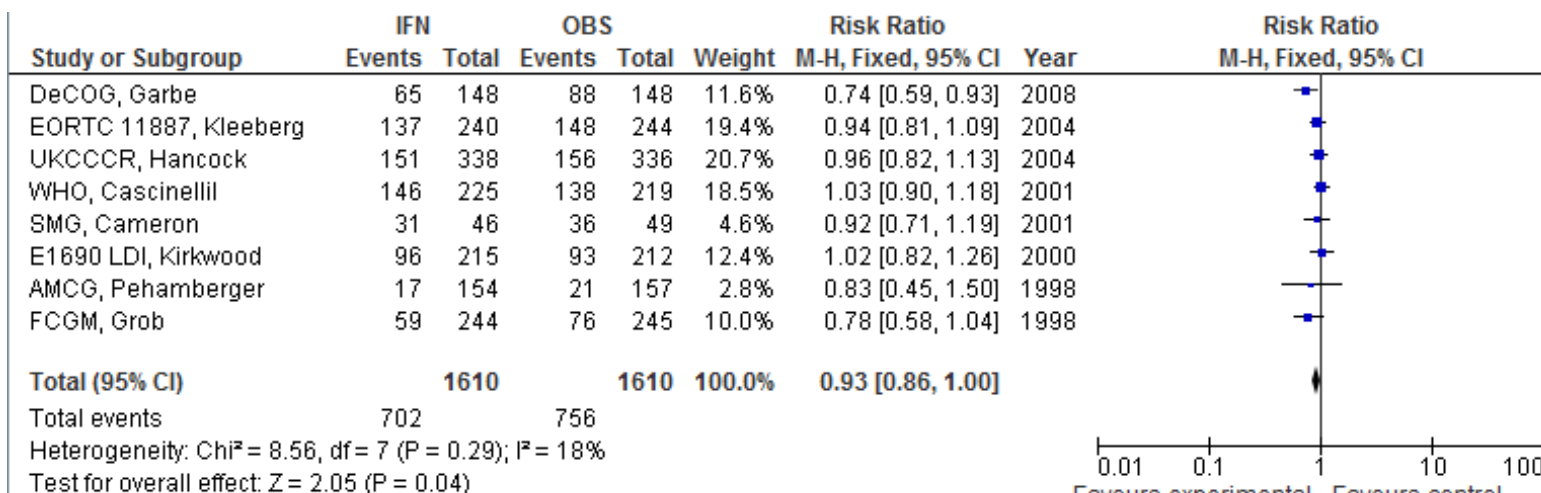
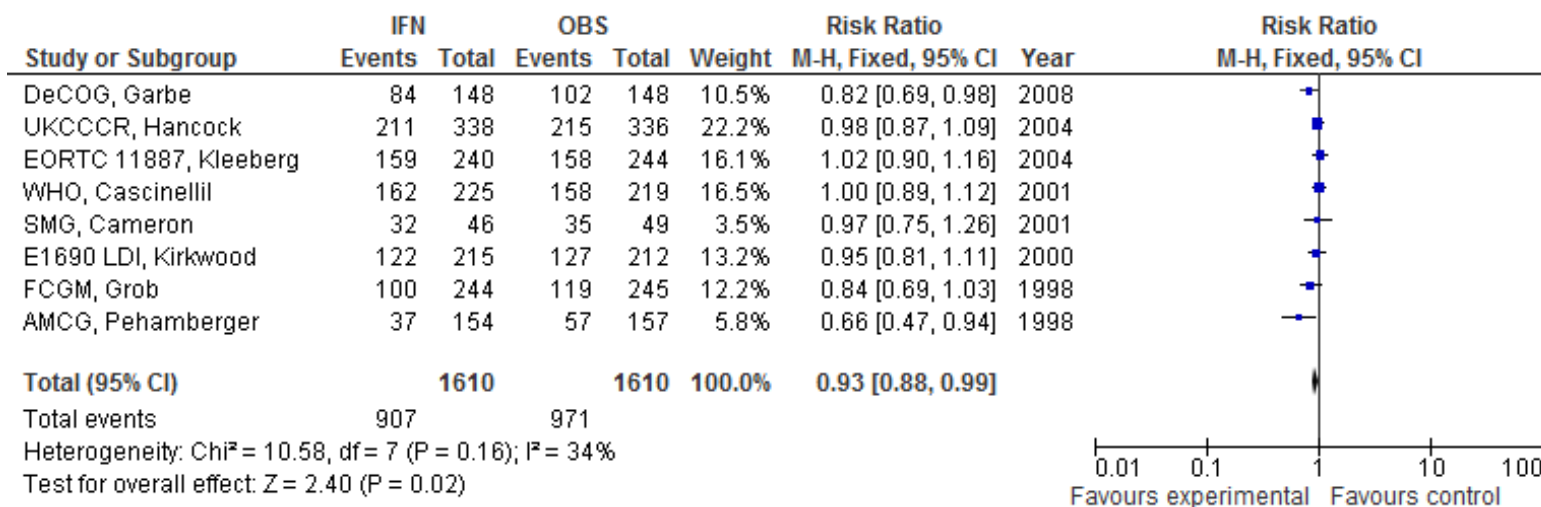


Abbildung 3: Niedrigdosis Interferon alpha versus Beobachtung

Outcome: Mortalität Risk Ratio: 0.93 CI [0.86, 1.00] **sign.**Outcome: Progression Risk Ratio: 0.93 CI [0.88, 0.99] **sign.**

5.5.10. Literatur

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6. AG Medikamentöse Therapie bei Metastasierung

6.1. Frage V.1. Lokale medikamentöse Therapie Intransitmetastasen – De novo Recherche

Frage V.1. Welche therapeutischen (außer operativen) Maßnahmen sind bei Satelliten- und Intransit-Metastasen effektiv?

6.1.1. PICO, Suchwörter

PICO - Schema

Population	Intervention	Comparison	Outcome
Melanoma patients with locoregional metastases	Local therapies (except surgery, radiotherapy, extremity perfusion)	Standard of care	Efficacy

Suchwörter

Stichwort	melanoma	Satellite Metastasis In-Transit Metastasis	therapy	interleukin-2, IL-2; rose bengal; imiquimod; DNCB, dinitrochlorobenzene; DPCP, diphenacyprone; interferon beta, interferon- β ; electrochemotherapy
Synonyme		Local recurrence Locoregional spread	treatment	
Ober-/Unterbegriffe				
Mesh Term	melanoma	Neoplasm Recurrence, Local	therapeutics	

6.1.2. Datenbanken, Suchstrategien, Trefferzahlen

6.1.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	("melanoma"[tiab] OR "melanoma"[MeSH]) AND ("Satellite metastases"[tiab] OR "Satellite metastasis"[tiab] OR "In-transit metastases"[tiab] OR "In-transit metastasis"[tiab] OR "Intransit metastases"[tiab] OR "Intransit metastasis"[tiab] OR "Local recurrence"[tiab] OR "Locoregional recurrence"[tiab] OR "Locoregional spread"[tiab] OR "Locoregional metastases"[tiab] OR "Locoregional metastasis"[tiab] OR intratumo*[tiab] OR "intralesional"[tiab] OR "Neoplasm Recurrence, Local"[MeSH]) AND ("therapy"[tiab] OR "treatment"[tiab] OR "therapeutics"[MeSH] OR "interleukin-2"[tiab] OR "IL-2"[tiab] OR "rose bengal"[tiab] OR "imiquimod"[tiab] OR "dinitrochlorobenzene"[tiab] OR „DNCB“[tiab] OR "diphencyprone"[tiab] OR "DPCP"[tiab] OR "interferon beta"[tiab] OR "interferon-β"[tiab] OR "electrochemotherapy"[tiab])	16.12.10	2322
Embase	(melanoma and ("satellite metast*" or "In-transit metast*" or "Intransit metast*" or "local recurrence" or "locoregional recurrence" or "locoregional spread" or "locoregional metast*" or "locoregional metast*") and (therapy or treatment)).ti,ab.	12.10.10	579
Medline - Erweiterung der Suchstrategie	("melanoma"[tiab] OR "melanoma"[MeSH]) AND ("Satellite metastases"[tiab] OR "Satellite metastasis"[tiab] OR "In-transit metastases"[tiab] OR "In-transit metastasis"[tiab] OR "Intransit metastases"[tiab] OR "Intransit metastasis"[tiab] OR "Local recurrence"[tiab] OR "Locoregional recurrence"[tiab] OR "Locoregional spread"[tiab] OR "Locoregional metastases"[tiab] OR "Locoregional metastasis"[tiab] OR intratumo*[tiab] OR "intralesional"[tiab])	06.04.11	2467

Datenbank	Suchstrategie	Datum	Treffer
	OR "Neoplasm Recurrence, Local"[MeSH] OR "cutaneous metastases" OR "skin metastases" OR "cutaneous melanoma metastases" OR "skin melanoma metastases") AND ("therapy"[tiab] OR "treatment"[tiab] OR "therapeutics"[MeSH] OR "interleukin-2"[tiab] OR "IL-2"[tiab] OR "rose bengal"[tiab] OR "imiquimod"[tiab] OR "dinitrochlorobenzene"[tiab] OR „DNCB“[tiab] OR "diphencyprone"[tiab] OR "DPCP"[tiab] OR "interferon beta"[tiab] OR "interferon-β"[tiab] OR "electrochemotherapy"[tiab])		
Update Suche			
Medline	s.o.	31.01.12	2586 (3 dazu: Boyd et al. 2011, Florin et al. 2011, Kis et al. 2011)
Cochrane Library	s.o.	31.01.12	13 (0 dazu)
Embase	s.o.	23.01.12	668 (0 dazu)

6.1.2.2. Aktualisierungsrecherche 2015

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	((("melanoma"[tiab] OR "melanoma"[MeSH])AND ("Satellite metastases"[tiab] OR "Satellite metastasis"[tiab]OR "In-transit metastases"[tiab] OR "In-transit metastasis"[tiab]OR "Intransit metastases"[tiab] OR "Intransit metastasis"[tiab]OR "Local recurrence"[tiab] OR "Locoregional	16.09.15	572

Datenbank	Suchstrategie	Datum	Treffer
	recurrence"[tiab]OR "Locoregional spread"[tiab] OR "Locoregional metastases"[tiab]OR "Locoregional metastasis"[tiab] OR intratumo*[tiab] OR "intralesional"[tiab] OR "Neoplasm Recurrence, Local"[MeSH] OR "cutaneous metastases"OR "skin metastases" OR "cutaneous melanoma metastases"OR "skin melanoma metastases")AND ("therapy"[tiab] OR "treatment"[tiab]OR "therapeutics"[MeSH] OR "interleukin-2"[tiab] OR "IL-2"[tiab]OR "rose bengal"[tiab] OR "imiquimod"[tiab] OR "dinitrochlorobenzene"[tiab]OR „DNCB“[tiab] OR"diphencyprone“[tiab] OR "DPCP"[tiab] OR "interferon beta"[tiab] OR "interferon-β"[tiab] OR "electrochemotherapy"[tiab])) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication])		
Cochrane Library	(melanoma and ("Satellite metastasis" or " In-transit metastases")).ti,ab.	16.09.2015	2 (0 dazu)

6.1.3. Auswahlkriterien

6.1.3.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer	3267
Einschlusskriterien	Thematische Übereinstimmung (gemeinsame Berichte verschiedener Tumorentitäten wurden ausgeschlossen) Sprachen: e, dt Klinische Studien Bei nicht Vorhandensein von Studien Einschluss von Fallserien ab 3 Patienten
Ausschlusskriterien	Nicht systematische Reviews Case Reports Intratumorale Therapie als Systemtherapie

Auswahl der Literatur	
Anzahl nach Abstractscreening, vorgesehen für Bewertung	63
Anzahl ausgewählter Volltexte	36
Die ausgewählten Arbeiten wurden wie folgt zusammengefasst: Immunmodulation (Interleukin-2, Imiquimod, BCG, Interferon beta, GM-CSF, Interferon gamma, Mycobacterium smegmatis) Ablative Therapien (Elektrochemotherapie, lokale Chemotherapie, Bengal Rosa, Carbon Laser) Contact Sensitizer (Dinitrochlorobenzene, Diphencyprone)	

6.1.3.2. Aktualisierungsrecherche 2015

Auswahl der Literatur	
Gesamttreffer	574
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e, dt Klinische Studien, Phase III Systematische Reviews
Ausschlusskriterien	Nicht systematische Reviews Case Reports Intratumorale Therapie als Systemtherapie
Anzahl ausgewählter Volltexte	5
Die ausgewählten Arbeiten wurden wie folgt zusammengefasst: Immunmodulation (Interleukin-2, Imiquimod, BCG, Interferon beta, GM-CSF, Interferon gamma, Mycobacterium smegmatis) Ablative Therapien (Elektrochemotherapie, lokale Chemotherapie, Bengal Rosa, Carbon Laser) Contact Sensitizer (Dinitrochlorobenzene, Diphencyprone)	

6.1.4. Evidenztabelle

6.1.4.1. Primärrecherche 2012

Immunmodulation (Interleukin-2, Imiquimod, Interferon alpha, Interferon beta, Interferon gamma, BCG)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Boyd et al. 2011	To document the response of in-transit metastases to intra-lesional IL-2 injection	Case Series Treatment: IL-2 intralesional biweekly	39 patients with 629 intransit metastases	Response 5 year survival	Patients: CR 51% PR 31% No response 18% Lesions: Responserate 76% Complete responders versus partial responder 80% versus 33% (p= 0.012)	Response was evaluated for patients and for treated lesions separately. Limitations: Lack of control group	4
Florin et al. 2011	To treat cutaneous metastases of malignant melanoma in a series of patients with imiquimod and 5-fluorouracil creams	Case Series Treatment: 5-fluorouracil cream in the morning and 5% imiquimod cream at night, 5 days per week, until response	5 patients with 45 intransit metastases	Response	CR = 19 lesions PR = 25 lesions SD = 1 lesion	Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Weide et al. 2010	To confirm the previous results with intralesional IL-2 in a larger cohort and to identify relevant patient or regimen characteristics associated with response to treatment and with overall survival.	Phase II prospective open label study Treatment was initiated at 3 MIU IL-2 daily, dose escalation 1.5 MIU each treatment day. Schedule: 3 times weekly	51 patients enrolled, 48 patients evaluable with injectable dermal or subcutaneous metastases, Stage III (69%) or Stage IV (31%) no concomitant systemic chemotherapeutic 894 of 917 separately treated metastases (97.5%) were evaluable for local tumor response	Clinical Response Overall Survival Toxicity	Patients: Complete local response 33 patients (69%), (Stage III 82%, Stage IV 40%) Lesions: 78.7% CR rate, 0.7% PR rate, 16.3% stable metastases, and 4.3% progressive lesions. Overall Survival after 2 years: Stage III 77%, Stage IV 53%) Toxicity: only grad 1 and 2 toxicity, (injection site reaction, injection pain, fever, nausea, fatigue)	Response was evaluated for patients and for treated lesions separately. Response for patients applied to local response. Limitations: Lack of control group	4
Dehesa et al. 2009	To describe the experience over 2 years with the use of intralesional IL-2 to treat cutaneous metastases of malignant melanoma in 7	Case Series Treatment: twice weekly, starting with 3 MIU IL-2	7 melanoma patients with satellitosis and cutaneous metastases 244 lesions no other organs	Response Toxicity	Lesions: Complete remission 95.9% of treated lesions Partial remission: 3.7% of treated lesions Toxicity: few mild	Limitations: Case Series, small sample size	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients.		involved		side effects (grade 1-2).		
Fujimura et al. 2009	To report 3 patients who were treated with peritumoral injection of interferon beta	Case Series Treatment: peritumoral interferon beta	3 melanoma patients Stage IV M1a	Reponse	Target lesion: 1 CR, 2 PR	Limitations: Case Series, small sample size	4
Green et al. 2006	To investigate the combination of topical imiquimod and intralesional IL-2, to treat a small cohort of patients with accessible melanoma metastases resistant to other treatments	Phase I/II prospective open label study Treatment: after 4 weeks of 5% imiquimod cream daily, start of IL-2 intralesional or subcutaneously in addition to imiquimod cream	13 patients, Stage III or IV with cutaneous and/or subcutaneous lesions 182 lesions	Response	Lesions: CR: 74 lesions (40,7%) PR: 18 lesions (9,9%) SD: 53 lesions (29,1%) PD: 33 lesions (18,1%) 4 lesions were not assessable (2,2%)	Regressed lesions with remained pigmentation were classified as PR (possible explanation for low CR rates compared to other studies) Limitations: heterogenous treatment schedules	4
Khorana et al. 2003	To determine the safety and tolerability of intratumoral injection with adeno-IFN-g, and to determine the maximum	Phase I single-center dose-escalation study Treatment: 4 successive dose levels: 107 infectious units (iu)	11 patients with histologically confirmed locally recurrent or metastatic malignant melanoma	Safety Toxicity	No treatment related death, no grade 4 or dose-limiting toxicities Most frequently observed toxicities grade 1 pain and/or	Limitations: Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	tolerated dose	(n=3), 108 iu (n=3), 109 iu (n=3), and 1010 iu (n=2) per injection per week for 3 weeks.		Response	redness at the injected site in 8/11 (72%) patients, and grade 1 fatigue in 5/11 (45%) patients. Local response: 5 of 11 patients: minor decrease in size (<25%) of the injected lesion Distant response: SD: 1 of 11 patients PD: 10 of 11 patients		
Paul et al. 2003	To examine the effect of intralesional beta- interferon injections combined with radiotherapy in patients with metastatic malignant melanoma	Case Series Treatment: simultaneous external beam radiotherapy and intralesional injection of beta- interferon. 3- 5 Mio IE / 3x/week	20 patients with inoperable melanoma metastases	Response	17 patients evaluatable CR: 12 patients (70%) PR: 5 patients (30%)	Limitations: Lack of control group Combined treatment with radiotherapy	4
Radny et al. 2003	To investigate the	Phase II	24 melanoma	Response	Lesions:	Response was	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	feasibility, efficacy, and safety of intralesionally injected IL-2 in 24 melanoma patients with skin and soft-tissue metastases	prospective open label study Treatment: 2-3 times weekly, 1-57 weeks, max. daily dose 12 MIU IL-2	patients with skin and soft-tissue metastases 16 patients Stage III 8 patients Stage IV 245 lesions	Safety	CR: 209 lesions (85%) PR: 21 lesions (6%) PD: 7 lesions (3%) 8 lesions (3%) were not assessable Patients, local response: CR: 15 patients PR: 3 patients Main toxicities (grade I+II): Local reaction, Fever, Flu-like symptoms, Pain, Fatigue, Nausea/vomiting	evaluated for patients and for treated lesions separately. Response for patients applied to local response. Limitations: single centre study, lack of control group	
Bong et al. 2002	to study imiquimod as an adjuvant for treating cutaneous metastases of malignant melanoma	Case Series Treatment: Twice daily application of imiquimod 5% cream, 21-28 weeks	3 melanoma patients with multiple cutaneous in-transit metastases	Response	>90% regression in 2 patients, in one patient complete response after addition of intralesional IL-2	Limitations: Small series	4
Si et al. 1996	To examine whether intralesional injections of GM-CSF induce regression of	Phase I study Treatment: weekly injections of 15-50mg GM-CSF into two subcutaneous	13 melanoma patients with at least 3 subcutaneous metastases Stage III or IV (6 patients)	Response	Local response: PR 1 patient SD 8 patients PD 4 patients	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	subcutaneous metastases in patients with melanoma and influence lymphoid infiltrates in and around the metastases	metastases up to 6 months					
Tan et al. 1993	To determine the role of BCG immunotherapy in malignant melanoma	Systematic review <i>Stage I and II: RCTs of BCG (adjuvant therapy)</i> Stage III: RCTs (combination BCG-chemotherapy) + trials on intralesional and oral BCG monotherapy	Stage III, intralesional therapy (local therapy): 15 non placebo controlled trials of intralesional BCG were identified	Response	Stage III, intralesional BCG trials: Pooled average complete response: 19%, PR 26%, extended survival 13% of patients. Threefold greater rate of regression with intralesional BCG for intradermal metastases compared with subcutaneous and/or visceral metastases	Selected intralesional BCG trials were not described in detail: number of treated lesions and lesions response not indicated, control groups not indicated	4*
Fierlbeck et al. 1992	To compare the effect of intralesional beta-	Case Series Treatment:	10 patients with cutaneous or subcutaneous	Lesion Response	Group 1 (n=8) CR:2, PR:1, SD:3, PD:2	Limitations: Small sample size	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	interferon at different dosages	Group 1: 5x10 ⁶ I.E. rIFN-beta 3x/week Group 2: 5x10 ⁶ I.E. rIFN-beta 1x/week Group 3: 3x10 ⁶ I.E. rIFN-beta 1x/week	melanoma metastases 19 lesions		Group 2 (n=8) CR:3, PR:2, SD:2, PD:1 Group 3 (n=3) CR:0, PR:0, SD:1, PD:2		
Von Wussow et al. 1988	To study the effects of higher IFN concentrations on malignant melanoma metastases, patients were treated with intralesional IFN injections.	Retrospective evaluation Treatment: Systemic and intralesional Interferon alpha	51 patients	Lesion Response	Intralesional treatment (lesions n= 51) CR n=16 PR n=7 NC n=26 PD n=2	26 patients were treated with human interferon alpha and 25 patients with recombinant interferon alpha	4
Lokich et al. 1979	To describe the treatment with intralesional methanol extraction residue of bacillus Calmette Guerin (MER-BCG)	Case Series Treatment: Single injection with MER-BCG	6 patients with cutaneous or subcutaneous melanoma metastases 9 lesions	Lesion response	Complete regression: 3 lesions Partial regression: 2 lesions Erythema/no regression: 4	-	4
Vosika et al. 1979	To investigate the clinical pharmacology and efficacy of	Phase I study Treatment: every 1 or 2 weeks CWS/P3	15 melanoma patients Stage III and IV (8 patients)	Response injected and non-injected lesions	In 6 (40%) of the 15 patients, response (CR+PR) of at least	Limitations: Small series, lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	intralesional immunotherapy utilizing a vaccine composed of Mycobacterium smegmatis cell wall skeleton and the mycobacterial glycolipid fraction				one injected lesion was observed. In 4 of these 6 patients, noninjected disease also responded. 1 patient had PR of pulmonary metastasis in addition to CR of injected lesion.		
Nathanson et al. 1979	To compare the efficacy of treatment with BCG when it was alternatively administered either by intralesional injection, or intradermally in a nontumor bearing site, using the multipuncture (Tine) technique	Randomised prospective study Treatment: IL-BCG Group: BCG intralesionally in the base of each lesion once a week for 6 weeks (up to 5 lesions) MPV-BCG: Multiple puncture BCG once a week for 6 weeks	59 patients with histologically proven, surgically incurable melanoma, with measurable lesions in or associated with the skin	Response Rate Survival Toxicity	IL-BCG vs. MPV-BCG (44 patients evaluable) 45% vs. 9% for 21.1 vs. 13.3 months More severe toxicity was observed in the IL-BCG group, but no deaths were seen due to toxicity in either group	the study design does not cover the question of literature search (efficacy of local treatments compared to standard treatment), the study is therefore downclassified as level 4 study Limitations: Imbalance of groups: more male patients in the IL-BCG group, randomization	4*

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						scheme not described	
Storm et al. 1979	To describe the treatment with intralesional bacille Calmette Guerin and hyperthermic perfusion	Case Series Treatment: Injection of lesions with Glaxo strain bacille Calmette Guerin every 2-3 weeks	27 melanoma patients with locally recurrent disease	Response	Complete or transient local disease control: 20 of 27 patients	number of treated lesions not indicated	4
Krown et al. 1978	To determine the optimal dose, schedule and toxicity of MER (methanol extraction residue of bacillus Calmette-Guerin) given by the il route, and to compare it with BCG in terms of tumor regression and side effects.	Phase I study Treatment: 1-5 lesions were injected with 0.1 - 0.5 mg of MER on the first day, the dose was adjusted daily, depending upon the degree of local reaction and systemic effects	22 patients with skin and subcutaneous metastases without visceral metastases	Response Toxicity	18 patients evaluable CR of all injected lesions: 8 patients PR: 4 patients 6 patients did not respond Fever (100%), Chills (45%), Malaise (50%), Headache (45%), Nausea and vomiting (18%), Hypotension (14%), Lethargy (14%), Cyanosis (9%), Confusion (5%)	number of treated lesions not indicated	4

Ablative Therapien (Elektrochemotherapie, lokale Chemotherapie, Bengal Rosa, Carbon Laser)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Kis et al. 2011	To investigate ECT treatment in melanoma patients	Case Series Treatment: ECT with i.v. bleomycin (15 mg/m ²) under general sedation	9 patients with 158 cutaneous and subcutaneous metastases	Response	CR 23% PR 39% No change 30% PD 8%	-	4
Foote et al. 2009	To report three cases of intralesional rose bengal treatment followed by radiotherapy	Case Series	3 patients with cutaneous metastases	Response	Local complete response in all 3 patients	-	4
Thompson et al. 2008	To investigate the therapeutic potential of PV-10 (Rose Bengal) in patients with stage III metastatic melanoma.	Open label phase II study Treatment: One single IL injection of PV-10 in 1-3 target lesions	11 patients with locoregionally recurrent melanoma, Stage III 26 lesions treated 28 lesions untreated (to assess potential bystander effect)	lesion response overall response bystander effect toxicity	25 lesions evaluable: CR 36% (n=9) PR 12% (n=3) SD 28% (n=7) PD 24% (n=6) Patients: CR 27% (n=3) PR 27% (n=3) SD 27% (n=3) PD 18% (n=2) Apparent bystander effect in untreated tumours in 27% of patients	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Toxicity: transient mild to-moderate pain at the treatment site (n=8), local inflammation (n=4), treatment site pruritus (n=3), mild photosensitivity reaction (n=1), mild insomnia secondary to injection site pain (n=1)		
Quaglino et al. 2008	To prospectively evaluate clinical activity and tolerability of ECT with i.v. bleomycin	Prospective Phase II study Treatment: ECT with i.v. bleomycin	14 patients, Stage III	Response (8 weeks after ECT) Local tumor control rate	Patients(n=14): CR n=7 (50%) PR n= 6 (43%) PD n= 1 (7%) Lesions (n=160): CR 62% PR 33% 2 years local tumor control rate: 74.5%	-	4
Gaudy et al. 2006	To assess whether EP therapy improves the local	A prospective internally controlled study	12 patients Stage III (4 patients) and Stage IV (8 patients)		Lesions treated with bleomycin + EP (n=30) versus	the study design does not cover the question of	4*

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	control of skin metastases of melanoma by intralesional bleomycin	with randomization of melanoma skin metastases in each individual to intralesional injections of bleomycin alone or to intralesional injections of bleomycin with EP	under chemotherapy) 54 lesions	Local response (lesions) Tolerance	bleomycin alone (n=24): CR 36% (11 of 30) vs. 8% (2 of 24) p = 0.016 All patients reported discomfort during the EP procedure, including local pain for 9 patients (75%) at the treatment site and muscle spasm with myoclonia in 3 cases (25%). No clinical or biologic systemic toxicity.	literature search (efficacy of local treatments compared to standard treatment), the study is therefore downclassified as level 4 study Limitations: No comparison to standard treatments (e.g. surgery, radiotherapy)	
Byrne et al. 2005	to evaluate the effect of EPT after intratumoral injection of bleomycin, and to compare this with the effect of intratumoral injection of bleomycin alone	Phase II, randomized, open-label study comparing intralesional bleomycin + EPT with intralesional bleomycin alone. Treatment: Injectin of	19 patients, stage III or IV with at least 2 cutaneous and/or subcutaneous metastases 36 evaluable lesions, lesions were randomized to treatment	lesion response	bleomycin only (19 Lesions) CR 26% (n=5) PR 5% (n=1) SD 15% (n=3) PD 53% (n=10) bleomycin plus EPT (17 lesions, plus 1 lesion crossed over)	Response was evaluated for treated lesions. No data available for duration of response Limitations: No comparison to standard treatments (e.g. surgery,	4*

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		bleomycin followed by electrical pulses, possible retreatment at week 4, 8 or 12			CR 72% (n=13) PR 5% (n=1) SD 18% (n=3) PD 5% (n=1) p=0.002	radiotherapy)	
Oratz et al. 2003	To evaluate the use of a novel intralesional chemotherapy - cisplatin / adrenaline injectable gel - for the treatment of refractory or recurrent cutaneous and soft tissue melanoma metastases	open-label, multicentre study Treatment: up to six weekly intratumoral injections of cisplatin/adrenaline gel within an 8 week period or until complete response	25 patients with 244 lesions were evaluable for efficacy	Response Toxicity	CR was achieved in 114 tumours (47%), PR in 16 tumours (7%). Median time to an individual tumour response was 62 days (range 1-534 days). Median duration of an individual tumour response (n = 124) was 347 days (range 30-783 days).		4
Rols et al. 2000	To apply the electrochemotherapy method	Case Series Treatment: 10 mg/m ² dose of bleomycin i.v. followed by short, intense electric pulses	4 patients 55 metastases	Response	Objective responses of treated metastases: more than 90% Complete response rate 9%	Small series	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Sersa et al. 2000	To evaluate the antitumor effectiveness of electrochemotherapy using intratumoral cisplatin administration on cutaneous tumor nodules in malignant melanoma patients	Phase II open-label Study Treatment: Intratumoral cisplatin followed by electrical pulses versus cisplatin alone versus electric pulses alone versus control	10 patients with cutaneous metastases, Stage III or IV ECT group: 82 lesions cisplatin group: 27 lesions electric pulses group: 2 lesions untreated controls: 22 lesions	Lesion response	ECT group (n=82): CR 68% (n=56), PR 10% (n=8), SD 15% (n=12), PD 7% (n=6) Cisplatin group (n=27): CR 19% (n=5), PR 19% (n=5), SD 30% (n=8), PD 33% (n=9) Electric pulses (n=2): SD 50% (n=1), PD 50% (n=1) Control group (n=22): SD 36% (n=8), PD 64% (n=14)	No details given how lesions are allocated to different treatment groups Limitations: No comparison to standard treatments (e.g. surgery, radiotherapy) Small sample size	4
Glass et al. 1996	To report the effects of ECT in 5 patients with metastatic malignant melanoma	Case Series Treatment: Intralesional bleomycin followed by pulses of electricity delivered via needle electrodes or caliper	5 patients with cutaneous metastatic melanoma 23 lesions treated with ECT 3 lesions with electric pulses alone 9 lesions	Lesion response	ECT: CR 78% (n=18) PR 17% (n=4) SD 4% (n=1) Electric pulses alone: No response Bleomycin alone: No response	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			bleomycin alone				

Contact Sensitizer (Dinitrochlorobenzene, Diphencyprone)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Terheyden et al. 2006	To gain more insight to criteria of response to combined treatment with epifocal DNCB and intravenous DTIC, data were collected in this retrospective study	retrospective study Treatment: epifocal DNCB and intravenous DTIC	72 evaluable patients with recurrent melanoma Stage III n=39 Stage IV n=33	Response Progression free survival Overall survival	Stage III, patients n=39 Response CR n=15 (39%) PR n=9 (23%) SD n=9 (23%) PD n=6 (15%) Median PFS: 10 months (range 3 - 120 months) median OS 14 months (range 3 - 120 months)	-	4
Damian et al. 2009	To report DPCP treatment of 7 patients with cutaneous metastatic melanoma	Case Series Treatment: 2 weeks after sensitization weekly applicatio of DPCP cream to all cutaneous metastases	7 patients with cutaneous metastases	Response	CR 4 patients PR 3 patients	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Trcka et al. 1998	To describe an immunochemotherapy for metastatic melanoma	Case Series Treatment: epifocal DNCB and intravenous DTIC	15 evaluable melanoma patients	Response	n=15 CR n=4 PR n=3	-	4
Strobbe et al. 1997	To describe the experience with a combination of DNCB and DTIC in selected patients with regional cutaneous metastases	Case Series Treatment: Local DNCB 2% solution in acetone alone for 4 weeks, start of DTIC i.v. after 4 weeks	59 patients with the presence of locoregional metastases, Stage III 63% (n=37) or Stage IV 37% (n=22).	Response	Overall Response (patients) CR 25% (n=15) PR+SD 12% (n=7) PD 63% (n=37) Local Response (patients) CR+PR 68% (n=40)	No detailed data regarding local response available Limitations: Combination therapy	4
Cohen et al. 1978	To compare efficacy and toxicity of intralesional BCG versus intralesional DNCB in patients with locoregional metastatic melanoma	Randomized prospective Study Treatment: BCG group: intralesional BCG injections every 4-6 weeks DNCB group: topical application until hypersensitivity occurred (within 2 weeks) thereafter intralesional	18 patients with intradermal or subcutaneous melanoma metastases, Stage III Randomisation in two treatment groups: 9 patients received BCG with 177 dermal and 22 subcutaneous lesions, 9 patients received DNCB	Response Survival	Lesion response: BCG group Regression dermal lesions: 90% (n=157), subcutaneous lesions: 45% (n=10) DNCB group Regression dermal lesions: 90% (n=453), subcutaneous lesions: 43% (n=27)	the study design does not cover the question of literature search (efficacy of local treatments compared to standard treatment), the study is therefore downclassified as level 4 study	4*

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		injections every 4-6 weeks	with 504 dermal and 63 subcutaneous lesions	Toxicity	Overall Survival at 39 months: 33% in both groups. Toxicity BCG vs. DNCB Fever (88% vs. 0%), Chills (84% vs. 0%), Nausea 1 (40% vs. 0%), Major ulceration (44% vs. 4%), Cellulitis (antibiotics) (16% vs. 2%), Distant infection (8% vs. 0%) Disseminated intravascular coagulation, including one near fatality. (12% vs. 0%)		

* the study design does not cover the question of literature search (efficacy of local treatments compared to standard treatment), the study is therefore downclassified as level 4 study

6.1.4.2. Aktualisierungsrecherche 2015

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Andtbacka et al. 2015	To evaluate whether treatment with T-VEC resulted in an improved durable response rate (DRR) compared with GM-CSF in patients with unresected stage IIIB to IV melanoma.	RCT Treatment: Group A: Talimogene Laherparepvec (n=295) Group B: GM-CSF (n=141)	Not surgically resectable, stage IIIB to IV melanoma suitable for direct or ultrasound-guided injection (at least one cutaneous, subcutaneous, or nodal lesion or aggregation of lesions 10 mm in diameter).	Durable Response Rate Overall Response Rate Overall Survival	DRR was higher with T-VEC (16.3%; 95% CI, 12.1% to 20.5%) than GM-CSF (2.1%; 95% CI, 0% to 4.5%]; odds ratio, 8.9; P <.001). Overall response rate was higher in the T-VEC arm (26.4%; 95% CI, 21.4% to 31.5% v 5.7%; 95% CI, 1.9% to 9.5%). Median OS was 23.3 months (95% CI, 19.5 to 29.6 months) with T-VEC and 18.9 months (95% CI, 16.0 to 23.7 months) with GM-CSF (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; P .051).	T-VEC efficacy was most pronounced in patients with stage IIIB, IIIC, or IVM1a disease and in patients with treatment-naive disease.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Byers et al. 2014	To evaluate the current evidence regarding the efficacy and side effect profile of intra-lesional IL-2 therapy for treating in-transit melanoma	<p>Systemic review</p> <p>Inclusion criteria: phase II or III studies that examined IL-2 injected directly into cutaneous/subcutaneous melanoma metastases and evaluated the clinical response.</p> <p>Exclusion criteria: Studies that were phase I, non-human, had fewer than five subjects, or had quality scores of less than three (of six) according to Newcastle-Ottawa Quality Assessment Scale for cohort studies.</p> <p>The literature search yielded 277 citations. 49</p>	140 patients with 2,182 lesions were treated in these six studies.	<p>Response Rates by Lesion</p> <p>Response Rates by Subject</p> <p>Side Effects</p>	<p>Heterogeneity was seen in IL-2 dosage and treatment interval. Response rate was variable as well. Pooling the lesions, complete response was seen in 78%.</p> <p>Pooling subjects, 50% achieved a complete response.</p> <p>Treatment was generally well tolerated, with localized pain and swelling, and mild flu-like symptoms.</p>	Problem with heterogeneity of includes studies regarding dosing of IL-2 described. However, IL-2 treatment intralesionally applied judged as sufficient and well tolerated	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		<p>unique and potentially relevant studies were identified and their abstracts further evaluated. 28 articles did not address the research question, 2 were phase I studies and 4 were case reports with too few subjects. Four studies were found to be evaluating systemically delivered IL-2 (not intra-lesional). 2 studies used IL-2 indirectly administered through vectors. 2 studies were found to be long-term follow-up of previous studies and one study did not assess the clinical outcome. The remaining 6</p>					

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		articles matched our criteria and were subjected to quality assessment.					
Sisti et al. 2015	To critically assess the studies evaluating the monotherapy with Imiquimod cream in the treatment of cutaneous metastases from melanoma	Systemic review MEDLINE, EMBASE, Cochrane Library, and Google Scholar databases were searched with the purpose of study selection. The terms "melanoma" combined with "metastases" and "imiquimod" were used as database queries. The only inclusion criterion was: clinical human studies evaluating IMG monotherapy in metastatic melanoma. Any simultaneous combination therapy was	17 patients treated in 11 studies	Not pre-specified in report Response rate and clinical outcome according to different dosing schedules reported	Response rate was variable. Pooling the lesions, complete regression of melanoma metastases was seen in 82.3% of the patients. There was no significant difference in terms of clinical outcome when comparing the frequency of Imiquimod application.	Review mainly included case reports, so baseline quality of selected papers was low. Whereas the search strategy is well described, outcomes objectives of the review are missing.	3a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		<p>excluded. 57 studies identified of which 46 did not meet inclusion criteria, leaving 11 case studies.</p> <p>A modified quality assessment tool for observational studies was used.</p>					
Mali et al. 2012	To consolidate current experience with clinical electrochemotherapy (ECT) of cutaneous or subcutaneous tumours from the effectiveness point of view and to provide a transparent and objective framework for discussion on differences in effectiveness of clinical ECT.	<p>Systematic search of 16 bibliographic databases was performed to obtain articles regarding clinical ECT using search terms “electrochemotherapy” and “clinical” and time range between 1st January 1991 and 18th October 2011.</p> <p>Results from initial search: 1181</p>	431 patients and 1,894 tumours	<p>Response of individual tumors:</p> <p>Complete response (CR),</p> <p>Partial response (PR),</p> <p>No change (NC),</p> <p>Progressive disease (PD) ,</p> <p>Objective response (OR; including CR and PR)</p>	<p>CR 56.8% (for Melanoma)</p> <p>Specified for each study only</p> <p>Specified for each study only</p> <p>OR 80.6% (for Melanoma)</p>	The search strategy is well described. More outcomes declared than reported	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		<p>references; 44 reports included in analysis</p> <p>The risk of bias of included studies was assessed independently by 2 out of 3 authors according to the recommendations of the Cochrane Collaboration.</p>		No response (NR; including NC and PD)	Specified for each study only		
Spratt et al. 2014	To perform the first meta-analysis of the efficacy of skin-directed therapies for cutaneous metastases.	<p>Systematic literature searches were conducted in four databases (MEDLINE [via PubMed], EMBASE, The Cochrane Library, and ClinicalTrials.gov) for human-only studies.</p> <p>The search strategy contained two major components linked together with the</p>	47 studies reporting on 915 patients with 4,313 cutaneous metastases of skin tumours (CMs) were included for analysis.	<p>Complete Response (CR)</p> <p>Objective response rate (ORR)</p>	<p>1,890 (54.4%) of the 3,477 assessable patients had a CR.</p> <p>All 4,313 CMs were assessable for ORR analyses, of which 2,970 (68.9%) had ORRs. ORR was defined in 42 studies as the sum of CR plus PR.</p> <p>The ORR for all</p>	Probably the most sufficient and comprehensive reviews including a meta-analysis of treatment of cutaneous metastases of skin tumors	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		AND operator: (1) skin-directed therapy: surgery, excision, topical, intralesional therapy, injection, photodynamic, photochemotherapy, electrochemotherapy, radiation, radiotherapy, brachytherapy AND (2) skin metastasis: cutaneous metastasis/metastases, dermal metastasis/metastases.			studies was 60.2% (95%CI, 50.6% to 69.0%).		

6.1.5. Literatur

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6.2. Frage V.2. und V.3. Systemtherapie Einzelsubstanzen – De novo Recherche

Frage V.2.: Für welche Substanzen konnten objektive Remissionen im metastasierten Stadium (First- und Secondline) gezeigt werden?

Frage V.3.: Für welche Substanzen konnte eine Verbesserung des Gesamtüberlebens im metastasierten Stadium (First- und Secondline) gezeigt werden?

6.2.1. PICO, Suchwörter

PICO – Schema

Population	Intervention	Comparison	Outcome
Advanced melanoma patients stage IV, unresectable stage III	Systemic treatment	Standard of care/Placebo/Standard of care+Placebo	Overall Survival, Response, Duration of Response

Suchwörter

Stichwort	melanoma	phase III phase 3	Chemotherapy	Stage IV Stage 4
Synonyme		random*		Palliative
Ober-/Unterbegriffe			Systemic therapy	Salvage metastatic Disseminated
Mesh Term	melanoma	Clinical Trial, Phase III Randomized Controlled Trial	Drug Therapy	

6.2.2. Datenbanken, Suchstrategien, Trefferzahlen

6.2.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (Clinical Trial, Phase III [Publication Type] OR Randomized Controlled Trial [Publication Type] OR "phase 3" OR "phase III"[tiab] OR random*[tiab]) AND ("systemic therapy"[tiab] OR chemotherapy[tiab] OR "drug therapy"[MeSH] OR metastatic[tiab] OR palliative[tiab] OR advanced[tiab] OR "stage IV"[tiab] OR "stage 4"[tiab] OR salvage[tiab])	26.07.11	1091 (Auswahl: 38)
Medline –erweiterte Suchstrategie	(melanoma[tiab] OR melanoma[MeSH]) AND (Clinical Trial, Phase III [Publication Type] OR Randomized Controlled Trial [Publication Type] OR "phase 3" OR "phase III"[tiab] OR random*[tiab]) AND ("systemic therapy"[tiab] OR chemotherapy[tiab] OR "drug therapy"[MeSH] OR disseminated [tiab] OR metastatic[tiab] OR palliative[tiab] OR advanced[tiab] OR "stage IV"[tiab] OR "stage 4"[tiab] OR salvage[tiab])	05.12.11	1142 (Avril et al. 2004 dazu)
Cochrane Library	(melanoma and (random* or phase 3) and (systemic therapy or chemotherapy or metastatic or palliative or advanced or salvage)).ti,ab.	17.10.11	385 (Auswahl: 25, abz. Dubletten: 2 dazu)
Embase	(melanoma and (random* or phase 3) and (systemic therapy or chemotherapy or metastatic or palliative or advanced or salvage)).ti,ab.	04.10.11	894 (Auswahl: 33, abz. Dubletten: 3 dazu)
Update Suche			
Medline	s.o.	30.01.12	1145 (2 dazu: Kim et al. 2012, Kirkwood et al. 2012)
Medline	s.o.	01.08.12	1221 (2 dazu: Flaherty et

Datenbank	Suchstrategie	Datum	Treffer
			al. 2012, Hauschild et al. 2012)
Cochrane Library	s.o.	30.01.12	389 (0 dazu)
Embase	s.o.	23.01.12	937 (0 dazu)

6.2.2.2. Aktualisierungsrecherche 2015

Datenbank	Suchstrategie	Datum	Treffer
Medline	((((melanoma[tiab] OR melanoma[MeSH]) AND (Clinical Trial, Phase III [Publication Type] OR Randomized Controlled Trial [Publication Type] OR "phase 3" OR "phase III"[tiab] OR random*[tiab]) AND ("systemic therapy"[tiab] OR chemotherapy[tiab] OR "drug therapy"[MeSH] OR disseminated[tiab] OR metastatic[tiab] OR palliative[tiab] OR advanced[tiab] OR "stage IV"[tiab] OR "stage 4"[tiab] OR salvage[tiab]))) AND ("2011.12.06"[Date - Publication] : "3000"[Date - Publication]))	16.09.15	451
Cochrane Library	(melanoma and (random* or phase 3) and (systemic therapy or chemotherapy or metastatic or palliative or advanced or salvage)).ti,ab.	16.09.15	67

6.2.3. Auswahlkriterien

6.2.3.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer	2547
Einschlusskriterien	RCTs zur medikamentösen Systemtherapie bei Melanompatienten im Stadium IV / nicht resektables Stadium III Interventionsarm: Monotherapie oder Monotherapie + Standardtherapie Beobachtungsarm: Placebo, Standardtherapie oder Placebo + Standardtherapie Publikationsjahr ab 1980
Ausschlusskriterien	Case Reports, Kohortenstudien Dosisfindungsstudie Kollektive mit gemischten Tumorentitäten
Anzahl nach Abstractscreening, vorgesehen für Bewertung	48
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	8
Anzahl ausgewählter Volltexte	40
Die ausgewählten Arbeiten wurden wie folgt zusammengefasst: Zielgerichtete Therapien /small molecules (Trametinib, Dabrafenib, Selumetinib, Bevacizumab, Vemurafenib, Intetumumab, Bosentan, Sorafenib, Elesclomol, Tamoxifen) Immuntherapien, Immunmodulation (Ipilimumab, Vakzine, Lenalidomide, Thymosin, PF-3512676, Interferon alpha, Thalidomide, Histamine) Chemotherapien/Chemosensitizer (DHA-paclitaxel, Dacarbazine, Temozolomide, Lomeguatrib, Oblimersen, Cisplatin, Fotemustine, Vindesine, Detorubicin)	

6.2.3.2. Aktualisierungsrecherche 2015

Auswahl der Literatur	
Gesamttreffer	518
Einschlusskriterien	Systematische Reviews / Metaanalysen Phase III RCTs zur medikamentösen Systemtherapie bei Melanompatienten im Stadium IV / nicht resektables Stadium III Interventionsarm: Monotherapie oder Monotherapie + Standardtherapie Beobachtungsarm: Placebo, Standardtherapie oder Placebo + Standardtherapie Publikationsjahr ab 1980
Ausschlusskriterien	Phase I/II RCTs Case Reports, Kohortenstudien Dosisfindungsstudie Kollektive mit gemischten Tumorentitäten
Anzahl ausgewählter Volltexte	N= 28
Zielgerichtete Therapien /small molecules-RCTs	7
Immuntherapien, Immunmodulation-RCTs	10
Chemotherapien/Chemosensitizer-RCTs	4
Reviews	7

6.2.4. Evidenztabelle

6.2.4.1. Primärrecherche 2012

Zielgerichtete Therapien / small molecules

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Flaherty et al. 2012	To compare trametinib (MEK Inhibitor) with dacarbazine or Taxol in patients with metastatic melanoma with the BRAF V600E or BRAF V600K mutation	RCT, open label Treatment: Group A trametinib (2 mg orally twice daily) Group B dacarbazine, 1000 mg/m ² i.v. or paclitaxel 175mg/m ² i.v. on day 1 every 3 weeks	322 patients with metastatic previously untreated or treated melanoma with the BRAF V600E or BRAF V600K mutation	Overall Survival - 6 months Progression free survival Overall Response rate Duration of Response	trametinib vs. chemotherapy 81% vs. 67% (HR 0.54; 95% CI, 0.32 to 0.92; p = 0.01) 4.8 vs. 1.5 months (HR 0.45; 95% CI, 0.33 to 0.63; P<0.001) 22% vs. 8% (p=0.01) 5.5 months vs. not yet reached	Jadad Score 4 Independent review of tumor assessment Funding: GlaxoSmithKline.	1b
Hauschild et al. 2012	To compare dabrafenib with dacarbazine chemotherapy in previously untreated mel	RCT, open label Treatment: Group A dabrafenib (150 mg orally twice	250 patients with previously untreated, metastatic melanoma with the BRAF V600E	Overall Survival	dabrafenib vs. dacarbazine HR 0,61 (95% CI, 0,25-1,48)	Jadad Score 4 Independent review of tumor assessment Funding:	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	anoma patients whose tumours harboured a BRAFV600E mutation.	daily) Group B dacarbazine, 1000 mg/m ² i.v. on day 1 every 3 weeks	mutation	Progression free survival Overall Response rate Duration of Response	5,1 vs. 2,7 months (HR 0,30; 95% CI, 0,18–0,51; p<0·0001) 50% vs. 6% 5.5 months vs. not yet reached	GlaxoSmithKline.	
Chapman et al. 2011	To compare vemurafenib with dacarbazine in 675 patients with previously untreated, metastatic melanoma with the BRAF V600E mutation	RCT, open label Treatment: Group A vemurafenib (960 mg orally twice daily) Group B dacarbazine, 1000 mg/m ² i.v. on day 1 every 3 weeks	675 patients with previously untreated, metastatic melanoma with the BRAF V600E	Overall Survival – 6 months Overall Response rate Duration of Response	Vemurafenib vs. DTIC 84% (95% CI, 78 to 89) vs. 64% (95% CI, 56 to 73), HR for death in the vemurafenib group 0.37 (95% CI, 0.26 to 0.55; P<0.001), sign. 48% vs. 5%, p<0.001, sign. not yet estimated	Jadad Score 2 no description of dropouts, tumor assessment not blinded, only 439 patients (65%) were evaluated for tumor response, 48 patients in the DTIC Group received no study treatment Funding: Hoffmann–La Roche	1b
O´day et al. 2011	To evaluate the safety and efficacy	RCT, double-blind (Group A+B)	129 chemotherapy-		DTIC vs. DTIC+ intetumumab vs.	Jadad Score 5	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of Intetumumab (CNTO 95), a fully human anti-alpha(v)-integrin monoclonal antibody	<p>Treatment q3w:</p> <p>Group A 1000 mg/m² dacarbazine + placebo, (n=32)</p> <p>Group B 1000 mg/m² dacarbazine + 10 mg/kg intetumumab (n=32)</p> <p>Group C 10 mg/kg intetumumab (n=33)</p> <p>Group C 5 mg/kg intetumumab (n=32)</p>	naive patients	<p>Median Overall Survival</p> <p>Overall Response Rate</p> <p>Duration of Response</p>	<p>intetumumab 10mg vs. intetumumab 5mg</p> <p>8 vs. 11 vs. 15 vs. 9.8 months, n.s.</p> <p>10% (n=3) vs. 3% (n=1) vs. 6% (n=2) vs. 0%, n.s.</p> <p>3.9, 7.3, and 10.3+ months vs. 7.0 months vs. 6.3 and 8.2+ months</p>	Funding: Centocor Ortho Biotech, Inc., Malvern, PA, USA.	
Kefford et al. 2010	To evaluate the effects of bosentan - a dual endothelin receptor antagonist - in patients receiving	<p>RCT, double-blind</p> <p>Treatment:</p> <p>Group A DTIC 1000 mg/m²</p>	80 patients with previously untreated metastatic melanoma	Median Overall Survival	<p>DTIC+Bosentan vs. DTIC+Placebo</p> <p>13.0 months (95% CI, 7.8-16.6) vs. 10.6 months (95%</p>	<p>Jadad Score 4 tumor assessment not described as blinded</p> <p>Funding:</p>	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	first-line dacarbazine therapy for stage IV metastatic cutaneous melanoma	every 3 weeks starting on Day 1 +Bosentan 500 mg twice a day (n=40) Group B DTIC 1000 mg/m ² every 3 weeks starting on Day 1+Placebo (n=40)		Overall Response Rate Duration of Response	CI, 6.9-14.7), n.s., (HR, 1.044; 95% CI, 0.584-1.865; p = 0.8841) not reported not reported	Actelion Pharmaceuticals Ltd., Allschwil, Switzerland.	
Hauschild et al. 2009	To evaluate the efficacy and safety of sorafenib with carboplatin and paclitaxel (CP) in patients with advanced melanoma	RCT, double-blind Treatment: Group A paclitaxel 225 mg/m ² plus carboplatin (AUC 6) + sorafenib 400mg (n=135) Group B paclitaxel 225 mg/m ² plus carboplatin (AUC 6) + placebo (n=135)	270 patients with advanced melanoma (unresectable stage III or stage IV) that had progressed during or after receiving at least one cycle of a regimen containing dacarbazine or temozolomide in the advanced setting	Median Overall Survival Overall Response Rate Duration of Response	C/P + Sorafenib vs. C/P + Placebo 42.0 weeks (9.7 months) vs. 42.0 (9.7 months), n.s., HR 1.01 (95% CI, 0.76 to 1.36; p=0.92) 12% (n=16) vs. 11% (n=15), n.s., p=1.0 not reported	Jadad Score 5 Funding: Bayer AG and Onyx Pharmaceuticals, Inc.	1b
O'Day et al. 2009	To evaluate	RCT, double-blind	81 metastatic		Elesclomol	Jadad Score 4	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	whether the addition of elesclomol to weekly paclitaxel could improve efficacy in patients with stage IV metastatic melanoma	<p>Treatment:</p> <p>Group A elesclomol 213 mg/m² plus paclitaxel 80 mg/m² (E + P) (n= 53)</p> <p>Group B paclitaxel 80 mg/m² alone (n= 28)</p>	melanoma patients with one or fewer prior standard chemotherapy regimens	<p>Median Overall Survival</p> <p>Progression Free Survival</p> <p>Overall Response Rate</p> <p>Duration of Response</p>	<p>+Paclitaxel vs. Paclitaxel</p> <p>11.9 vs. 7.8 months</p> <p>3.7 months vs. 1.8 months, sign., p=0.035</p> <p>15.1% (n=8) vs. 3.6% (n=1) (p=0.153) ,n.s., p=0.153</p> <p>range 58+ to 188+ days (censored patients), 107, 136 days vs. 115 days</p>	<p>Tumor assessment by investigators, Randomization without stratification, M1c patients unbalanced (25.8% vs. 75%)</p> <p>Funding: Synta Pharmaceuticals, Lexington, MA.</p>	
McDermott et al. 2008	To evaluate the efficacy and safety of sorafenib plus dacarbazine in patients with advanced melanoma	<p>RCT, double-blind</p> <p>Treatment:</p> <p>Group A sorafenib plus dacarbazine (n = 51)</p> <p>Group B</p>	101 chemotherapy-naive patients with stage III (unresectable) or IV melanoma	<p>Median Overall Survival</p> <p>Overall Response Rate</p>	<p>Sorafenib + DTIC vs. Placebo + DTIC</p> <p>45.6 weeks vs. 51.3 weeks, n.s., p=0.927</p> <p>24% (n=12) vs. 12% (n=6), n.s.,</p>	<p>Jadad Score 5</p> <p>Funding: Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals Inc.</p>	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		placebo plus dacarbazine (n = 50)		Duration of Response	p=0.193 26.9 vs. 23.0 months, n.s., p=0.194		
Agarwala et al. 1999	To test the benefit of adding tamoxifen to dacarbazine and carboplatin chemotherapy for previously untreated patients with metastatic melanoma	RCT, open label Treatment: Group A carboplatin 300 mg/m ² and dacarbazine 1g/m ² plus tamoxifen 20 mg/day (D+C+T) Group B (D+C)	56 metastatic melanoma patients, without prior chemotherapy	Median Overall Survival Overall Response Rate Duration of Response	D+C+T vs. D+C 4.6 months vs. 7 months, n.s., p=0.1377 14.3% (n=4) vs. 10.7% (n=3), n.s., (p=1.0) 3, 3, 6, and 6 months vs. 2, 16 months + lost to follow up at 31 months	Jadad Score 2 unblinded tumor assessment, no description of dropouts and withdrawals, small sample size Funding: Not declared	1b

Immuntherapien, Immunmodulation

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hersh et al. 2011	To evaluate the safety and efficacy of ipilimumab	RCT, open label Treatment:	72 chemotherapy-naive patients		Ipi alone (n=32) vs. Ipi+DTIC (n=32)	Jadad Score 2 small sample size randomization	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	alone and in combination with dacarbazine (DTIC) in patients with unresectable, metastatic melanoma	Group A ipilimumab at 3 mg/kg every 4 weeks for four doses alone (n=37) Group B ipilimumab at 3 mg/kg every 4 weeks for four doses with up to six 5-day courses of DTIC at 250 mg/m ² /day (n=35)		Median Overall Survival Overall Response Rate Durable Complete Response	11.4 months (95% CI, 6.1-15.6) vs. 14.3 months (95% CI, 10.2-18.8), n.s. 5.4% (95% CI, 0.7-18.2) vs. 14.3% (95% CI, 4.8-30.3), n.s. n=2 (1.6+/1.85+ years) vs. n=2 (1.73+/1.76+ years)	scheme not described, tumor assessment not blinded Funding: Bristol-Myers Squibb Co.	
Robert et al. 2011	To evaluate ipilimumab (10 mg per kilogram) plus dacarbazine in patients with previously untreated metastatic melanoma	RCT, double-blind Treatment: Group A Ipilimumab (10 mg per kilogram) plus dacarbazine (850 mg/m ²) Group B dacarbazine (850 mg/m ²) plus placebo	502 patients with previously untreated metastatic melanoma	Median Overall Survival Overall Survival 1 year 2 years 3 years	Ipi+DTIC vs. Placebo+DTIC 11.2 months (95% CI, 9.4 to 13.6) vs. 9.1 months (95% CI, 7.8 to 10.5) (hazard ratio for death with DTIC+Ipi, 0.72; p<0.001) 47.3% vs. 36.3% 28.5% vs. 17.9% 20.8% vs. 12.2%	Jadad Score 5 Funding: Bristol-Myers Squibb.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hodi et al. 2010	To compare ipilimumab , administered with or without a glycoprotein 100 (gp100) peptide vaccine with gp100 alone in patients with previously treated metastatic melanoma	RCT, double-blind Treatment: Group A ipilimumab plus gp100 (n=403) Group B ipilimumab alone (n=137) Group C gp100 alone (n=136)	676 HLA-A*0201-positive patients with previously treated unresectable stage III or IV melanoma	Median Overall Survival Overall Response Rate Median Duration of Response Treatment related deaths	ipilimumab +gp100 vs. ipilimumab vs. gp100 10.0 months vs. 10.1 months vs. 6.4 months, sign., (hazard ratio for death, 0.68; p<0.001). 5.7% (n=23) vs. 11% (n=15) vs. 1.5% (n=2), sign., p=0.04 11.5 (5.4-NR) vs. NR (28.1-NR) vs. NR (2.0-NR) months n=14	Jadad Score 5 tumor assessment by investigators Funding: Medarex and Bristol-Myers Squibb	1b
Eisen et al. 2010	To compare the treatment with lenalidomide to placebo in 306 patients with metastatic	RCT, double-blind Treatment: Group A lenalidomide (25	306 patients with previously treated metastatic malignant melanoma	Median Overall Survival	lenalidomide vs. placebo median 5.9 months (range 5.1-7.7) vs. 7.4	Jadad Score 5 Funding: Celgene Corporation, Summit, New	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	malignant melanoma	mg/d on Days 1-21 of a 28-day cycle (n=154) Group B placebo (n=152)		Overall Response Rate Duration of Response	months range 5.5-8.2); n.s., p=0.32 5.3% vs 5.8%; n.s., p=0.82 not reported	Jersey.	
Maio et al. 2010	To evaluate the efficacy and safety of combining Thymosin alpha 1 with dacarbazine and interferon alfa in patients with metastatic melanoma	RCT, open label Treatment: Group A: DTIC+IFN alpha+ Thymosin alpha 1 (1.6mg) Group B: DTIC+IFN alpha+ Thymosin alpha 1 (3.2mg) Group C: DTIC+IFN alpha+ Thymosin alpha 1 (6.4mg) Group D: DTIC+Thymosin alpha 1 (3.2mg) Group D: DTIC+IFN alpha	571 chemotherapy-naive patients	Median Overall Survival Overall Response Rate Median duration of Response Clinical benefit	DIT1.6 vs. DIT3.2 vs. DIT6.4 vs. DT3.2 vs. DI 9.3 vs. 8.6 vs. 10.3 vs. 9.3 vs. 6.6 months, n.s. DTI+DT vs. DI, PP population: HR = 0.74; 95% CI, 0.57-0.95; p=0.02 7.2% vs. 10.3% vs. 6.1% vs. 12.1% vs. 4.1%, n.s. 7.4 vs. 8.3 vs. 7.9 vs. 7.7 vs. 6.3 months DT3.2 vs. DI:	Jadad Score 4 tumor assessment blinded Funding: Sigma-Tau SpA, Pomezia, Italy	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				(CR+PR+SD)	49.5% vs. 32.0% P=0.009		
Weber et al. 2011	To assess the objective response rate of PF-3512676 , a CpG oligodeoxynucleotide, alone in 2 doses or in combination with dacarbazine (DTIC) in patients with unresectable stage IIIB/C or stage IV malignant melanoma	RCT, open label Treatment: Group A PF-3512676 10 mg (n=46) Group B PF-3512676 40 mg (n=46) Group C PF-3512676 40 mg plus DTIC (850 mg/m ²) (n=45) Group D DTIC (850 mg/m ²) alone (n=39)	184 patients with previously untreated metastatic melanoma	Median Overall Survival Overall Response Rate Duration of Response	PF-3512676 10mg vs. PF-3512676 40mg vs. PF-3512676 40 mg + DTIC vs. DTIC 9.4 vs. 8.4 vs. 9.0 vs. 11.7 months, n.s. 2% vs. 0% vs. 16% vs. 8%, n.s. not estimated (number too small)	Jadad Score 3 Funding: not declared	1b
Schadendorf et al. 2006	To demonstrate the superiority of	RCT, open label	108 metastatic melanoma patients		DC vaccination vs. DTIC	Jadad Score 3	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	autologous peptide-loaded dendritic cell (DC) vaccination over standard dacarbazine (DTIC) chemotherapy in stage IV melanoma patients	Treatment: Group A DC vaccines loaded with MHC class I and II-restricted peptides (n=53) Group B DTIC 850 mg/m ² (n=55)	with no prior systemic chemotherapy	Median Overall Survival Overall Response Rate	9.3 months vs. 11.6 months n.s. ITT: 3.8% (n=2) vs. 5.5% (n=3), n.s. (PP:4.9 vs. 4.8%)	Funding: German Cancer Aid	
Kaufmann et al. 2005	To compare TMZ alone and TMZ plus IFN-alpha in terms of objective response (OR), overall survival, and safety	RCT, open label Treatment: Group A TMZ alone (n=146) Group B TMZ + s.c. IFN-alpha (n=148)	294 patients with untreated stage IV metastatic melanoma	Median Overall Survival Response Rate Duration of Response	TMZ vs. TMZ + s.c. IFN-alpha 8.4 months (95% CI, 7.07 to 9.27) vs. 9.7 months (95% CI, 8.26 to 11.18), n.s., p=0.16 13.4% (n=18 of 134 patients) vs. 24.1% (n=33 of 137 patients, sign., p=0.036) Longer in Group B	Jadad Score 3 unblinded tumor assessment by investigators Funding: Essex Pharma GmbH (Munich, Germany)	1b
Danson et al. 2003	To determine	RCT, open label	181 patients		TMZ vs. TMZ+IFN	Jadad Score 2	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE	
	response rates, overall survival, and tolerability of the regimens temozolomide with interferon alfa-2b and, separately, with thalidomide in patients with advanced metastatic melanoma.	Treatment: Group A TMZ (n=59) Group B TMZ + Interferon alfa-2b (n=62) Group C TMZ + Thalidomide (n=60)			Median Overall Survival Overall Response Rate Response duration	vs. TMZ+Thalidomide 5.3 vs. 7.7 vs. 7.3 months 9% vs. 18% vs. 15% range 2.4 - 21.2 months	dropouts and withdrawals not described	
Agarwala et al. 2002	To determine whether the addition of histamine to a subcutaneous regimen of interleukin-2 (IL-2) would improve the survival of metastatic melanoma patients	RCT, open label Treatment: Group A IL-2 plus histamine (n=152) Group B IL-2 alone (n=153)	305 metastatic melanoma patients with or without previous systemic therapy except IL-2	Median Overall Survival Overall Response Rate	IL-2 + histamine vs. IL-2 alone 272 days (9.1 months) vs. 245 days (8.2 months), n.s., p=0.125 3% (n=5) vs. 3% (n=5), n.s.	Jadad Score 2 unblinded tumor assessment dropouts and withdrawals not described Funding: not declared	1b	
Young et al. 2001	To evaluate DTIC + IFN-alpha in patients with metastatic melanoma	RCT, open label Treatment: Group A	61 advanced melanoma patients without previous DTIC or IFN	Median Overall Survival	DTIC + IFN-alpha Vs. DTIC 4.8 months (95% CI 2.0-8.0) vs. 7.2	Jadad Score 3 unblinded tumor assessment, small sample size	1b	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		DTIC +IFN-alpha (n=30) Group B DTIC (n=31)		Survival 6 months Overall Response Rate Duration of Response	months (95% CI 4.4-9.0), n.s., p=0.70 40% vs. 58% 18% (n=4) vs. 23% (n=6), n.s., p=0.59 median 212 days (95% CI 140-648) vs. median 180 days (95% CI 131-349)	Funding: Cancer Research Campaign and Roche Pharmaceuticals	
Falkson et al. 1998	To investigate the response rate, time to treatment failure (TTF), overall survival, and toxicity in patients with metastatic melanoma treated with dacarbazine alone, dacarbazine plus interferon (IFN) , dacarbazine plus tamoxifen (TMX), or dacarbazine plus	RCT, open label Treatment: Group A DTIC alone (n=69) Group B (n=68) DTIC + IFN Group C (n=66) DTIC + TMX Group D DTIC + IFN + TMX (n=68)	271 metastatic melanoma patients with no prior chemotherapy except for adjuvant IFN	Median Overall Survival Overall Response Rate	DTIC alone vs. DTIC + IFN vs. DTIC + TMX vs. DTIC + IFN + TMX pooled over the 4 Groups: 8.90 months (95% CI, 8.08 -10.8), n.s., p=0.85 15% vs. 21% vs. 18% vs. 19% (of 250 patients)	Jadad Score 3 unblinded tumor assessment Funding: in part by Public Health grants no. CA 21692, CA 23318, CA 07190, CA 18663, CA 16395, CA 66636, and CA 21115 from the National Cancer Institute, National Institutes	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	IFN plus TMX					of Health, and the Department of Health and Human Services, Bethesda, MD	
Sparano et al. 1993	To compare the response rate, survival, and toxicity of treatment with high-dose intravenous bolus interleukin-2 (IL-2) plus interferon alfa-2a (IFN-alpha) with high-dose IL-2 alone in patients with advanced melanoma	RCT, open label Treatment: Group A IL-2 + Interferon alfa-2a Group B IL-2 alone	85 patients	Median Overall Survival Response Rate Duration of Response	IL-2 + IFN alpha vs. IL-2 alone 9.7 months vs. 10.2 months, n.s. 10% (4 of 41 patients) vs. 5% (2 of 44 patients), n.s., p=0.30 11.5 months (range, 2.0 to 15.7+)	Jadad Score 3 unblinded but independently reviewed tumor assessment Funding: National Institutes of Health, Bethesda, MD, contracts no. NO1-CM73702, NO1-CM73703, NO1-CM73704, NO1-CM73705, NO1-CM73706, and NO1-CM73707; National Institutes of Health Clinical Research Center grant no. MOI-RR00054 to Tufts University School of Medicine; and by Hoffman La-Roche,	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Inc	
Thompson et al. 1993	To assess the combination of dacarbazine and interferon-alpha 2a versus dacarbazine alone as systemic therapy for metastatic malignant melanoma	RCT, open label Treatment: Group A DTIC plus IFN alpha 2a Group B DTIC alone	170 patients	Median Overall Survival Response Rate Duration of Response	DTIC + IFN alpha2a vs. DTIC 229 vs. 269 days 21% (95% CI 13-31%) vs. 17% (95% CI 10-27%) 258 vs. 286 days		1b
Falkson et al. 1991	To assess if results with DTIC could be improved by using a combination of DTIC and IFN alfa-2b in metastatic malignant melanoma.	RCT, open label Treatment: Group A DTIC plus interferon alfa-2b (n=30) Group B DTIC alone (n=31)	64 metastatic melanoma patients	Median Overall Survival Overall Response Rate Duration of Response	DTIC + IFN alfa-2b vs. DTIC 17.6 months vs. 9.6 months, sign., p < 0.01 53% (n=16) vs. 20% (n=6), sign., p=0.007 Not reported	Jadad Score 2 Randomization scheme not described, unblinded tumor assessment, small sample size, imbalance of groups (more male patients in Group B) Funding: IFN alfa-2b was supplied by Scherag South Africa,	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Johannesburg.	

Chemotherapy/Chemosensitizer

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bedikian et al. 2011	To compare the efficacy and toxicity profiles of Docosahexaenoic acid (DHA)-paclitaxel with those of dacarbazine	RCT, open label Treatment: Group A DHA-paclitaxel, 900 mg/m ² i.v. on day 1 every 3 weeks (n=194) Group B Dacarbazine, 1000 mg/m ² i.v. on day 1 every 3 weeks (n=199)	393 chemo-naive patients with metastatic melanoma	Median Overall Survival Overall Response rate Duration of Response	DHA-paclitaxel vs. DTIC 267 days (8.8 months) (95% CI 220–297) vs. 226 days (7.4 months) (95% CI 192–263), n.s. 5.2% (n=10) vs. 5.5% (n=11), n.s. 134 days (4.4 months) (95% CI 77 to not estimated) vs. not estimated due to censoring pattern	Jadad Score 3 tumor assessment not described as blinded Funding: Luitpold Pharmaceuticals, Inc.	1b
Patel et al. 2011	To compare the efficacy of an extended schedule escalated dose of	RCT, open label Treatment:	859 chemotherapy-naive patients	Median Overall	TMZ vs. DTIC 9.1 months vs.	Jadad Score 3 tumor assessment was not blinded	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	temozolomide versus standard dose dacarbazine	<p>Group A oral temozolomide 150mg/m²/day for seven consecutive days every 2weeks (n=429)</p> <p>Group B Dacarbazine, i.v. 1000mg/m²/day on day 1 every 3 weeks (n=430)</p>		<p>Survival</p> <p>Overall Response Rate</p> <p>Duration of Response</p>	<p>9.4months, n.s. (p=1.0)</p> <p>14.5% (n=58) vs.9.8% (n=38), p=0.05</p> <p>4.6 vs. 11.2 months, p=0.015, sign.</p>	Funding: Schering Plough, UK National Cancer Research Network	
Ranson et al. 2007	To evaluate tumor response, pharmacodynamic effects, and safety of a combination of lomeguatrib (LM), an O6-methylguanine DNA-methyltransferase (MGMT) inactivator, and temozolomide (TMZ), TMZ alone, and LM/TMZ after disease progression on TMZ alone in	<p>RCT, open label</p> <p>Treatment:</p> <p>Group A lomeguatrib 40mg/d, 2h later TMZ 125mg/m²/d, orally, 5 days every 4 weeks (n=52)</p> <p>Group B TMZ 125mg/m²/d, orally, 5 days every 4 weeks (n=52)</p>	104 patients with unresectable stage III or IV cutaneous melanoma who had no prior systemic chemotherapy	<p>Median Overall Survival</p> <p>Overall Response Rate</p>	<p>LM/TMZ vs. TMZ</p> <p>7.6 months (95% CI, 6.9 - 10.3 months) vs. 7.7 months (95% CI, 6.3 - 10.7 months), n.s.</p> <p>13.5% (n=7) vs. 17.3% (n=9), n.s.</p>	<p>Jadad Score 2 Randomization scheme not described, tumor assessment not blinded</p> <p>Funding: Kudos Pharmaceuticals, owned by AstraZeneca.</p>	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with advanced melanoma						
Bedikian et al. 2006	To evaluate whether targeting Bcl-2 using an antisense oligonucleotide (oblimersen sodium) could improve the efficacy of systemic chemotherapy in patients with advanced melanoma.	RCT, open label Treatment: Group A Oblimersen (7 mg/kg/d by continuous i.v.infusion for 5 days) + DTIC (n=386) Group B DTIC (n=385)	771 chemotherapy-naïve patients	Median Overall Survival PFS Overall Response Rate DurableResponse	Oblimersen + DTIC vs. DTIC 9.0 v 7.8 months; p=0.077 2.6 v 1.6 months; p=0.001 13.5% vs. 7.5% p=0.007 7.3 vs. 3.6% p=0.027	Jadad Score 4 Independent blinded tumor assessment Funding: Genta, Inc.	1b
Bafaloukos et al. 2005	To evaluate and compare the activity and safety profile of the combination Cisplatin + TMZ versus single-agent TMZ in patients with advanced melanoma	RCT, open label Treatment: Group A TMZ 200 mg/m ² /day orally d1-5q28 (n=66) Group B TMZ + Cisplatin 200 mg/m ² daily	132 metastatic melanoma patients with no previous chemotherapy	Median Overall Survival Overall Response Rate Duration of Response	TMZ vs. TMZ + Cisplatin 11.5 months vs. 12 months, n.s. 16 patients (26%) vs. 19 patients (29%), n.s. 5.7 months vs. 9.4 months, n.s.,	Jadad Score 2 Randomization scheme not described, tumor assessment not blinded Funding: Kudos Pharmaceuticals, owned by AstraZeneca.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		on days 1-5 and 75 mg/m ² of cisplatin on day 1 (n=66)			p=0.35		
Avril et al. 2004	To compare fotemustine and dacarbazine (DTIC) in patients with disseminated cutaneous melanoma.	RCT, open label Treatment: Group A Fotemustine 100mg/m ² ; weekly, 3 weeks, (n = 112) Group B DTIC 250 mg/m ² /d; 5d every 4 weeks, (n = 117)	229 patients	Median Overall Survival Response Rate Duration of Response	Fotemustine vs. DTIC 7.3 vs. 5.6 months, p = 0.067 13.4% vs. 6.0% (p= 0.057) n.s. difference	Jadad Score 3 Funding: Institut de Recherches Internationales Servier, Courbevoie, France	1b
Middleton et al. 2000	To compare temozolomide and dacarbazine (DTIC) in terms of overall survival, progression-free survival (PFS), objective response, and safety	RCT, open label Treatment: Group A Temozolomide (n=156) Group B DTIC (n=149)	305 advanced melanoma patients without previous treatment for metastatic disease	Median Overall Survival PFS	TMZ vs. DTIC 7.7 months vs. 6.4 months, n.s., HR 1.18 (95% CI, 0.92 to 1.52), p=0.20 (ITT population) 1.9 vs. 1.5 months; HR 1.37; sign., p=0.012	Jadad Score 3 unblinded tumor assessment, different time points for assessment between groups Funding: Not declared	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Overall Response Rate	13.5% (21 of 156) vs. 12.1% (18 of 149), n.s.		
				Duration of Response	longer in the TMZ group; 18 of the 21 TMZ responders survived longer than 12 months vs. 11 of the 18 DTIC responders		
Keilholz et al. 1997	To determine whether the addition of Cisplatin to a cytokine treatment regimen with IFN alpha and high-dose IL-2 influences survival of patients with metastatic melanoma	RCT, open label Treatment: Group A IFN alpha 10 x 10 ⁶ U/m ² sc. on days 1 through 5 + IL-2 on days 3 through 8 (18 mIU/m ² /6 h, 18 mIU/m ² /12 h, 18 mIU/m ² /24 h, and 4.5 mIU/m ² /24 h x 3) Group B IFN alpha + IL-2 +	138 metastatic melanoma patients, no prior therapy with Cisplatin	Median Overall Survival Overall Response Rate Duration of Response	IFN alpha + IL-2 vs. IFN alpha + IL-2 + Cisplatin all patients: 9 months, n.s. between groups 18% vs. 33%, sign., p=0.04 17 vs. 6 months, n.s., p=0.057	Jadad Score 3 tumor assessment not blinded Funding: Chiron BV, Amsterdam, the Netherlands and Hoffmann-La Roche AG, Grenzach, Germany	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Cisplatin 100 mg/m ² on day 1					
Jungnelius et al. 1998	To investigate if the addition of Cisplatin to the combination DTIC and Vindesine could increase survival.	RCT, open label Treatment: Group A dacarbazine + vindesine + cisplatin (DVP) (n=161) Group B dacarbazine + vindesine (DV) (n=165)	326 metastatic melanoma patients, no prior chemotherapy	Median Overall Survival Overall Response Rate Duration of Response	DVP vs. DV 7.2 months vs. 5.9 months, n.s., p=0.22 31.4% vs. 21%, n.s. 6.0 months for the whole study population	Jadad Score 2 Randomization scheme not described, unblinded tumor assessment Funding: Not declared	1b
Ringborg et al. 1989	To evaluate treatment with dacarbazine alone or in combination with vindesine in patients with disseminated malignant melanoma	RCT, open label Treatment: Group A dacarbazine + vindesine (n=59) Group B dacarbazine alone (n=51)	119 patients (110 evaluable)	Median Overall Survival Overall Response Rate Duration of Response	dacarbazine + vindesine vs. dacarbazine alone 5.8 months vs. 4.7 months, n.s. 25% vs. 18%, n.s., p>0.20 171 days vs. 123 days, n.s.	Jadad Score 1 No description of dropouts, randomization scheme not described, unblinded tumor assessment Funding: Swedish Cancer Society and Eli Lilly Company	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Chauvergne et al. 1982	To evaluate the efficacy of detorubicin in combination with DTIC versus DTIC alone	<p>RCT, open label</p> <p>Treatment:</p> <p>Group A DTIC (250 mg/m², i.v., over 4 days every three weeks) + detorubicin (120 mg/m², i.v. every three weeks)</p> <p>Group B DTIC alone</p>	51 patient	<p>Median Overall Survival</p> <p>Overall Response Rate</p> <p>Duration of Response</p>	<p>DTIC + detorubicin vs. DTIC alone</p> <p>8 months vs. 5 months, n.s.</p> <p>36% (n=8 of 22 patients) vs. 15% (n=4 of 26), n.s.</p> <p>6 months vs. 5 months, n.s.</p>	<p>Jadad Score 2</p> <p>Randomization scheme not described, unblinded tumor assessment, small sample size</p> <p>Funding: Not declared</p>	1b

6.2.4.2. Aktualisierungsrecherche 2015

6.2.4.2.1. RCTs- Chemotherapy/Chemosensitizer

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bedikian et al. 2014	To prospectively investigate whether Dacarbazine in combination with oblimersen was superior to Dacarbazine plus placebo in patients with advanced melanoma and low baseline LDH levels (r0.8ULN).	2-arm, phase III RCT Group A: Oblimersen 7mg/kg/day by continuous iv infusion for 5 days (120h), immediately followed by Dacarbazine 1000mg/m ² iv (n=157) Group B: Placebo by continuous iv infusion for 5 days (120h), immediately followed by Dacarbazine 1000mg/m ² iv (n=157)	Chemotherapy-naive patients with advanced melanoma and LDH at 0.8ULN	OS PFS Overall Response Rate (ORR) Durable Response Rate	13.5m vs 13.1m (HR: 1.04; p=0.73) 2.8m vs. 2.7m (HR: 0.85, p=0.23) 17.2% vs. 12.1% (p=0.19) 10.8% vs. 7.5% (p=0.32)	Jaded-Score: 5 Funding: Genta	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Daponte et al. 2013	To assess the effect of adding fotemustine and/or IFN to standard therapy with dacarbazine alone in patients with advanced malignant melanoma	<p>4-arm, phase III RCT</p> <p>Group A: Fotemustin 100mg/m² d1 Dacarbazine 900mg/m² d2 q21 (n=64)</p> <p>Group B: Fotemustin 100mg/m² d1 Dacarbazine 900mg/m² d2 q21 Interferon-α2b 5UI 3x/week (n=68)</p> <p>Group C: Dacarbazine 900mg/m² d2 q21 (n=70)</p> <p>Group D: Dacarbazine 900mg/m² d2 q21</p>	Patients with advanced melanoma	<p>OS</p> <p>PFS</p>	<p>Median OS was 7.9 months (95% CI 6.6-10.2) for patients receiving fotemustine (groups A + B) compared with 8.6 months (95% CI 6.3-10.4) without fotemustine (groups C + D) (p=0.28). Median OS was 9.1 months (95% CI 6.3-11.1) with IFN-α2b (groups B + D) and 7.7 months (95% CI 6.3-9.7) without (groups A + C) (p=0.68).</p> <p>Median PFS was 2.7 months (95% CI 2.4-3.8) with fotemustine and 2.5 months (95% CI 2.3-3.7) (p=0.55) without. Median PFS was 2.8 months (95% CI 2.4-3.9) in IFN-</p>	<p>Jaded-Score: 3</p> <p>Funding: National Cancer Institute, Naples</p>	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Interferon- α 2b 5UI 3x/week (n=58)		Response Toxicity	α 2b-treated patients compared with 2.5 months (95% CI 2.3-2.9) without IFN- α 2b (p=0.28). n (%) Group A: 32 (34%) Group B: 33 (26%) Group C: 34 (27%) Group D: 31 (23%) Provided as table only		
Flaherty et al. 2014	To determine whether carboplatin, paclitaxel, and sorafenib improve overall survival compared with carboplatin and paclitaxel in chemotherapy-naive patients with metastatic melanoma.	2-arm, phase III RCT Group A: Carboplatin AUC 6 q21 Paclitaxel 225mg/m ² q21 Sorafenib 400mg po BID (n=410) Group B: Carboplatin AUC 6 q21	Cutaneous, mucosal, or unknown primary site melanoma, metastatic or unresectable disease.	OS PFS Objective Tumor Response (ORR)	11.1 months (95% CI, 10.3 to 12.3 months) for CPS and 11.3 months (95% CI, 9.8 to 12.2 months) for CP (p=.878) 4.9 months for CPS and 4.2 months for CP (p=.092) 20% for CPS and 18% for CP	Jaded-Score: 5 Funding: National Cancer Institute (NCI)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Paclitaxel 225mg/m ² q21 (n=413)		Toxicity	(p=.427) More patients on the CPS arm had grade 3 or higher toxicities (84% v 78%; p=.027), with increased rash, hand-foot syndrome, and thrombocytopenia accounting for most of the difference.		
O'Day et al. 2013	To confirm the efficacy and tolerability of Elesclomol in combination with paclitaxel versus paclitaxel alone in patients with advanced melanoma	2-arm, phase III RCT Group A: Elesclomol 213 mg/m ² and Paclitaxel 80 mg/m ² weekly for 3 weeks followed by one week drug holiday Group B: Placebo + Paclitaxel 80 mg/m ² weekly for 3 weeks followed	Patients with advanced (stage IV) melanoma of cutaneous origin and one or more measurable lesions	PFS	Median PFS was 3.4 months in the combination group and 1.9 months in the paclitaxel group (HR, 0.89; 95% CI, 0.73 to 1.08). A prospectively defined subgroup analysis revealed a statistically significant improvement in median PFS for the combination in patients with	Jaded-Score: 5 Funding: Synta Pharmaceuticals	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		<p>by one week drug holiday</p> <p>Patients were stratified by prior systemic treatment, M1 subclass, and baseline lactate dehydrogenase (LDH) levels</p>		OS	<p>normal baseline LDH.</p> <p>The study was stopped when an early overall survival data analysis indicated an imbalance in total deaths favouring paclitaxel, predominantly in patients with high LDH levels.</p> <p>Median OS was 10.6 months in the combination group and 11.4 months in the paclitaxel group (HR, 1.10; 95% CI, 0.92 to 1.32;p=.18).</p>		

6.2.4.2.2. RCTs- Immuntherapie/Immunmodulation

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Andtbacka et al. 2015	To evaluate whether treatment with T-VEC resulted in an improved durable response rate (DRR) compared with GM-CSF in patients with unresected stage IIIB to IV melanoma.	2-arm, phase III RCT Treatment: Group A: Talimogene Laherparepvec (n=295) Group B: GM-CSF (n=141)	Not surgically resectable, stage IIIB to IV melanoma suitable for direct or ultrasound-guided injection (at least one cutaneous, subcutaneous, or nodal lesion or aggregation of lesions 10 mm in diameter).	Durable Response Rate Overall Response Rate Overall Survival	DRR was higher with T-VEC (16.3%; 95% CI, 12.1% to 20.5%) than GM-CSF (2.1%; 95% CI, 0% to 4.5%]; odds ratio, 8.9; P <.001). Overall response rate was higher in the T-VEC arm (26.4%; 95% CI, 21.4% to 31.5% v 5.7%; 95% CI, 1.9% to 9.5%). Median OS was 23.3 months (95% CI, 19.5 to 29.6 months) with T-VEC and 18.9 months (95% CI, 16.0 to 23.7 months) with GM-CSF (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; P .051).	Jadad-Score: 3 T-VEC efficacy was most pronounced in patients with stage IIIB, IIIC, or IVM1a disease and in patients with treatment-naive disease. Funded by: AMGEN	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Larkin et al. 2015	To confirm and extend [<i>findings of a phase 2 trial</i>], we report one of the coprimary end points (progression-free survival) of a randomized, double-blind, multi-center, phase 3 trial (CheckMate 067) that was conducted to evaluate the safety and efficacy of nivolumab alone or nivolumab combined with ipilimumab in comparison with ipilimumab alone in patients with previously untreated metastatic melanoma.	<p>3-arm, phase III, RCT</p> <p>Group A: Nivolumab alone (n=316) 3mg/kg q14 (plus ipilimumab-matched placebo);</p> <p>Group B: Nivolumab combined with Ipilimumab (n=314) Nivolumab 1mg/kg q21 plus Ipilimumab 3 mg/kg q21 for 4 doses, followed by Nivolumab 3mg/kg q14</p> <p>Group C: Ipilimumab alone (n=315) 3mg/kg q21 for 4 doses (plus Nivolumab-matched placebo).</p>	<p>Stage III (unresectable) or stage IV melanoma patients, no prior systemic treatment for advanced disease.</p> <p>Availability of tissue collected from metastatic or unresectable tumors (archival or recently biopsied samples) for the assessment of PD-L1 status; and known BRAF V600 mutation status.</p>	<p>Progression-free survival (PFS)</p> <p>Overall survival Objective Response Rate</p> <p>Tumor PD-L1 expression as a predictive biomarker for efficacy outcomes.</p>	<p>Median PFS: 11.5 months (95% CI, 8.9 to 16.7) with nivolumab plus ipilimumab, vs. 2.9 months (95% CI, 2.8 to 3.4) with ipilimumab (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; P<0.001), vs 6.9 months (95% CI, 4.3 to 9.5) with nivolumab (HR for the comparison with ipilimumab, 0.57; 99.5% CI, 0.43 to 0.76; P<0.001).</p> <p>Not reported on</p> <p>In patients with tumors positive for the PD-L1, median PFS was 14.0</p>	<p>Jadad-Score: 5</p> <p>Overall survival data (coprimary end point) not available so far. Study not powered to confirm benefit of Nivo+Ipi vs Nivo alone.</p> <p>PD-L1 status of tumor tissue as stratification factor</p> <p>Funded by: Bristol-Myers Squibb</p>	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Safety	<p>months in the nivolumab-plus-ipilimumab group and in the nivolumab group, but in patients with PD-L1-negative tumors, progression-free survival was longer with the combination therapy than with nivolumab alone (11.2 months [95% CI, 8.0 to not reached] vs. 5.3 months [95% CI, 2.8 to 7.1]).</p> <p>Treatment-related adverse events of grade 3 or 4 occurred in 16.3% of the patients in the nivolumab group, 55.0% of those in the nivolumab-plus-ipilimumab group, and 27.3% of those</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					in the ipilimumab group.		
Maio et al. 2015	To conduct a milestone survival analysis of data from a randomized controlled phase III trial to confirm the survival benefit of ipilimumab in patients with advanced melanoma.	OS follow up from a RCT Group A: Ipilimumab 10mg/kg q21 + DTIC 850mg/m ² (n=250) Group B: DTIC 850mg/m ² + Placebo (n=252)	Untreated stage IIIc, N3 (unresectable) or stage IV melanoma	Overall survival 5-Y-OS	Median survival follow-up for the ipilimumab plus dacarbazine group was 11.0 months (range, 0.4 to 71.9 months) and was 8.9 months (range, 0.1 to 73.2 months) for the placebo plus dacarbazine group. The updated median OS was 11.2 months (95% CI, 9.5 to 13.8 months) in the ipilimumab plus dacarbazine group and was 9.1 months (95% CI, 7.8 to 10.5 months) in the placebo plus dacarbazine group (HR, 0.69; 95% CI, 0.57 to 0.84). OS	Jadad-Score: Not applicable Updated OS data from a previously published trial. Different dosing of Ipilimumab in contrast to the approved one in the EU Funded by: Bristol-Myers Squibb	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>rates in the ipilimumab plus dacarbazine group were consistently higher than those in the placebo plus dacarbazine group. At a minimum follow-up of 5 years, 18.2% of patients in the ipilimumab plus dacarbazine group were still alive compared with 8.8% of patients in the placebo plus dacarbazine group (P.002).</p>		
McDermott et al. 2013	To describe the safety and long-term efficacy of ipilimumab among patients from the pivotal phase III MDX010-20 study who survived 2 years or longer	<p>Updated data from a 3-arm phase III RCT</p> <p>Of 676 patients treated in MDX010-20, 474 were randomized at least 2 years before the study cut-off date and</p>	Patients with unresectable stage III or IV melanoma who had been treated previously with chemotherapy or interleukin-2 (IL-2) were randomized 3:1:1.	Long term OS (2-3 Y OS rate)	<p>≥2 years Ipi+gp100 54 of 284 (19%) Ipi 24 of 95 (25%) gp100 16 of 95 (17%)</p> <p>≥3 years Ipi+gp100 24 of 156 (15%)</p>	<p>Jadad-Score: Not applicable</p> <p>Subset analysis of the MDX010-20 study</p> <p>Funded by: Bristol-Myers Squibb</p>	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		<p>were eligible for this analysis.</p> <p>Group A: Ipilimumab 3mg/kg q21 for 4 doses plus gp100 vaccine 2mL sc q21 for 4 doses (n=284)</p> <p>Group B: Ipilimumab 3mg/kg q21 for 4 doses (n=95)</p> <p>Group C: gp100 2mL sc q21 for 4 doses (n=95)</p>		Safety	<p>Ipi 13 of 53 (25%) gp100 5 of 50 (10%)</p> <p>Safety in patients with ≥ 2 years' survival was comparable to that in the overall study population.</p>		
Ribas et al. 2013	To evaluate overall survival (OS) and other safety and efficacy end points in patients with advanced melanoma treated with tremelimumab or	<p>2-arm RCT, phase III</p> <p>Group A: Tremelimumab 15 mg/kg once every 90 days (n=328)</p>	Patients with treatment-naive, unresectable stage IIIc or IV melanoma	OS	Median OS by ITT was 12.6 months (95%CI, 10.8-14.3 months) in the tremelimumab arm and 10.7 months (95% CI, 9.4 to 12.0 months) in the chemotherapy	<p>Jadad-Score: 3</p> <p>Funded by: Pfizer</p>	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	standard-of-care chemotherapy.	Group B: Physician's choice of standard-of-care chemotherapy (temozolomide or dacarbazine, n=327).		ORR	<p>arm (HR,0.88;P.127).</p> <p>Survival at 2 and 3 years was 26.4% (95% CI, 22.0% to 31.7%) and 20.7% (95% CI, 16.7% to 25.6) in patients treated with tremelimumab and 22.7% (95% CI, 18.5% to 27.8%) and 17.0% (95% CI, 13.3% to 21.7%), in patients in the chemotherapy arm.</p> <p>ORR based on investigator assessment were similar in both study arms:10.7% in the tremelimumab arm and 9.8% in the chemotherapy arm There were no significant differences</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Response duration	<p>between study arms in rate of complete or partial response.</p> <p>Median response duration (defined as time from random assignment to progression or death resulting from disease progression for the objective responders) was significantly longer among tremelimumab responders compared with chemotherapy responders: 35.8 months (range, 5.6 to 44.3 months) versus 13.7 months (range, 4.0 to 44.3 months; P .0011).</p>		
				Safety	<p>Grade 3/4 AEs</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Tremelimumb: 52% Chemo: 37% Grade 5: Tremelimumab: 7% Chemo: 4%		
Robert et al. 2013	To describe the rationale for retreatment with ipilimumab and to provide resultant efficacy and safety outcomes	<p>Subset of a 3-arm RCT</p> <p>Group A: Ipilimumab 3mg/kg q21 for 4 doses plus gp100 vaccine 2mL sc q21 for 4 doses (n=29)</p> <p>Group B: Ipilimumab 3mg/kg q21 for 4 doses (n=9)</p> <p>Group C: gp100 2mL sc q21 for 4 doses (n=2)</p>	Patients with unresectable stage III or IV melanoma who had been treated previously with chemotherapy or interleukin-2 (IL-2) were randomized 3:1:1.	<p>BOOR</p> <p>Safety</p>	<p>Best overall response rates (CR+PR) for 31 retreatment-eligible patients in the ipilimumab plus gp100 and ipilimumab plus placebo groups were 3 of 23 (13.0%) and 3 of 8 (37.5%), respectively, and disease control rates were 65.2% and 75.0%.</p> <p>Drug-related adverse events were reported in 25 patients (86.2%), 7 patients (77.8%), and 2 patients (100%) in the ipilimumab</p>	<p>Jadad-Score: not applicable</p> <p>Subset analysis of the MDX010-20 study</p> <p>Funded by: Bristol-Myers Squibb</p>	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					plus gp100, ipilimumab plus placebo, and gp100 plus placebo arms, respectively. The most common adverse events were irAEs, occurring in 15 patients (51.7%), 7 patients (77.8%), and 1 patient (50.0%) in the respective groups.		
Robert et al. 2015	To determine whether nivolumab, as compared with dacarbazine, improves overall survival among previously untreated patients who have advanced melanoma without a BRAF mutation	2-arm RCT, phase III 1:1 randomisation Group A: Nivolumab 3mg/kg q14 plus a dacarbazine-matched placebo every 3 weeks Group B: Dacarbazine 1000mg/m ² q21	Unresectable, previously untreated stage III or IV melanoma without a BRAF mutation.	OS Investigator-	1 Y-OS rate of survival was 72.9% (95% confidence interval [CI], 65.5 to 78.9) in the nivolumab group, as compared with 42.1% (95% CI, 33.0 to 50.9) in the dacarbazine group (HR for death, 0.42; 99.79% CI, 0.25 to 0.73; P<0.001).	Jadad-Score: 5 BRAF wt patients only PD-L1 status of tumor tissue as stratification factor Funded by: Bristol-Myers Squibb	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		plus a nivolumab-matched placebo every 2 weeks.		assessed PFS ORR PD-L1 expression in the tumor as a predictive biomarker of OS	Median PFS was 5.1 months in the nivolumab group vs 2.2 months in the dacarbazine group (HR for death or progression of disease, 0.43; 95% CI, 0.34 to 0.56; P<0.001). ORR was 40.0% (95% CI, 33.3 to 47.0) in the nivolumab group vs 13.9% (95% CI, 9.5 to 19.4) in the dacarbazine group (odds ratio, 4.06; P<0.001). Regardless of PD-L1 status, nivolumab-treated patients had improved OS, as compared with dacarbazine-treated patients (unad-justed HR		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>for death among patients with positive PD-L1 status, 0.30 [95% CI, 0.15 to 0.60]; unadjusted hazard ratio for death among those with PD-L1 negative or indeterminate PD-L1 status, 0.48 [95% CI, 0.32 to 0.71]). In the nivolumab group, the median OS was not reached in either PD-L1 subgroup. In the dacarbazine group, the median OS was slightly longer in the subgroup with positive PD-L1 status than in the subgroup with negative or indeterminate PD-L1 status (12.4 vs. 10.2 months)</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				ORR	pembrolizumab every 3 weeks, 0.69; 95% CI, 0.52 to 0.90; P=0.0036).		
				Duration of response	ORR was improved with pembrolizumab administered every 2 weeks (33.7%) and every 3 weeks (32.9%), as compared with ipilimumab (11.9%) (P<0.001 for both comparisons). Responses were ongoing in 89.4%, 96.7%, and 87.9% of patients, after a median follow-up of 7.9 months.		
Schadendorf et al. 2015	To provide a more precise estimate of long-term survival observed with ipilimumab therapy, we	Primary analysis pooled OS data for 1,861 patients from 10 prospective and two retrospective	Patients with advanced melanoma	OS	Among 1,861 patients, median OS was 11.4 months (95% CI, 10.7 to 12.1 months).	Jadad-Score: not applicable Mixed cohorts, maybe data from EAPs more	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	conducted a pooled analysis of OS data across multiple studies in advanced melanoma.	<p>studies of ipilimumab, including two phase III trials. Patients were previously treated (n=1,257) or treatment naive (n=604), and the majority of patients received ipilimumab 3 mg/kg (n=965) or 10 mg/kg (n=706).</p> <p>Secondary analysis of OS data (n=4,846) with an additional 2,985 patients from an expanded access program.</p>			<p>The survival curve began to plateau around year 3, with follow-up of up to 10 years. Three-year survival rates were 22%, plateau around year 3, with follow-up of up to 10 years.</p> <p>Three-year survival rates were 22%, 26%, and 20% for all patients, treatment-naive patients, and previously treated patients, respectively.</p> <p>Including data from the expanded access program, median OS was 9.5 months (95% CI, 9.0 to 10.0 months), with a plateau at 21% in</p>	<p>valuable because it reflects the standard of care more precisely.</p> <p>Funded by: Bristol-Myers Squibb</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					the survival curve beginning around year 3.		
Weber et al. 2015	To assessed the efficacy and safety of nivolumab compared with investigator's choice of chemotherapy (ICC) as a second-line or later-line treatment in patients with advanced melanoma.	2-arm phase III RCT Randomisation schedule 2:1 Group A: Nivolumab 3 mg/kg q14 (n=272) Group B: Investigator's choice of chemotherapy (ICC) (dacarbazine 1000 mg/m ² q21 or paclitaxel 175 mg/m ² combined with carboplatin area under the curve 6 q21) (n=133)	Patients had unresectable or metastatic melanoma, and progressed after ipilimumab, or ipilimumab and a BRAF inhibitor if they were BRAFV600 mutation-positive.	ORR PFS Safety	38 (31.7%, 95% CI 23.5–40.8) of the 120 patients in the nivolumab group and in five (10.6%, 3.5–23.1) of the 47 patients in the ICC group archived an objective response. Median PFS was 4,7 months (95% CI 2,3–6,5) for the nivolumab group and 4,2 months (2,1–6,3) for the ICC group (HR 0.82; 99.99% CI 0.32–2.05) 6-month PFS was 48% (95% CI 38–56) in the nivolumab group and 34% (18–51) in the ICC group. Grade 3–4	Jadad-Score: 3 BRAF-Mutation status, PDL1-expression and best response to Ipilimumab used as stratification factors. ORR/PFS only reported for a subset of patients Funded by: Bristol-Myers Squibb	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					treatment-related adverse events occurred in 24 (9%) of the 268 patients in the nivolumab group versus 32 (31%) of the 102 patients in the ICC group.		

6.2.4.2.3. Zielgerichtete Therapien /small molecules

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Flaherty et al. 2012	Not specified in report	Open-label, 2-armed Phase III RCT Group A: Trametinib (n=214) Group B: Chemotherapy (DTIC or Paclitaxel) (n=108)	Patients who had histologically confirmed, unresectable stage IIIC or IV cutaneous melanoma with a V600E or V600K BRAF mutation were eligible. Up to one previous chemotherapy schedules allowed.	Progression-free survival (PFS) Overall survival (OS)	4.8 months in the Trametinib group as compared with 1.5 months in the chemotherapy group (HR for progression, 0.45; 95% CI, 0.33-0.63; P<0.001) 6-month OS rate in the ITT population was 81% in the Trametinib group and 67% in the chemotherapy	Jaded-Score: 3 Funding: GlaxoSmithKline	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE	
					<p>group. The HR for death in the Trametinib group was 0.54 (95% CI, 0.32-0.92; P=0.01), even though 51 of 108 patients (47%) in the chemotherapy group crossed over to receive Trametinib. Median overall survival had not been reached at the time of this report.</p> <p>Overall response rate (ORR)</p> <p>Duration of response</p>	<p>ORR 22% (95% CI, 17-28) in the Trametinib group and 8% (95% CI, 4-15) in the chemotherapy group</p> <p>Median duration of response was 5.5 months (95% CI, 4.1 to 5.9) in the Trametinib group</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Safety	(in 47 pts.) and had not been reached in the chemotherapy group (in 9 pts). Rash, diarrhoea, and peripheral oedema were the most common toxic effects in the Trametinib group and were managed with dose interruption and dose reduction; asymptomatic and reversible reduction in the cardiac ejection fraction and ocular toxic effects occurred infrequently. Secondary skin neo-plasms were not observed.		
Hauschild et al. 2012	To assess whether Dabrafenib was better than	Open-label, 2-armed Phase III RCT, randomly	Patients aged 18 years or older with previously	PFS (by investigator)	Median PFS was 5.1 months for Dabrafenib and 2.7	Jaded-Score: 3 Funding:	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<p>standard Dacarbazine chemo-therapy, we did a phase 3, multi-centre, randomised trial in previously untreated melanoma patients whose tumours harboured a BRAFV600E mutation.</p>	<p>assigned 3:1</p> <p>Group A: Dabrafenib 150mg bid p.o. (n=187)</p> <p>Group B: Dacarbazine 1000mg/m² iv q21 (n=63)</p>	<p>untreated, stage IV or unresectable stage III BRAFV600E mutation-positive melanoma</p>	<p>PFS (by Independent Review)</p> <p>OS</p> <p>ORR</p>	<p>months for Dacarbazine, with a HR of 0.30 (95% CI 0.18–0.51; p<0.0001).</p> <p>Median PFS for Dabrafenib was 6.7 months versus 2.9 months for Dacarbazine (HR 0.35; 95% CI 0.20–0.61).</p> <p>The overall survival HR was 0.61 (95% CI 0.25–1.48) in favour of Dabrafenib.</p> <p>Confirmed OR was reported by the IR in 93 (50%, 95% CI 42.4–57.1) of 187 patients randomly assigned to Dabrafenib (6 [3%] had a complete response and 87 [47%] had a partial response). In the</p>	<p>GlaxoSmithKline</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>Dacarbazine group, confirmed responses were seen by the IR in four (6%, 95% CI 1.8-15.5) of 63 patients.</p> <p>Confirmed OR was reported by the investigator in 99 (53%, 95% CI 45.5-60.3) of the 187 patients (6 [3%] had a CR and 93 [50%] had a PR). Confirmed responses for the Dacarbazine group were reported by the investigator in 12 (19%, 10.2-30.9) patients (all 12 patients had a partial response).</p> <p>28 patients randomly assigned to Dacarbazine have crossed over to Dabrafenib at</p>		
				PFS after cross-over			

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>data cutoff; 13 (46%) patients have had PR but, among these patients, no CR has been noted.</p> <p>Duration of response</p> <p>The estimated median duration of response for Dabrafenib was 5.5 months for IR and 5.6 months for investigator assessment. The estimated median duration of response for Dacarbazine was not reached at time point of data cut.</p> <p>Quality of life</p> <p>Quality of life analyses are ongoing and will be reported separately.</p> <p>Safety & Tolerability</p> <p>In patients receiving</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Dabrafenib, the most common AEs were cutaneous (hyperkeratosis, papillomas, palmar-plantar erythrodysesthesia), pyrexia, fatigue, headache, and arthralgia. Toxic effects of grade 3-4 were uncommon.		
Larkin et al. 2014	To confirm and build on these early data, we report on the primary end point of coBRIM, an inter-national, multicenter, randomized phase 3 study that evaluated the efficacy and safety of cobimetinib combined with vemurafenib in previously untreated patients with advanced	<p>Double-blinded, 2-armed Phase III RCT</p> <p>Group A: Vemurafenib 960 mg bid po Cobimetinib (at a dose of 60 mg once daily for 21 days, followed by 7 days off) (n=247)</p> <p>Group B: Vemurafenib 960 mg bid po Placebo (n=248)</p>	Histologically confirmed unresectable, locally advanced stage IIIC or stage IV melanoma with a BRAF V600 mutation detected with the use of a real-time polymerase-chain-reaction assay (Cobas 4800 BRAF V600 Mutation Test, Roche Molecular Systems)	<p>PFS as assessed by the investigator,</p> <p>Overall Survival</p>	<p>VEM+COBI: Median PFS of 9.9 months (95% CI, 9.0 to not reached), as compared with 6.2 months (95% CI, 5.6 to 7.4) in patients treated with VEM and placebo. HR for death or progression of disease: 0.51 (95% CI, 0.39 to 0.68; P<0.001)</p> <p>The interim analysis of OS in</p>	<p>Jaded-Score: 5</p> <p>Funding: F Hoffmann-La Roche-Genentech</p>	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	BRAF-mutated melanoma.			<p>ORR</p> <p>Duration of response</p>	<p>the ITT-population showed that the rate of overall survival at 9 months for the combination of VEM+COBI was 81% (95% CI, 75-87), as compared with 73% (95% CI, 65-80) with VEM+Placebo</p> <p>68% of patients in the combination group had an objective response, as compared with 45% in the control group (P<0.001). The rate of complete response was also significantly higher in the combination group than in the control group (10% vs. 4%).</p> <p>The median duration of</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				PFS as assessed by an independent review facility	response was 7.3 months in the control group, and the median was not reached in the combination group.		
				Safety	11.3 months for VEM+COBI (95% CI 5.6-7.5) vs 6.0 months for VEM+Placebo (95% CI 8.5-NE); HR 0.6 (95% CI 0.45-0.79, p=0.0003)		
					The combination of VEM and COBI was associated with a higher frequency of certain events than the single-agent therapy, including central serous retinopathy, gastrointestinal events (diarrhoea, nausea, or vomiting), photo-		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					sensitivity, elevated aminotransferase levels, and an increased creatine kinase level; the majority (>50%) of these individual events were grade 1 or 2. We observed equivalent rates of grade 3 events (49%) in the two study groups and substantially fewer grade 4 events (9% in the control group vs. 13% in the combination group).		
Long et al. 2014	To compare the combination of Dabrafenib and Trametinib with Dabrafenib alone as first-line therapy in patients who had metastatic melanoma with	Double-blinded, 2-armed Phase III RCT Group A: Dabrafenib 150mg bid po Trametinib 2mg/d (n=211)	Histologically confirmed, unresectable stage IIIC or stage IV metastatic melanoma with BRAF V600E or V600K mutations, as determined by	PFS (investigator-assessed)	In the ITT population, median PFS was longer in the Dabrafenib-Trametinib group than in the Dabrafenib-only group (9.3 months vs. 8.8	Jaded-Score: 5 Funding: GlaxoSmithKline	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<p>BRAF V600E or V600K mutations</p>	<p>Group B: Dabrafenib 150mg bid po Placebo (n=212)</p>	<p>means of an investigational-use-only polymerase-chain-reaction assay (ThxID BRAF Assay, bioMérieux) performed at a central reference laboratory.</p>	<p>OS</p> <p>Response rate</p>	<p>months); the hazard ratio for disease progression or death was 0.75 (95% CI, 0.57 to 0.99; P = 0.03).</p> <p>At the time of the interim survival analysis, 40 patients (19%) in the Dabrafenib-Trametinib group and 55 patients (26%) in the Dabrafenib-only group had died (HR for death, 0.63; 95% CI, 0.42 to 0.94; P = 0.02). At 6 months, the OS rate was 93% in the Dabrafenib-Trametinib group and 85% in the Dab-rafenib-only group. At the time of this report, neither group had reached a median</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Response duration	<p>overall survival.</p> <p>The ORR as assessed by investigators was 67% (95% CI, 60-73) in the Dabrafenib-Trametinib group vs 51% (95% CI, 45-58) in the Dabrafenib-only group (P=0.002) In the Dabrafenib-Trametinib group, 22 patients (10%) had a complete response, and 118 (56%) had a partial response. In the Dabrafenib-only group, 18 (9%) had a complete response, and 90 (43%) had a partial response.</p> <p>The median duration of response was 9.2 months in the</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Safety	<p>Dabrafenib-Trametinib group and 10.2 months in the Dabrafenib-only group on the basis of data that were highly censored because the majority of investigator-assessed responses (60%) were still ongoing.</p> <p>Rates of AEs were similar in the two groups, although more dose modifications occurred in the Dabrafenib-Trametinib group. The rate of cutaneous squamous-cell carcinoma was lower in the Dabrafenib-Trametinib group than in the Dabrafenib-only</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					group (2% vs. 9%), whereas pyrexia occurred in more patients (51% vs. 28%) and was more often severe (grade 3, 6% vs. 2%) in the Dabrafenib-Trametinib group.		
Long et al. 2015	To report the final overall survival analysis for the randomised, double-blind phase 3 study of Dabrafenib combined with Trametinib compared with Dabrafenib combined with placebo in previously untreated patients with BRAF Val600Glu/Lys mutation-positive metastatic melanoma, and provide the latest	Double-blinded, 2-armed Phase III RCT Group A: Dabrafenib 150mg bid po Trametinib 2mg/d (n=211) Group B: Dabrafenib 150mg bid po Placebo (n=212)	Histologically confirmed, unresectable stage IIIC or stage IV metastatic melanoma with BRAF V600E or V600K mutations, as determined by means of an investigational-use-only polymerase-chain-reaction assay (ThxID BRAF Assay, bioMérieux) performed at a central reference laboratory.	PFS (investigator-assessed) OS Response rate	11.0 months for the combination (95% CI: 8.0-13.9) vs. 8.8 months for the Dabrafenib-only group (95% CI: 5.9-9.3), HR=0.67 (0.53-0.84),p=0.0004 Median OS for the Dabrafenib+Trametinib group was 25.1 months (95% CI: 19.2-NR) vs. 18.7 months (95% CI 15.2-23.7); HR=0.71 (95% CI: 0.55-0.92), p=0.0107	Jaded-Score: 5 Funding: GlaxoSmithKline Same as previous trial but with longer follow up and overall survival data	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	findings for progression-free survival, response rate, duration of response, and safety.			Response duration	69% (95% CI: 62-75) for the Dabrafenib+Trametinib group vs. 53% (95% CI: 46-60), p=0.014		
				Safety	12.9 months (95% CI: 9.4-19.5) vs. 10.6 months (95% CI: 9.1-13.8)		
					Treatment-related AEs occurred in 181 (87%) of 209 patients in the Dabrafenib and Trametinib group and 189 (90%) of 211 patients in the Dabrafenib only group; the most common was pyrexia (108 patients, 52%) in the Dabrafenib and Trametinib group, and hyperkeratosis (70 patients, 33%) in the Dabrafenib only group. Grade		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					3 or 4 adverse events occurred in 67 (32%) patients in the Dabrafenib and Trametinib group and 66 (31%) patients in the Dabrafenib only group.		
McArthur et al. 2014	To present an update of safety and efficacy for the BRIM-3 study with extended follow-up for the entire population, and also analyse the efficacy and safety of Vemurafenib versus Dacarbazine in patients with BRAFV600E and BRAFV600K mutation-positive disease	Open-label, Phase III RCT Group A: Vemurafenib (960 mg bid po) (n=337) Group B: Dacarbazine 1000mg/m ² iv q21 (n=338)	Treatment-naive metastatic melanoma (unresectable stage IIIc or stage IV M1a, M1b, or M1c disease) with tumour tissue positive for the presence of BRAFV600 mutations by the cobas test.	OS	Median OS censored at crossover, was 13.6 months (95% CI 12.0–15.2) in the Vemurafenib group versus 9.7 months (7.9–12.8) in the Dacarbazine group; 12 month overall survival was 56% (95% CI 50–61) for Vemurafenib and 44% (38–51) for Dacarbazine censored at crossover. HR for death was 0.70 (95% CI 0.57–0.87; p=0.0008). An ITT	Jaded-Score: 3 Funding: F Hoffmann-La Roche-Genentech Updated data for the BRIM3 trial	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				PFS	analysis of OS using the observed survival times, without regard to crossover, resulted in an HR of 0.76 (95% CI 0.63–0.93; $p=0.0068$).		
				Proportion of patients with a confirmed response (CR or PR).	Median PFS censored at crossover was also significantly longer in the Vemurafenib group than in the Dacarbazine group (6.9 months [95% CI 6.1–7.0] vs 1.6 months [1.6–2.1]), respectively; HR 0.38, 95% CI 0.32–0.46; log-rank $p<0.0001$ Objective responses, confirmed by an IR, were noted in 57% of patients receiving Vemurafenib and		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Time to response	9% of patients treated with Dacarbazine Independently confirmed CR were attained by 6% of the patients in the Vemurafenib group and 1% of patients in the Dacarbazine group.		
				Duration of response	Not reported		
				Time to treatment failure	Not reported		
				Pharmacokinetic profile	Not reported		
				Tolerability and safety	Not reported		
					Most common grade 3/4 AEs of interest in patients treated with Vemurafenib were cutaneous squamous-cell carcinomas,		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Validation of the cobas test	<p>increased liver function tests, keratoacanthomas, rash, and arthralgia. Grade 4 or worse adverse events occurred in 29 (8%) patients in the Vemurafenib group (three [1%] increased liver function test, one [$<1\%$] neutropenia), and 32 (11%) patients in the Dacarbazine group (nine [3%] were neutropenia). Seven (2%) patients in the Dacarbazine group and eight (2%) in the Vemurafenib group had grade 5 events. Additionally, eight (2%) patients in the Vemurafenib group reported new primary melanomas.</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>673 of the 675 patients (336 patients in the Vemurafenib group and 337 in the Dacarbazine group) to differentiate BRAFV600E and BRAFV600K mutations. Of these 673 patients, Sanger/454 sequencing could not provide a valid result for 14 patients. Therefore, 657 (98%) of 671 patients had tumours that were cobas-positive at screening and for whom Sanger 454 sequencing results were available. Of these 657 tumours, 598 (91%) carried the BRAFV600E</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					mutation, 57 (9%) had the BRAFV600K mutation		
Robert et al. 2015	To evaluate the effect of combination therapy with Dabrafenib plus Trametinib versus Vemurafenib monotherapy on overall survival in previously untreated patients with unresectable stage IIIC or IV melanoma with BRAF V600E or V600K mutations.	Open-label, Phase III RCT Group A: Dabrafenib 150mg bid po Trametinib 2mg/d (n=211) Group B: Vemurafenib 960mg/d bid po	Patients with metastatic melanoma with a BRAF V600 mutation. The presence of BRAF V600E or V600K mutations was centrally determined with the investigational use of the THxID BRAF assay (bioMérieux).	OS PFS	100 patients (28%) in the combination-therapy group and 122 (35%) in the Vemurafenib group had died (HR for death in the combination-therapy group, 0.69; 95% CI, 0.53-0.89; P=0.005) Median OS was 17.2 months for patients in the Vemurafenib group and had not been reached for patients in the combination group Median PFS was longer in the combination group than in the Vemurafenib group	Jaded-Score: 3 Funding: Glaxo-SmithKline	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				ORR	(11.4 months vs. 7.3 months; of response was 13.8 months (95% CI, 11.0 to not reached) and 7.5 months (95% CI, 7.3-9.3), respectively.		
				Duration of response	The response rate for the BRAF V600E subgroup was similar to that in the overall population in both study groups: 64% in the combination group and 52% in the Vemurafenib group; in the BRAF V600K subgroup, the response rates were 65% and 44%, respectively.		
				Safety	13.8 months (95% CI: 11.0-NR) vs 7.5 months (95% CI: 7.3-9.3)		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Rates of severe adverse events and study-drug discontinuations were similar in the two groups. Cutaneous squamous-cell carcinoma and keratoacanthoma occurred in 1% of patients in the combination-therapy group and 18% of those in the Vemurafenib group.		

6.2.4.2.4. Reviews

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Aubin et al. 2013	To review the available literature on liver resection for metastatic melanoma in a systematic manner, and to compare oncological outcomes for surgery with standard therapy using meta-analytical techniques.	Systemic review and meta-analysis Initial literature search revealed 423 potential reports Finally 22 selected for full review after checking eligibility criteria	579 patients who underwent liver resection	Overall survival (OS) Hazard ratios (HRs) Disease-free survival (DFS)	Median OS: 14-41 months (R0, 22–66months, R2, 10–16months; R0 versus R1/R2: HR 0.52, 95% CI 0.37 to 0.73). Comparison of OS with resection and non-operative management favoured resection (HR 0.32, 95% CI 0.22 to 0.46). Median DFS: 8 to 23months	5 studies describe a comparison between surgical excision of liver metastases and systemic treatment of patients suffering from hepatic metastases. Overall, there is a trend to a favourable prolongation in OS for patients receiving excision of liver lesions. Overall a valuable review/meta-analysis, however – as the authors admit – with studies of low quality involved.	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Buder et al. 2013	To review the present status of systemic treatment of metastatic uvea melanoma and evaluate therapy outcome measured by overall response rate (ORR)	Systematic review PubMed search was performed for “metastatic” [and] “uveal” [and] “melanoma” as well as for “melanoma” [and] “eye” [and] “treatment” for the time period between 1980 and May 2013. “Web of Knowledge” and congress abstract search via the ASCO homepage was per-formed. The ClinicalTrials.gov website was searched for terms “melanoma” and “eye”. Of 2017 references, 40 studies were selected for final analyses	841 patients out of 40 studies	Overall response rate (ORR)	39/841 patients with remission (overall response rate [ORR] 4.6%; 95% confidence intervals [CI] 3.3-6.3%) No responses were observed in 22/40 studies. Progression-free survival ranged from 1.8 to 7.2, median overall survival from 5.2 to 19.0 months as reported in 21/40 and 26/40 studies, respectively. Best responses were seen for chemoimmunotherapy (ORR 10.3%; 95% CI 4.8-18.7%) though mainly in first-line patients. Immunotherapy	Uvea melanoma only. Well described, however due to lack of appropriate studies, no phase III data included	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					with ipilimumab, antiangiogenetic approaches, and kinase inhibitors have not yet proven to be superior to chemotherapy.		
Dequen et al. 2012	To perform a systematic literature review and network meta-analysis to compare overall survival with 3 mg/kg ipilimumab with alternative therapies in the treatment of pre-treated patients with unresectable stage III or IV melanoma.	<p>Systematic review of randomized controlled trials unresectable stage III or IV melanoma,</p> <p>Systematic literature search performed in MEDLINE, MEDLINE-In-Process, EMBASE, and the Cochrane Library.</p> <p>Key words and free text were combined to include the disease-specific search terms "skin-neoplasms" and</p>	2739 patients from 15 studies	Mean OS	Ipilimumab, at a dose of 3 mg/kg, was associated with a greater mean OS time (18.8 months; 95% credible interval [CrI], 15.5–23.0 months) than single-agent chemotherapy (12.3 months; 95% CrI, 6.3–28.0 months), chemotherapy combinations (12.2 months; 95% CrI, 7.1–23.3 months), biochemotherapies (11.9 months; 95% CrI, 7.0–22.0 months), single-	<p>Statistically sophisticated review with a Bayesian network meta-analysis approach. Interestingly, a parametric survival distribution (Gompertz) was selected for analysis.</p> <p>Meta-analyses missed BRAF/MEK inhibitors.</p>	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		<p>“melanoma”; the disease-staging terms “metastatic,” “advanced,” and “stage III/3 or IV/4”; and non-proprietary drug names.</p> <p>1,793 references detected, 38 studies finally included. During evaluation the number of studies had to be reduced to 15 studies</p>			<p>agent immunotherapy (11.1 months; 95% CrI, 8.5–16.2 months), and immunotherapy combinations (14.1 months; 95% CrI, 9.0–23.8 months).</p>		
Jiang et al. 2014	To comprehensively analyse the data from clinical RCTs to evaluate the efficacy and safety of DTIC alone versus DTIC combined targeted therapy in treatment of metastatic melanoma.	<p>Systematic review and meta-analyses</p> <p>The Cochrane Library, MEDLINE, EBSCO, EMBASE, Ovid databases and clinical trial websites from 2003 to 2013 were scanned. The search strategy included the</p>	2,221 patients included in 8 randomized controlled trials	<p>Overall response (CR+PR).</p> <p>1-year survival</p>	<p>The overall response in the arm for DTIC combined targeted therapy was higher than that in the arm for DTIC alone (combined RR=1.60; 95% CI, 1.27–2.01, Z=3.98)</p> <p>The 1-year survival in the arm for DTIC</p>	Meta-analyses also for adverse events	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		<p>keyword “DTIC” combined with the Medical Subject Headings (MeSH) “metastatic melanoma” and “randomized controlled trials”. Chinese databases such as CNKI and CBMDisc using the above search terms were used.</p> <p>1,286 records identified. 8 studies included for final evaluation.</p>		<p>Adverse event: Nausea</p> <p>Adverse Event: Vomiting</p> <p>Adverse Event: Fatigue</p>	<p>combined targeted therapy was higher than that in the arm for DTIC alone (combined RR=1.34; 95% CI, 1.20-1.49, Z=5.25, P<0.00001)</p> <p>Significant difference between DTIC combined targeted therapy and DTIC alone (combined RR=1.22, 95% CI: 1.10-1.37, Z=3.64, P=0.0003)</p> <p>significant difference between DTIC combined targeted therapy and DTIC alone (combined RR=1.73, 95% CI: 1.41-2.12, Z=5.19, P<0.00001)</p> <p>Failed to show a significant</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Adverse Event: Constipation	difference between DTIC combined targeted therapy and DTIC alone (combined RR=1.09, 95% CI: 0.96-1.24, Z=1.29, P=0.20)		
				Adverse Event: Anaemia	Failed to show a significant difference between DTIC combined targeted therapy and DTIC alone (combined RR=1.07, 95% CI: 0.87-1.32, Z=0.67, P=0.51)		
				Adverse Event: Neutropenia	Significant difference between DTIC combined targeted therapy and DTIC alone (combined RR=1.36, 95% CI: 1.06-1.74, Z=2.39, P=0.02)		
					Significant		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					difference between DTIC combined targeted therapy and DTIC alone (combined RR=1.63, 95% CI: 1.28-2.06, Z=4.03, P<0.0001)		
Jiang et al. 2013	To evaluate the efficacy and safety of temozolomide alone and temozolomide - based combination chemotherapy on melanoma by using meta-analysis research methodology	Systematic review and meta-analysis Search of the Cochrane library, MEDLINE, EBSCO, EMBASE, and Ovid databases as well as clinical trial websites with the search term "temozolomide" as a keyword combined with "melanoma" and "randomized controlled trials" as medical subject headings. Chinese databases such as CNKI and CBMDisc using the above	703 patients in 5 RCTs	Overall response (CR+PR). 1-year survival Adverse event: Nausea+Vomiting	ORR in the TMZ-based combination drug therapy was greater than that in TMZ alone (RR:1.44 [(95 % CI, 1.06-1.95), Z=2.30, P=0.02] 1-year survival rate in the two groups was not significantly different (RR=1.13; 95 % CI, 0.92-1.40; P=0.87. Incidence of nausea and vomiting between TMZ and combination	Meta-analyses also for adverse events	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		<p>search terms were used.</p> <p>1,064 records identified. 5 RCTs included for final evaluation.</p>		<p>Adverse Event: Headache, Fatigue</p> <p>Adverse Event: Constipation</p> <p>Adverse Event: Anaemia, neutropenia, thrombocytopenia</p>	<p>chemo-therapy not significantly different [RR=1.16, (95 %CI, 0.90-1.48), Z=1.15, P=0.25>0.05].</p> <p>No significant difference for the incidence of headache and fatigue. RR=0.53 (95% CI 0.21-1.37) and RR=0.77 (95% CI 0.49-1.22).</p> <p>No difference for the incidence of constipation between the two groups (RR= 1.05 [95% CI, 0.71-1.56])</p> <p>No a significant toxicity between single-agent TMZ and combination chemotherapy. RR: 1.24 (95% CI 0.72-2.14) for</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					anaemia, RR: 1.52 (95% CI 0.53–4.34) for neutropenia RR=0.98 (95% CI 0.46–2.09) for thrombocytopenia.		
Mai et al. 2015	To establish the optimum treatment for metastatic melanoma, we did a random-effects network meta-analysis to compare combined BRAF and MEK inhibition	Systemic review and meta-analysis Search of PubMed, the Cochrane Collaboration Central Register of Controlled Clinical Trials, Cochrane Systematic Reviews, and ClinicalTrials.gov for RCT without year and language restrictions, using the following algorithm: combined targeted therapy AND melanoma. After the combinations of dabrafenib-trametinib or	5,976 patients randomized to receive two of the six treatment strategies in 16 different trials	PFS OS	Combined BRAF-MEK inhibition improved significant prolonged PFS, as compared with BRAF inhibition (HR: 0.58, 95%CI: 0.51-0.67, P < 0.0001) or MEK inhibition alone (HR: 0.29, 95%CI: 0.22-0.37, P < 0.0001). Ranking probabilities of treatment from the network meta-analysis of OS indicated that, of the 6 therapeutic strategies,	Statistically sophisticated report using a comprehensive (Bayesian) network meta-analysis approach.	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		<p>vemurafenib-cobimetinib have been identified, the keywords of individual inhibition of BRAF (dabrafenib, vemurafenib, sorafenib) and MEK (trametinib, cobimetinib, selumetinib), trial and melanoma were used to search relevant studies</p> <p>451 relevant records identified, 16 eligible RCTs</p>		ORR	<p>combined BRAF-MEK inhibition had the highest probability of being the best treatment arm for MM. Combined BRAF-MEK inhibition improved significant prolonged OS comparing with BRAF inhibition (HR: 0.67, 95%CI: 0.56-0.81, P < 0.0001) or MEK inhibition alone (HR: 0.48, 95%CI: 0.36-0.65, P < 0.0001). Single BRAF inhibition had a statistically significantly longer in OS than MEK inhibition alone (HR: 0.72, 95%CI: 0.56-0.91, P = 0.008), and combined BRAF</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>inhibition and chemotherapy (HR: 0.60, 95%CI: 0.47-0.73, P < 0.0001).</p> <p>Compared with chemotherapy, combined BRAF-MEK inhibition improved highest ORR (OR: 29.46, 95%CI: 20.04-43.57, P < 0.0001), followed by BRAF inhibition alone (OR: 14.65, 95%CI: 10.49-20.90, P < 0.0001), and combined MEK-chemotherapy (OR: 2.18, 95%CI: 1.10-4.23, P = 0.5982).</p> <p>ORR was superior in patients who received combined BRAF-MEK inhibition compared with those who received BRAF inhibition</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>(OR: 2.00, 95%CI: 1.66-2.44, P < 0.0001) or MEK inhibition alone (OR: 20.66, 95%CI: 12.22-35.47, P < 0.0001).</p> <p>The single BRAF inhibition yielded better response rate than MEK inhibition alone (OR: 10.34, 95%CI: 6.23-17.60, P < 0.0001).</p>		
Teimouria et al. 2013	To compare the efficacy and side effects of dacarbazine with those of temozolomide in the treatment of malignant melanoma	Systemic review and meta-analysis PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched. The search terms were 'dacarbazine' and 'temozolomide' and 'malignant melanoma'.	1,314 patients from 3 clinical trials	Response to treatment (CR/PR/SD)	<p>CR RR=0.83 (95% CI= 0.26–2.64), which was nonsignificant (P=0.76).</p> <p>PR: RR=1.35 (95% CI=0.95–1.91), which was nonsignificant (P=0.1)</p> <p>SD:</p>	Methodically correct meta-analysis, but nly 3 studies included. Also analyses for adverse events presented.	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		547 relevant records identified, 3 eligible head-to-head studies taken for meta-analysis			<p>RR=1.05 (95% CI=0.85-1.3), which was nonsignificant (P=0.65)</p> <p>Disease control rate: RR=2.64 (95% CI=0.97-1.36), which was nonsignificant (P=0.11).</p> <p>Anaemia, neutropenia, and thrombocytopenia: RR (for all grades) = 1.14 (95% CI=0.57-2.27), 1.09 (95% CI=0.74-1.60), and 0.97 (95% CI=0.65-1.46). All of which were nonsignificant.</p> <p>The summary of RR for anaemia, neutropenia, and thrombocytopenia</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>(for grades 3 and 4) was 1.8 (95% CI=0.9-3.62), 0.97 (95% CI=0.48-1.97), and 1.44 (95% CI=0.9-2.3). All of which were nonsignificant.</p> <p>The summary of RR for lymphopenia (for grades 3 and 4) of temozolomide in comparison with DTIC was 3.79 (95% CI=1.38-10.39), which was significant (P=0.01).</p>		

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6.3. Frage V.4. Biochemotherapie - Adaptation

Frage V.4. Führt die Gabe von Biochemotherapien im metastasierten Stadium zu mehr objektiven Remissionen / zu einer Verbesserung des Gesamtüberlebens ?

6.3.1. Synopse Quelleitlinien

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
Führt die Gabe von Biochemotherapien im metastasierten Stadium zu mehr objektiven Remissionen?	Ja Interferon-alpha und IL-2 verbessern Ansprechen von Monotherapien aber nicht das Gesamtüberleben allein oder in Kombination mit Chemotherapien.	Ja Dacarbazin plus Interferon alpha führt zu besserem Ansprechraten, nicht zu einer Verlängerung des Gesamtüberlebens.	<i>Leitlinie enthält keine Empfehlungen zu Therapien im fernmetastasierten Stadium</i>	Ja
Zugrunde liegende Evidenz	level of evidenz II (4 Studien)	Evidenz Review, S.315 (1 Metaanalyse)		9 Studien zu Biochemotherapien (Standardchemotherpie mit IL-2 oder IFN) 7 Studien geben Ansprechraten an, 2 Studien mit verbessertem Ansprechen, 5 Studien kein Unterschied, gepoolt: besseres Ansprechen
Führt die Gabe von Biochemotherapien im metastasierten Stadium zu	Nein Interferon-alpha und IL-2	Nein Durch Verwendung einer	-	Nein

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
einer Verbesserung des Gesamtüberlebens?	verbessern Ansprechen von Monotherapien aber nicht das Gesamtüberleben allein oder in Kombination mit Chemotherapien.	Polychemotherapie wird das Gesamtüberleben nicht verlängert		
Zugrunde liegende Evidenz	level of evidenz II (4 Studien)	Evidenz Review, S.315 (1 Metaanalyse, 1 Review, 1 Leitlinie)		9 Studien zu Biochemotherapien (Standardchemotherapie mit IL- 2 oder IFN). Keine Studie zeigt ein verbessertes Gesamtüberleben

6.3.2. Empfehlung, Hintergrundtext und Literatur Kanadische Quell Leitlinie

Quelleitlinie: Biochemotherapy for the Treatment of Metastatic Malignant Melanoma: A Clinical Practice Guideline (Cancer Care Ontario) 2007

Question: What is the role of biochemotherapy in the treatment of metastatic malignant melanoma?

For the purposes of this report, "biochemotherapy" is defined as a therapeutic regimen that includes, at a minimum, chemotherapy (either single agent or combination) and interleukin-2. Outcomes of interest include response rate, disease-free survival, overall survival, quality of life, and incidence of grade 3 and 4 toxicities.

Recommendation

Due to the inconsistent results of the available studies with regard to benefit (response, time-to-progression, and survival) and consistently high toxicity rates, biochemotherapy is not recommended for the treatment of metastatic melanoma.

Key Evidence

Nine randomized controlled trials of biochemotherapy for patients with metastatic malignant melanoma were eligible for inclusion in this systematic review of the evidence. Six randomized controlled trials compared chemotherapy alone to chemotherapy combined with interleukin-2 and interferon, two randomized trials compared a combination of chemotherapy and interferon with chemotherapy combined with interleukin-2 and interferon, and one trial compared interferon and interleukin-2 with versus without chemotherapy.

Seven of the nine trials reporting on response rate outcomes provided statistical comparisons. Only two trials reported statistically significant response rates favouring treatment with biochemotherapy, while five trials failed to detect any significant differences. None of the nine trials detected a statistically significant survival improvement with biochemotherapy.

When data were pooled, biochemotherapy was superior to chemotherapy in terms of better response (relative risk, 1.52; 95% confidence interval, 1.24 to 1.87; $p < 0.0001$) and delayed progression at six months (relative risk, 0.85; 95% confidence interval, 0.75 to 0.96; $p = 0.008$) but not decreased mortality at 12 months (relative risk, 0.98; 95% confidence interval, 0.84 to 1.16; $p = 0.85$).

Biochemotherapy is a toxic therapy, and patients are likely to experience serious hematologic, gastrointestinal, cutaneous, and constitutional toxicities. In addition, there are risks of cardiovascular toxicities such as myocardial events and arrhythmias, hypotension, capillary leak syndrome, hepatotoxicity, and renal toxicity. When conducted in the correct setting, grade 3 and 4 toxicities appear to be manageable, and treatment-related death can be minimized.

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9. Rosenberg SA, Yang JC, Schwartzentruber DJ, et al. Prospective randomized trial of the treatment of patients with metastatic melanoma using chemotherapy with cisplatin, dacarbazine, and tamoxifen alone or in combination with interleukin-2 and interferon alfa-2b. *J Clin Oncol* 1999;17:968-975

6.4. Frage V.5. Polychemotherapie – De novo Recherche

Frage V.5. Führt die Gabe von Polychemotherapien im metastasierten Stadium zu mehr objektiven Remissionen / zu einer Verbesserung des Gesamtüberlebens als die Gabe von Dacarbazin?

6.4.1. PICO, Suchwörter

PICO – Schema

Population	Intervention	Comparison	Outcome
Advanced melanoma patients stage IV, unresectable stage III	Polychemotherapy	DTIC	Response, Overall Survival

Suchwörter

Stichwort	melanoma	review	Chemotherapy	Stage IV Stage 4
Synonyme				palliative
Ober-/Unterbegriffe			Systemic therapy	Salvage metastatic
Mesh Term	melanoma	Review [Publication Type]	Drug Therapy	

6.4.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (review [ti] AND system*[ti]) AND ("systemic therapy"[tiab] OR chemotherapy[tiab] OR "drug therapy"[MeSH] OR metastatic[tiab] OR palliative[tiab] OR disseminated[tiab] OR advanced[tiab] OR "stage IV"[tiab] OR "stage 4"[tiab] OR salvage[tiab])	05.12.2011	27 (Auswahl 2 Reviews)
Update Suche			
Medline	s.o.	07.02.2012	28 (0 dazu)
Cochrane Library	(melanoma and (random* or phase 3) and (systemic therapy or chemotherapy or metastatic or palliative or advanced or salvage)).ti,ab. and (review).ti.	07.02.2012	14 (Auswahl 3 Reviews)

6.4.3. Auswahlkriterien

Auswahl der Literatur		
Gesamttreffer		69
Einschlusskriterien	Systematische Reviews zur medikamentösen Systemtherapie bei Melanompatienten im Stadium IV, nicht resektables St. III, die Studien zu Kombinationschemotherapien versus DTIC enthalten	
Ausschlusskriterien	Nicht systematische Reviews, RCTs, Kohortenstudien, Case Reports, Dosisfindungsstudie, Kollektive mit gemischten Tumorentitäten	
Anzahl nach Abstractscreening, vorgesehen für Bewertung		5
Anzahl ausgewählter Volltexte		4

6.4.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Eigentler et al. 2003	To investigate rates of response to various treatment modalities and the outcome for the melanoma patients	Systematic Review	41 RCTs, patients with metastatic melanoma 7 RCTs Polychemotherapy vs. DTIC included Chiarion Sileni et al. 2001 Chapman et al. 1999 Ringborg et al. 1989 Luikart et al. 1984 Chauvergne et al. 1982 Carter et al. 1976 Moon et al. 1975	Response Rate Overall Survival	DTIC vs. Polychemotherapy (without IFN), 7 RCTs benefit No difference	quality assessment of studies reported Search terms and databases not mentioned	1a
Huncharek et al. 2001	To report the results of a meta-analysis comparing the response rates of DTIC as single agent therapy for metastatic melanoma with combination chemotherapy	Systematic Review Treatment: DTIC versus Combination therapies	20 RCTs, 3273 patients with metastatic melanoma	Response Rate Overall Survival	DTIC versus Combination therapies (without IFN) 10 RCT´s OR 1.33 (95% CI 0.99-1.78) No difference	Literature search reported no quality assessment of studies	1a

Ausgeschlossene Studien

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
<i>Garbe et al. 2011</i>	<i>To present the success of current treatments and the promise of those still in clinical development that may yield incremental improvements in the treatment of advanced, metastatic melanoma</i>	<i>Systematic Review Treatment: Adjuvant and palliative treatment</i>	<i>RCTs Adjuvant and palliative treatment No RCTs for Polychemotherapy vs. DTIC included</i>			<i>No RCTs for Polychemotherapy vs. DTIC included → study excluded</i>	
<i>Sasse et al. 2009</i>	<i>To compare the effects of chemotherapy alone versus combined therapy with chemotherapy and immunotherapy (chemoimmunotherapy) in people with metastatic malignant melanoma.</i>	<i>Systematic Review Treatment: Chemotherapy versus Chemoimmunotherapy</i>	<i>18 RCTs, 2625 patients with metastatic melanoma</i>	<i>1 year Survival Response Rates</i>	<i>n.s. RR 1.06 (95% CI 0.91 -1.24) p = 0.48 sign. difference in favor of chemoimmunotherapy RR 1.40 (95% CI 1.20 -1.63), p < 0.0001</i>	<i>No RCTs for Polychemotherapy vs. DTIC included → study excluded</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
<i>Crosby et al. 2009</i>	<i>To review the benefits from the use of systemic therapies in metastatic cutaneous melanoma compared to best supportive care/placebo, and to establish whether a 'standard' therapy exists which is superior to other treatments</i>	<i>Systematic Review Treatment: Systemic therapies versus best supportive care/placebo</i>	<i>0 RCTs</i>	<i>Overall survival Median survival Progression free survival</i>	<i>No RCTs were retrieved, so no analysis of the effects of the interventions was carried out.</i>	<i>No RCTs for Polychemotherapy vs. DTIC included → study excluded</i>	

6.4.5. Literatur

- Carter RD, Kremenz ET, Hill GJ, 2nd, et al. DTIC (nsc-45388) and combination therapy for melanoma. I. Studies with DTIC, BCNU (NSC-409962), CCNU (NSC-79037), vincristine (NSC-67574), and hydroxyurea (NSC-32065). *Cancer Treat Rep* 1976;60:601-609
- Chapman PB, Einhorn LH, Meyers ML, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol* 1999;17:2745-2751
- Chauvergne J, Bui NB, Cappelaere P, et al. Chemotherapy in advanced malignant melanoma. Results of a controlled trial comparing a combination of dacarbazine (DTIC) and detorubicin with dacarbazine alone. *Sem Hop* 1982;58:2697-2701
- Chiaroni Sileni V, Nortilli R, Aversa SM, et al. Phase II randomized study of dacarbazine, carmustine, cisplatin and tamoxifen versus dacarbazine alone in advanced melanoma patients. *Melanoma Res* 2001;11:189-196
- Crosby T, Fish R, Coles B, et al. Systemic treatments for metastatic cutaneous melanoma. *Cochrane Database of Systematic Reviews* 2009;1
- Eigentler TK, Caroli UM, Radny P, et al. Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomised clinical trials. *Lancet Oncol* 2003;4:748-759
- Garbe C, Eigentler TK, Keilholz U, et al. Systematic review of medical treatment in melanoma: current status and future prospects. *Oncologist* 2011;16:5-24
- Huncharek M, Caubet JF, McGarry R. Single-agent DTIC versus combination chemotherapy with or without immunotherapy in metastatic melanoma: a meta-analysis of 3273 patients from 20 randomized trials. *Melanoma Res* 2001;11:75-81
- Luikart SD, Kennealey GT, Kirkwood JM. Randomized phase III trial of vinblastine, bleomycin, and cis-dichlorodiammine-platinum versus dacarbazine in malignant melanoma. *J Clin Oncol* 1984;2:164-168
- Moon JH, Gailani S, Cooper MR, et al. Comparison of the combination of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and vincristine with two dose schedules of 5-(3,3-dimethyl-1-triazino)imidazole 4-carboxamide (DTIC) in the treatment of disseminated malignant melanoma. *Cancer* 1975;35:368-371

Ringborg U, Rudenstam CM, Hansson J, et al. Dacarbazine versus dacarbazine-vindesine in disseminated malignant melanoma: a randomized phase II study. *Med Oncol Tumor Pharmacother* 1989;6:285-289
Sasse AD, Sasse EC, Clark GOL, et al. Chemoimmunotherapy versus chemotherapy for metastatic malignant melanoma. *Cochrane Database of Systematic Reviews* 2011;1

6.5. Frage V.7. Lebermetastasen – De novo Recherche

Frage V.7. Welche medikamentösen Therapien können bei Lebermetastasierung empfohlen werden?

6.5.1. PICO, Suchwörter

PICO – Schema			
Population	Intervention	Comparison	Outcome
Melanoma patients with liver metastases	Local therapies, specific therapies	Standard chemotherapy	Response, Overall Survival

Suchwörter				
Stichwort	melanoma	liver metastasis/metastases	treatment	chemoembolization, perfusion, TACE, immunoembolization, IHP, HAI, resection, surgery, „radiofrequency ablation“, RFA, radioembolization, brachytherapy
Synonyme		hepatic metastasis/metastases	therapy	
Ober-/Unterbegriffe				
Mesh Term	melanoma			

6.5.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	("melanoma"[tiab] OR "melanoma"[MeSH]) AND ((liver[tiab] AND metastas*[tiab]) OR (hepatic[tiab] AND metastas*[tiab])) AND (treatment[tiab] OR therapy[tiab] OR "chemoembolization"[tiab] OR TACE[tiab] OR immunoembolization[tiab] OR IHP[tiab] OR HAI[tiab] OR perfusion[tiab] OR resection[tiab] OR surgery[tiab] OR "radiofrequency ablation"[tiab] OR RFA[tiab] OR radioembolization[tiab] OR brachytherapy[tiab])	18.01.11	722
Embase	(melanoma and (liver or hepatic) and (treatment or therapy or chemoembolization or TACE or immunoembolization or IHP or HAI or perfusion or resection or surgery or radiofrequency ablation or RFA or radioembolization or brachytherapy)). ti,ab.	11.05.11	1579
Cochrane Library	(melanoma and (liver or hepatic) and (treatment or therapy or chemoembolization or TACE or immunoembolization or IHP or HAI or perfusion or resection or surgery or radiofrequency ablation or RFA or radioembolization or brachytherapy)). ti,ab.	21.07.11	35
Update Suche			
Medline	s.o.	30.01.12	792 (3 dazu: Heusner et al. 2011, Farolfi et al. 2011, Gonsalves et al. 2011)
Embase	s.o.	23.01.12	1691 (0 dazu)
Cochrane Library	s.o.	30.01.12	37 (0 dazu)

6.5.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	2520
Einschlusskriterien	Studien zur medikamentösen Therapie von Lebermetastasen bei Melanompatienten Mangels RCTs: Einschluss von Phase I/II Studien, Fallserien ab 10 Patienten Mangels ausreichender Daten zu Lebermetastasen kutaner Melanome, Einschluss von Studien mit Lebermetastasen uveal Melanome Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Studien zu Lebermetastasen anderer Tumorentitäten
Anzahl Volltexte	36
Ausgeschlossene Studien	6
Ausgewählte Studien	30
Die ausgewählten Arbeiten wurden wie folgt zusammengefasst:	
<ul style="list-style-type: none"> - Resektion - Isolierte hepatische Perfusion (IHP) - Hepatische arterielle Infusion (HAI) - Hepatische arterielle Chemoembolisation (HACE) / Trans-arterielle Chemoembolisation (TACE) - Radioembolisation (selektive interne Radio-Therapie – SIRT) 	

6.5.4. Evidenztabelle

Resektion

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Caralt et al. 2010	To analyze the outcome of patients undergoing hepatic resection for melanoma liver metastases.	Case Series Treatment: Liver resection	14 patients Ocular melanoma n=6 Cutaneous melanoma n=8	Recurrence Survival	liver recurrence 46.2% systemic recurrence 76.9% 1- and 3-year survivals: 77 and 49%	Small series	4
Frenkel et al. 2009	To evaluate the posthepatectomy survival of uveal melanoma patients with liver metastases.	Retrospective cohort study Treatment: - Liver resection - No liver resection	74 uveal melanoma patients with metastases operated patients n=35 non-operated patients n=39	Survival	median survival operated patients: 23 months (95% CI: 13.3 – 41.3) non-operated patients: 6.8 (95% CI: 3.6 – 12.5)	No cutaneous melanoma patients Risk of selection bias Although similar demographic and ocular characteristics between the groups are mentioned, no baseline data are presented.	4* Poor quality cohort study
Mariani et al. 2009	To review the surgical management of	Retrospective evaluation	798 uveal melanoma patients with liver	Survival	median overall postoperative survival	No cutaneous melanoma patients Multivariate	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	liver metastases from uveal melanoma in a single institution with regard to survival and the determination of predictive factors for the optimal surgical candidate	Treatment: - Surgery	metastase surgical resection n= 255	Predictive factors	All patients n=255: 14 months R0 resection n=76: 27 months R1 resection n=22: 17 month R2 resection n=157: 11 months 4 variables independently correlate with prolonged survival: interval from primary diagnosis to liver metastases >24 months comprehensiveness of surgical resection (R0) number of metastases resected (< or = 4) absence of effects disease	analysis included Lack of control group	
Woon et al. 2008	To assess the survival of melanoma patients	Retrospective evaluation	15 patients with hepatic melanoma metastases, 9	Survival	Median survival for all patients: 7 months.	Small series	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	with hepatic metastases who underwent surgery	Treatment: Lobectomy Cryotherapy	patients suitable for surgical resection		Curative surgical group: 22 months palliative group: 6 months.		
Herman et al. 2007	To evaluate the experience of liver resection for patients with metastatic melanoma	Case Series Treatment: Liver resection	18 patients with metastatic melanoma, 10 were operated Ocular melanoma n=5 Cutaneous melanoma n=5	Survival	Overall median survival: 22 months Cutaneous melanoma n=5 (Follow up 46 months): 3 dead, 1 alive, disease free, 1 alive, recurrent disease	Small series	4
Pawlik et al. 2006	To evaluate the efficacy of hepatic resection in patients with metastatic ocular versus cutaneous melanoma and to assess additional factors that may affect survival after resection of melanoma metastatic to the	Retrospective evaluation Treatment: Liver resection	40 patients with hepatic melanoma metastasis underwent resection at 4 major hepatobiliary centers Ocular melanoma n=16 Cutaneous	Recurrence Median time to recurrence Survival	Cutaneous melanoma N=24 Tumor recurrence n=18 (75.0%) Median time to recurrence: 4.7 months Median Survival: 23.6 months 2-year-survival	17 of 24 patients with cutaneous melanoma received systemic therapy	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	liver.		melanoma n=24		rate: 20.5% 5-year-survival rate: 0%		
Rose et al. 2001	To identify patients treated by surgical resection for metastatic melanoma to the liver and to determine if any factors would be useful for identifying patients who should be treated with surgery	Retrospective evaluation Treatment: Liver resection	1750 patients with hepatic metastases surgery n=34 extensive intraabdominal disease identified at exploratory celiotomy, no resection n=10 curative resection n=18 (75%) palliative debulking n=6 (25%)	median disease-free survival (DFS) Overall survival (OS)	Median DFS 12 months Median OS 28 months 5-year DFS and OS: 12% and 29%. Macroscopically, complete resection of disease (P =.001) and histologically negative resection margins (P =.03) significantly improved DFS by univariate analysis	Uveal or cutaneous origin not mentioned	4
Salmon et al. 1998	To present the preliminary results of the therapeutic approach of laparotomy with hepatic resection	Prospective study Treatment: surgical approach removing as much liver disease as	75 uveal melanoma patients with liver metastases	Survival	Median overall survival all patients: 9 months. Surgery plus chemotherapy	No cutaneous melanoma patients Combined treatment Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(whenever possible), implantation of an intraarterial catheter and intraarterial chemotherapy (IACH).	possible and intraarterial chemotherapy for 6 months			(n=61): 10 months curative resection (n=19): 22 months		

Isolierte hepatische Perfusion (IHP)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Heusner et al. 2011	To assess the overall survival time of patients suffering from metastasized uveal melanoma undergoing conventional transarterial hepatic chemoperfusion using melphalan	Case series	61 uveal melanoma patients with liver metastases	Response Survival	Response after first session (N=61) PR n=5 (8%) SD n=29 (49%) PD n=26 (43%) Median OS 10 months	Lack of control group	4
Rizell et al. 2008	To analyze the outcome of three treatment strategies using	Case series Treatment: IHP with	27 melanoma patients with liver metastases	Response	Response (N=27): CR n=2 PR n=17 SD n=2	Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	isolated hyperthermic liver perfusion (IHP) with melphalan for liver metastases of malignant melanoma	modifications during 3 different time periods (IHP I, IHP II and IHP III), in technique and temperature (amount of melphalan: 0.5, 1.0 and 2 mg/kg body weight in the perfusate; 41, 40 and 40°C)	Ocular melanoma n=20 Cutaneous melanoma n=5 Anal melanoma n=2	Mortality Survival	Overall response rate 70% Postoperative mortality n=6 Median Survival: 7.5 months (range 0 - 57), postoperative deaths excluded: 12.6 months (range 2.5-57 months)		
Alexander et al. 2003	To evaluate isolated hepatic perfusion (IHP) for patients with unresectable liver metastases from ocular melanoma	Case series Treatment: 60-min hyperthermic IHP using 1.5 mg/kg of melphalan	29 patients with unresectable liver metastases from ocular melanoma	Response Progression-free survival (PFS) Overall Survival (OS) Toxicity	Response (N=29) CR n=3 (10%) PR n=15 (52%) Median PFS: 8 months median OS: 12.1 months Grade 3 or greater hepatic toxicity (reversible) n=19 (65%)	No cutaneous melanoma patients	4

Hepatische arterielle Infusion (HAI)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Farolfi et al. 2011	To investigate direct hepatic intra-arterial chemotherapy of fotemustine or carboplatin in melanoma patients with liver metastases	Case Series Treatment: Hai, Fotemustine, Carboplatin	23 melanoma patients with unresectable liver metastases 78% uvea melanoma	Response	PR n=3 (16.7%) SD n=4 (22.2%) PD n=11 (61.1%)	-	4
Melichar et al. 2009	To evaluate hepatic arterial infusion of the combination of cisplatin, vinblastine and dacarbazine in patients with liver metastases of uveal melanoma.	Case Series Treatment: hepatic arterial infusion (HAI) of the combination of cisplatin, vinblastine and dacarbazine	10 patients with hepatic metastases of uveal melanoma	Response Survival	Response (n=10) PR n=2 SD n=4 PD n=4 Median survival 16 months (range 5 - 69)	Small series	4
Siegel et al. 2007	To compare the effectiveness of hepatic arterial Fotemustine infusion between liver metastases from ocular and cutaneous melanoma.	Retrospective evaluation	36 patients with hepatic metastases from ocular or cutaneous melanoma, 30 patients were treated Ocular melanoma n=18	Response Survival Toxicity	cutaneous melanoma patients (N=12) PR n=4 (33%) SD n=4 (33%) PD n=4 (33%) Median survival: 12 months. Toxicity (all patients N=30)		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			Cutaneous melanoma n=12		grade III-IV thrombocytopenia: 30% grade III-IV neutropenia: 7% nausea/vomiting: 17% (max. gr. I-II) abdominal pain 7% (max. gr. I-II)		
Peters et al. 2006	To investigate the use of fotemustine via direct intra-arterial hepatic (i.a.h.) administration in patients with uveal melanoma metastases	Retrospective evaluation Treatment: fotemustine, administered intra-arterially weekly for a 4-week induction period, and then as a maintenance treatment every 3 weeks	101 uveal melanoma patients from 7 centers with liver metastases	Response Survival	CR n=15 (15%) PR n=21 (21%) SD n=48 (48%) PD n=17 (17%) Median overall survival: 15 months (95% CI: 12.1-17.6) 1-year survival rate 67%, 3-year survival rate 12%	No cutaneous melanoma patients	4
Agarwala et al. 2004	To evaluate the addition of embolization to chemotherapy and to determine the role of escalation of intrahepatic arterial	Phase I/II trial escalating doses of intrahepatic chemotherapy with cisplatin with or without polyvinylsponge	19 patients with ocular melanoma and liver metastases	Toxicity Response	Toxicity: Grade 3 n=7 Grade 4 n=9 PR n=3 (16%) SD n=13 (68%) PD n=1 (5%) Not evaluable n=2	No cutaneous melanoma patients	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cisplatin dose, either alone or as part of chemoembolization.	(PVS)			(11%)		
Becker et al. 2002	To evaluate the activity of sequential fotemustine, interferon alpha, and interleukin 2 for metastatic uvea melanoma patients in a prospective phase II trial.	Phase I/II study Treatment: Fotemustine 100mg/m ² via hepatic artery or i.v. followed by s.c. IL-2 on day 31 and s.c. interferon alpha on day 36	48 patients with metastatic ocular melanoma	Response Survival	CR n=1 (2%) PR n=6 (12.5%) SD n=18 (37.5%) Intraarterial versus i.v. fotemustin Responses 21.7% vs 8% Overall survival 369 vs 349 days	No cutaneous melanoma patients Study stratified according to presence or absence of extrahepatic metastases, resulting in different prognostic factors between the groups.	4
Leyvraz et al. 1997	To evaluate the effectiveness and toxicity of hepatic intraarterial fotemustine when administered through the hepatic arterial route in the treatment of liver metastases from ocular melanoma	Phase II study Treatment: intraarterial fotemustine 100 mg/m ² (4 hour infusion)	31 patients with liver metastases from ocular melanoma	Response Survival	Response liver metastases (30 patients assessable) CR n=4 (13%) PR n=8 (27%) Minor Response n=2 SD n=13 PD n=3 Median overall survival 14 months	No cutaneous melanoma patients No overall response data	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Khayat et al. 1991	To evaluate hepatic intra-arterial infusion (HIAI) of fotemustine	Phase II Study Treatment: intraarterial fotemustine 100 mg/m ² (4 hour infusion)	17 patients with exclusive or predominant liver metastases from malignant melanoma. 13 patients evaluable	Response	Hepatic Response (N=13) CR n=2 PR n=6 MR n=1 SD n=3 PD n=1 Overall extrahepatic response rate 6/14 (42.8%)	Uveal or cutaneous origin not mentioned	4
Storm et al. 1982	To evaluate combined treatment with intraarterial DTIC infusion and localized hyperthermia of patients with advanced liver metastases	Case Series Treatment: IA-DTIC plus heat	10 melanoma patients with liver metastases Ocular melanoma n=3 Cutaneous melanoma n=4 Unknown primary n=2	Response Survival	Response CR n=1 PR n=2 SD n=5 PD n=2 Median survival 8.5 months (range 3.5-18)	Small series	4

Hepatische arterielle Chemoembolisation (HACE) / Trans-arterielle Chemoembolisation (TACE)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ahrar et al. 2011	To evaluate the response rates and survival durations of patients with metastatic cutaneous melanomas who underwent chemoembolization.	Retrospective evaluation Treatment: Intra-arterial embolic agent followed by cisplatin (100 - 150mg)	42 patients with cutaneous melanoma metastatic to the liver extrahepatic disease n=36 no extrahepatic disease n=6 Evaluable n=36	Response Overall Survival (OS) Time to progression (TTP)	Response (N=36) CR n=0 PR n=5 (13.9%) MR n=9 (25%) SD n=17 (47.2%) PD n=5(13.9%) Median overall survival: 7.69 months TTP of liver disease: 6.01 months	Multivariate analysis included Lack of control group	4
Huppert et al. 2010	To evaluate response and survival in patients with liver metastases from uveal melanoma treated by chemoembolization following an invariable treatment protocol over a period of more than 6 years.	Phase II Study Treatment: Hepatic transarterial chemoembolization (TACE) 100mg/m ² of cisplatin was continuously infused by means of a power injector preceding embolization by manual injection of	14 patients with hepatic metastases from uveal melanoma 34 TACE's were performed	Response Time to progression Survival	Response (N=14) CR n=0 PR n=8 (57%) SD n=4 (29%) PD n=2(14%) Median time to progression 8.5 months (5-35 months) Median survival: 14.5 months in responders versus 10 months in nonresponders	No cutaneous melanoma patients	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		polyvinyl alcohol particles			(p=0.18, not significant)		
Schuster et al. 2010	To report the experience with transarterial chemoembolization (TACE) in uveal melanoma patients with pretreated liver metastases	Case Series Treatment: fotemustine-based or cisplatin-based TACE after treatment failure of systemic therapy	25 uveal melanoma patients with liver metastases	Toxicity Response progression-free survival (PFS) Overall survival (OS)	Toxicity: No grade IV toxicity or catheter-associated complications Response (N=25) CR n=0 PR n=4 (16%) SD n=14 (56%) PD n=7 (28%) PFS: 3 months (95% CI: 2-4 months) OS: 6 months (95% CI: 5-7 months)	No cutaneous melanoma patients	4
Yamamoto et al. 2009	To retrospectively evaluate prognostic factors for survival in patients with uveal melanoma who received chemoembolization (CE) with 1,3-bis(2-chloroethyl)-1-	Retrospective evaluation (of patients treated within 2 different Phase II studies) Treatment: Chemoembolization with BCNU or with	53 patients with uveal melanoma CE n=19 IE n=34	Overall survival (OS) Progression-free survival (PFS)	Median OS CE: 9.8 months Low-dose IE: 13.0 months High-dose IE: 20.4 months Median Liver PFS CE: 6.4 months Low-dose IE: 4.2	No cutaneous melanoma patients	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	nitrosourea or immunoembolization (IE) with granulocyte-macrophage colony-stimulating factor (GM-CSF) for hepatic metastases	GM-CSF			months High-dose IE: 9.3 months		
Fiorentini et al. 2009	To assess the safety and efficacy of TACE with irinotecan as drug-eluting beads	Phase II study Treatment: TACE-containing beads preloaded with IRI (100 mg)	10 patients with liver metastases from uveal melanoma	Response	Partial response: 10 patients	No cutaneous melanoma patients	4
Sharma et al. 2008	To present the outcomes with hepatic arterial chemoembolization for metastasis of stage 4 melanoma	Retrospective evaluation Treatment: hepatic arterial chemoembolization	20 patients with liver-dominant metastasis of ocular or cutaneous melanoma Ocular melanoma n=17 Cutaneous melanoma n=3	Response Overall survival Progression-free survival	Response CR n=0 PR n=0 SD n=13 (65%) PD n=7 (35%) median overall survival: 271 days no deaths within 30 days of treatment median progression-free survival: 185 days	Presence or absence of extrahepatic metastases not mentioned	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Vogl et al. 2006	To evaluate results in the palliative treatment of patients with liver metastases of uveal malignant melanoma using transarterial chemoembolization (TACE)	Case Series Treatment: transarterial chemoembolization (TACE) embolization suspension: 10 mg/m ² Mitomycin C, 10 ml Lipiodol, and an injection of 200-450 mg resorbable microspheres for vascular occlusion	12 patients with liver metastases of uveal malignant melanoma	Side effects Response Survival	no relevant side effects. Response PR n=3 SD n=5 PD n=4 Mean survival after first embolization 19.5 months. Lower survival rates for the progressive group (16.5 months).	No cutaneous melanoma patients	4
Patel et al. 2005	To evaluate chemoembolization of the hepatic artery with BCNU for metastatic uveal melanoma	phase II study Treatment: chemoembolization of the hepatic artery with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) dissolved in ethiodized oil. Gelatin sponge particles were used as a transiently occlusive agent.	30 patients with hepatic metastases from uveal melanoma, 24 patients evaluable	responses in hepatic metastases Overall survival	Response (n=24) CR n=1 PR n=4 SD n=13 PD n=6 Median Survival ITTP 5.2 months CR+PR 21.9 months SD 8.7 months PD 3.3 month	No cutaneous melanoma patients	4

Radioembolisation (selektive interne Radio-Therapie – SIRT)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Gonsalves et al. 2011	to assess the safety and efficacy of radioembolization in the management of hepatic metastasis of uveal melanoma after failure of immunoembolization or chemoembolization	Retrospective evaluation	32 patients with hepatic metastases from uveal melanoma	responses in hepatic metastases Median overall survival	CR n=1 PR n=1 SD n=18 PD n=12 10 months CR+PR+SD 14.7 months PD 4.9 months	No cutaneous melanoma patients	4
Kennedy et al. 2009	To evaluate Yttrium-90 microspheres (radioembolization) delivered via the hepatic artery	Case Series Treatment: Yttrium-90 microspheres (radioembolization) delivered via the hepatic artery	11 patients with liver metastases from uveal melanoma	Toxicity Response Survival	Toxicity: Grade 3: n=1 Response CR n=1 PR n=6 SD n=1 PD n=1 1 year survival 80%	No cutaneous melanoma patients	4

6.5.5. Literatur

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6.6. Frage V.8. Lebensqualität – De novo Recherche

Frage V.8. Welche medikamentösen Therapieverfahren haben im metastasierten Stadium einen (positiven) Effekt auf die Lebensqualität?

6.6.1. PICO, Suchwörter

PICO – Schema			
Population	Intervention	Comparison	Outcome
Melanoma patients, clinical stage III and IV	Systemic treatment	Observation, other systemic treatments	Quality of life

Suchwörter				
Stichwort	melanoma	Quality of life		
Synonyme		Qol		
Mesh Term	melanoma	Quality of life		

6.6.2. Datenbanken, Suchstrategien, Trefferzahlen

6.6.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			

Datenbank	Suchstrategie	Datum	Treffer
Medline	("melanoma"[tiab] OR "melanoma"[MeSH]) AND ("Quality of life" OR "QoL" OR "Quality of life" [Mesh])	24.02.11	399
Update Suche			
Medline	s.o.	31.01.12	435 (3 dazu: Hofmann et al. 2011, Robinson et al. 2011, Ziefle et al. 2011, Brandberg et al. 2011)
Cochrane Library	(melanoma and ("quality of life" or "QoL")).ti,ab.	31.01.12	42 (0 dazu)
Embase	(melanoma and ("quality of life" or "QoL")).ti,ab.	24.01.12	497 (0 dazu)

6.6.2.2. Aktualisierungsrecherche 2015

Datenbank	Suchstrategie	Datum	Treffer
Medline	((("melanoma"[tiab] OR "melanoma"[MeSH]) AND ("Quality of life" OR "QoL" OR "Quality of life" [Mesh]))) AND ("2011.02.25"[Date - Publication] : "3000"[Date - Publication])	16.09.2015	243
Cochrane Library	(melanoma and ("quality of life" or "QoL")).ti,ab.	16.09.2015	61 (0 dazu)

6.6.3. Auswahlkriterien

6.6.3.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer	974
Einschlusskriterien	Studien / System. Reviews zu Lebensqualität bei Melanompatienten unter Therapie Klinische adjuvante und palliative Therapiestudien / system. Reviews zum Melanom, die Lebensqualität als primären oder sekundären Endpunkt messen Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitäten Lebensqualität bei Melanompatienten nach/während chirurgischer Therapie Lebensqualität bei Melanompatienten ohne Therapie
Anzahl nach Abstractscreening, vorgesehen für Bewertung	28
Anzahl ausgewählter Studien nach Handsuche (Durchsicht der Literaturlisten)	3
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	10
Anzahl ausgewählter Volltexte	21
Die ausgewählten Arbeiten wurden wie folgt zusammengefasst:	
<ul style="list-style-type: none"> - Reviews zu QoL bei Melanompatienten unter Therapie - Adjuvante Therapiestudien die QoL als Endpunkt enthalten - Palliative Therapiestudien die QoL als Endpunkt enthalten 	

6.6.3.2. Aktualisierungsrecherche 2015

Auswahl der Literatur		
Gesamttreffer		304
Einschlusskriterien	System. Reviews zu Lebensqualität bei Melanompatienten unter Therapie Klinische palliative Phase III Therapiestudien / system. Reviews zum Melanom, die Lebensqualität als primären oder sekundären Endpunkt messen Sprachen: e,dt	
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitäten Lebensqualität bei Melanompatienten nach/während chirurgischer Therapie Lebensqualität bei Melanompatienten ohne Therapie	
Die ausgewählten Arbeiten wurden wie folgt zusammengefasst:		
<ul style="list-style-type: none"> • Reviews zu QoL bei Melanompatienten unter Therapie • Palliative Therapiestudien die QoL als Endpunkt enthalten 		
Anzahl ausgewählter Volltexte		5

6.6.4. Evidenztabelle

6.6.4.1. Primärrecherche 2012

Reviews zu QoL bei Melanompatienten unter Therapie

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Cashin et al. 2008	To examine all of the information published so far on the impact of interventions on QoL, including all available treatment strategies or screening programs for MM	Systematic review Inclusion criteria: reports of original research related to QoL in MM and/or economics of MM	13 QoL studies (5 economic studies)	QoL Instruments Main QoL Results (Interventions, Clinical Outcome, Adverse Events)	QoL Instruments used: EORTC, EORTC QLQ-36, QLQ C30, QWB-SA, Linear analog self-assessment scale including the GLQ-8, GLQ-8, SF-36, Rotterdam Checklist Symptom questionnaire, QWB-SA QOL Results: no significant improvements in QoL for any alternative for treating MM	Detailed description of studies and results	1a
Cornish et al. 2009	To systematically review the available literature on health-related quality of life (HRQOL) and	Systematic review Inclusion criteria: (HR)QOL assessment in cutaneous	13 selected studies	HRQOL in patients with cutaneous melanoma	- 20 different instruments were used within the 13 studies - 3 distinct periods of HRQOL impact:	Results of QoL measurements within the studies are not presented in detail.	1a-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma	melanoma			diagnosis, treatment and follow-up - systemic drugs decreased patients' HRQOL during treatment.	Methodological quality of included studies was measured by 14 not validated criteria	

Adjuvante Therapiestudien die QoL als Endpunkt enthalten

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ziefle et al. 2011	To evaluate QoL in patients with melanoma using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) before and during the first 12 months of adjuvant treatment with IFN-a-2a	QoL evaluation within a phase III trial QoL instrument: EORTC QLQ-C30 Time points: baseline, month 3, 6 and 12 Treatment: Group 1: IFN-a-2a 18 months Group 2: IFN-a-2a 60 months	QoL Assessment no. of forms received (expected) Baseline n=725 (850) all timepoints n=282 (850)	HRQOL at baseline HRQOL during treatment	HRQoL compared with the healthy reference population significant decrease of 9 of 15 QLQ-C30 subscales peaked at 3 months	No assessment of long term QoL Data (Group 2)	1b
Brandbert et al.	To compare	QoL evaluation	QoL Assessment	HRQOL during	significant	-	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
2011	health-related quality of life (HRQoL) and side-effects in patients with high-risk melanoma participating in a randomised phase III trial of adjuvant interferon alfa-2b	<p>within a phase III trial</p> <p>QoL instrument: EORTC QLQ-C30</p> <p>Time points: baseline, month 3, 6 and 12</p> <p>Treatment: Arm A: Observation Arm B: 1 year intermediate Dose IFN-a-2b Arm C: 2 years intermediate Dose IFN-a-2b</p>	<p>no. of forms received > 80%</p> <p>all timepoints n=282 (850)</p>	<p>treatment compared to baseline</p> <p>HRQOL differences between groups</p>	<p>interactions between randomisation arm and time after randomisation for almost all EORTC QLQ-30 variables</p> <p>Arm A improved or remained at baseline levels ARM B+C significant negative impact on HRQoL of IFN treatment.</p> <p>the impact were reversible when treatment was stopped.</p>		
Bottomley et al. 2009	To examine the health-related quality of life effects of adjuvant pegylated IFN-alpha-2b (PEG-IFN-alpha-2b) versus observation in patients with stage	<p>QoL evaluation within a phase III trial</p> <p>QoL instrument: EORTC QLQ-C30</p> <p>Time points: baseline, month 3, 12, 24, 36, 48, 60.</p>	<p>QoL Assessment</p> <p>no. of forms received (expected)</p> <p>Baseline Gr. 1: n=521 (629) Gr. 2: n=520 (627)</p>	HRQOL at month 3	<p>PEG-IFN-alpha-2b treatment arm: -decreased global HRQOL at month 3 (-11.6 points; 99% CI, -8.2 to -15.0) and year 2 (-10.5 points; 99% CI, -6.6 to -14.4)</p>	<p>Analysis was restricted to the first 3 years, as limited data existed at years 4 and 5.</p> <p>Conflict of interest 5 of 18 authors</p>	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	III melanoma	Treatment: Group 1 observation (n = 629) Group 2 PEG-IFN-alpha-2b (n = 627)	36 months Gr. 1: n=158 (352) Gr. 2: n=134 (347) 60 months Gr. 1: n=10 (26) Gr. 2: n=9 (30) of 1,256 patients with stage III melanoma		-statistically significant impaired (P< 0.0001) at 3 months after baseline: Social functioning Role functioning (at other timepoints no clinically meaningful differences between both treatment groups) -statistically significant impaired (P<.0001) over time: Appetite loss Fatigue	received funding, honoraria or had consultant/advisory role (Schering Plough)	
Garbe et al. 2008	To evaluate adjuvant Interferon alpha and DTIC in terms of overall survival, recurrence-free survival and occurrence of adverse events.	QoL Evaluation within a RCT QoL Instrument: EORTC QLQ-C30 Time points: Baseline + 6 months	HRQOL assessment No. of patients= 238 (54%)	HRQOL at month 6	better outcome for the general dimensions of QoL for patients with adjuvant therapy physical functioning (Arm A vs. Arm C: p = 0.007)	Baseline HRQOL data not presented	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	Health-related quality of life (QoL) was measured by a questionnaire.	Treatment: Arm A: Interferon alpha (n=146) Arm B: Interferon plus Dacarbazine (n=148) Arm C: Observation (n=147)			role functioning (Arm A vs. Arm C: p = 0.008) emotional functioning (Arm A vs. Arm C: p = 0.048) more drug-related symptoms fatigue symptom scale (Arm A vs. Arm C: p = 0.036) nausea and vomiting scale (Arm B vs. Arm C: p = 0.037)		
Dixon et al. 2006	To evaluate data on health-related quality of life (HRQoL) and costs of low-dose extended duration adjuvant interferon-alpha therapy in the treatment of malignant melanoma	QoL Evaluation within a RCT QoL Instrument: EORTC QLQ-C30 Time points: Baseline, 3, 6, 12, 24, 36, 48, 60 months Treatment: Group 1: IFN low	QoL assessment (%) Group 1 n= 211 (68%) Group 2 n= 187 (56%) of 674 melanoma patients (clinical stage not indicated)	HRQoL over time between groups (Costs)	OBS group: significantly better mean follow-up QoL on 5 of 6 dimensions of the functional scales: RF (role functioning), EF (emotional f.), CF (cognitive f.), SF (social f.) and QL significantly better mean follow-up	due to missing data, follow-up QoL responses for each individual subject were summarised by taking the average of their follow-up QoL responses over time.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		dose, 60 months Group 2: Observation (OBS)			QoL symptom scores on 7 of 9 dimensions: FA, NV, DY, AP, CO, DI and FI (after adjustment for baseline QoL and overall survival status (dead or censored))		
Loquai et al. 2011	To evaluate the impact on quality of life (QOL) in patients treated with once weekly 2 µg/kg PEG-IFN-α2b and to examine whether there is a difference in patients' and physicians' perception of QOL	Retrospective evaluation QoL Instrument: EORTC QLQ-C30 Time points: Baseline, every 3 months Treatment: 2 µg/kg PEG-IFN-α2b	30 patients	QOL changes Patients questionnaires compared to physician assessment	impairment in most QOL single dimensions QOL documented by physicians was significantly higher than QOL from the patients' questionnaires in all QOL dimensions	Small sample size	4
Ratai et al. 2005	to evaluate the impact of interferon (IFN) treatment on patients' quality of life (QoL) after	Comparative Study QoL Instrument: EORTC QLQ-C30 Time points:	220 patients Group 1 n=110 Group 2 n=110	QoL	The IFN-alpha-2b treatment significantly affected patients' physical condition, mental health, and	Allocation to groups not indicated Baseline data not presented Timepoints of assessment not	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	radical surgery of cutaneous melanoma	Baseline und during treatment Treatment: Group 1: INF-alpha-2b Group 2: Observation			social life. In spite of several adverse effects, the patients assessed their QoL as good	indicated	
Trask et al. 2004	To assess the the longitudinal course of depression, fatigue, and QoL before and during interferon therapy	Observational study QoL Instruments: -BSI -FACT-BRM -RPFS -BDI Time points: Baseline, 1, 2, 3, 6 months post treatment Treatment: high dose interferon-alpha	16 patients	Depression QoL Fatigue	6-month post high-dose assessment: significantly increased somatic complaints, depression, and fatigue, reductions in QoL in the areas of Physical Well-Being, Functional Well-Being, and Additional Symptoms. QoL did not improve over the course of therapy	Small sample size data presented in detail	4
Cohen et al. 2002	To prospectively assess QoL in patients with malignant	QoL Evaluation within a Phase Ib study	QoL assessment Baseline n=29 Week 3 n=28 Follow up n=27	Changes of PCS, MCS and IES over time	QoL remained stable during treatment, no significant time	Missing data at all 3 timepoints. 2 of 3 missing assessments at	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma participating in a phase Ib immunotherapy cancer clinical trial of an autologous tumour-derived vaccine	<p>QoL Instruments: -SF-36 (RAND scoring method, 8 scales, range 0 (worst) to 100 (best). Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores, computed by using items from the 8 subscales -Impact of Event Scale (IES)</p> <p>Time points: baseline, week 3 and follow-up</p> <p>Treatment: vaccine</p>	of 30 evaluable patients with stage III or IV malignant melanoma	Association between IES, PCS and MCS Scores	<p>effect for the PCS score, MCS scores or the IES scores</p> <p>significant negative association between IES scores at baseline and mental health scores at each time point (< 0.002 for all).</p>	<p>follow up due to progressive disease.</p> <p>Mixed model regression analyses, analyses using the last observation carried forward and analyses using a complete cases approach were performed.</p>	
Bender et al. 2000	To describe short- and long-term changes in cognitive function and quality of life in patients with melanoma receiving	<p>Pilot Study</p> <p>QoL instrument: FACT-G scale</p> <p>Time points: baseline, 3, 6, 9, 12 and 15 months</p>	<p>18 melanoma patients (part of ECOG EST 1690 trial)</p> <p>baseline Group A: n=6 Group B: n=6</p>	QoL (cognitive function)	significant difference on the physical wellbeing dimension of quality of life from T1 to T2 in Goup A Group A and B: trend to	Limitations: small sample size Baseline characteristics (e.g. gender, age) are not presented	<p>4</p> <p>Poor quality case control study</p>

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	interferon (IFN) alpha-2b	Treatment: Group A: high dose IFN alpha-2b n=6, Group B: low dose IFN alpha-2b n=6, Group C: control group n=6	Group C: n=6 15 months Group A: n=2 Group B: n=3 Group C: n=2		diminished overall quality of life		

Palliative Therapiestudien die QoL als Endpunkt enthalten

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Robinson et al. 2012	To determine patient-reported signs, symptoms, and functioning, HRQoL questionnaire psychometrics, and treatment impact on HRQoL	QoL Evaluation within a randomized phase II study QoL instrument: Melanoma Subscale (MS) of the Functional Assessment of Cancer Therapy-Melanoma Brief Pain Inventory (BPI) Treatment: DTIC + Intetumumab versus DTIC + Placebo	QoL Assessment 127 patients	Baseline QoL QoL at week 3	Baseline HRQoL scores differed according to ECOG performance status trend for HRQoL response in the dacarbazine+ 10 mg/kg intetumumab arm versus dacarbazine + placebo: MS 22 versus 10%, BPI 23 versus 5%	no. of forms received not indicated	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hofmann et al. 2011	To compare best supportive care (BSC) alone with cisplatin, vindesine and dacabazine-based (CVD) chemotherapy and BSC in terms of overall survival, disease control rate and quality of life	QoL Evaluation within a cohort study QoL instrument: EORTC QLQ-C30 Treatment: Arm A: BSC (n=34) Arm B: BSC+CVD (n=83)	QoL Assessment no. of forms received (expected) Baseline n=83 (117) Arm A: 58.8% Arm B: 75.9%	Baseline QoL QoL at week 8	Arm A versus Arm B no significant differences in the function and symptom scales increase in dyspnoea and fatigue Arm B, not significant reduction in the Global Health status in both arms, not significant	Initial protocol: random assignment. Due to lack of patients consent for randomization the protocol was changed to treatment assignment based on patients choice	2b
Avril et al. 2004	To compare fotemustine and dacarbazine (DTIC) in terms of overall response rate (ORR) as primary end-point and overall survival, duration of responses, time to progression, time to occurrence of brain metastases	QoL Evaluation within a randomized phase III study QoL instrument: EORTC QLQ-C30 Time points: baseline and after induction period Treatment: Fotemustine	QoL assessment N=156 Fotemustine group n=83 (of 112) DTIC group n=73 (of 117) of 229 Stage IV melanoma patients	Quality of life (overall response rate, overall survival, duration of responses, time to progression, time to occurrence of brain metastases)	QoL: no statistically significant difference between groups. general tendency: degradation for all (presented) functional and symptom scales over time in both groups.	QoL analysis only available for induction phase due to high number of missing questionnaires Data are presented for 7 scales only. Missing scales: Emotional functioning, Cognitive functioning,	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(BM), and to assess safety and quality of life	versus DTIC			disease progression and performance status were the main factors for QoL impairment.	Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties	
Chiarion-Sileni et al. 2003	To analyse the health related quality of life (HRQOL) of advanced melanoma patients, in a randomised trial comparing bio-chemotherapy (bio-CT) versus chemotherapy (CT)	<p>QoL Evaluation within a randomized phase III study</p> <p>QoL Instrument: Rotterdam Symptom Checklist (RSCL)</p> <p>Time points: Baseline, Cycle 1, 2, 3, 4, 5 and 6</p> <p>Treatment: CT: cisplatin and DTIC alone Bio-CT: cisplatin, DTIC, IL-2 and IFN a-2b</p>	<p>Available QoL scores</p> <p>Baseline n=140 (of 178)</p> <p>Cycle 6 n=16 (of 57)</p>	HRQOL difference HRQOL at baseline as prognostic factor	<p>between treatment arms over time: statistically significant difference in the overall quality of life score (P=0.03) , decrease of 6.28 points in the bio-CT arm</p> <p>no significant difference between treatments:</p> <p>activity level (P=0.20)</p> <p>physical symptom distress (P=0.08)</p> <p>psychological distress (P=0.25) (values always slightly inferior in the bio-CT arm)</p> <p>deterioration over</p>		1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>time: bio-CT arm: significantly in all domains (most important reduction in the activity level) CT arm: significant only for the activity level and the physical symptom distress (P<0.001).</p> <p>Prognostic Factors: overall quality of life score, the physical symptom distress score, and the serum LDH level were confirmed as independent prognostic factors in in multivariate analysis.</p>		
Kiebert et al. 2003	To report detailed HRQL results of a phase III clinical trial comparing temozolomide	QoL Evaluation within a Phase III study QoL Instrument:	Available HRQL scores Baseline TMZ n=110 Baseline DTIC	HRQL differences -Between groups -Over time	between groups: baseline: no significant differences 12 weeks: TMZ	At week 24 not enough data for interpretations. More missing data in the DTIC group.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(TMZ) to dacarbazine (DTIC) in patients with metastatic melanoma	EORTC QLQ-C-30 Time points: baseline, week 12, 24 Treatment: Group 1 DTIC Group 2 Temozolomide	n=110 Week 12 TMZ n=50 Week 12 DTIC n=31 Week 24 TMZ n=22 Week 24 DTIC n=8 (of 305 advanced melanoma patients)		group significantly better physical functioning, less fatigue and sleep disturbances, cognitive functioning equivalent, worse on nausea and vomiting. 24 weeks: all subscales (exception diarrhea) better for TMZ patients Over time: TMZ patients: clinically meaningful improvements in emotional functioning, cognitive functioning, and sleep disturbances at week 12. DTIC patients: poorer physical functioning, improved	Limited external validity: Privilege of receiving the new, maybe "better" drug in the TMZ group may influence the functioning scales more than the drug itself. p-values are only indicated for baseline characteristics.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					emotional well-being, and less nausea and vomiting, pain, appetite loss, and diarrhea at week 12. (not statistically significant or considered clinically meaningful)		
Young et al. 2001	To report the results of DTIC +IFN-alpha in patients with metastatic melanom	<p>QoL evaluation within a phase III study</p> <p>QoL instrument: EORTC QLQ C30 (+3)</p> <p>Time points: baseline, at each visit</p> <p>Treatment: Group 1 DTIC Group 2 DTIC + IFN-alpha</p>	<p>41 (of 57) advanced melanoma patients completed at least 1 questionnaire</p> <p>Baseline n=38 Timepoint of tumor assessment n=27</p>	<p>QoL</p> <p>-between groups</p> <p>-over time</p>	<p>-no significant differences between the groups, both at baseline (z =70.82, P=0.41) and for the change in scores over time (z = 71.29, P=0.20)</p> <p>-for both groups the level of symptoms worsened over time, but patients' functioning ability appeared to be stable</p>	Limitations: missing data	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Middleton et al. 2000	To compare temozolomide and dacarbazine (DTIC) in terms of overall survival, progression-free survival (PFS), objective response, and safety, and to assess health-related quality of life (QoL) and pharmacokinetics of both drugs.	Randomized phase III study QoL Instrument: EORTC QLQ-C30 Timepoints: baseline, week 12 Treatment: Group 1 Temozolomide (TMZ) Group 2 DTIC	QoL Scores available Baseline n=251 Week 12 TMZ group n=51 DTIC group n=31 of 305 patients with advanced metastatic melanoma	QoL (secondary objective) -Differences of Scores at week 12 between groups -Differences of maintenance or improvement of scores compared to baseline between groups (primary objective: overall survival, further secondary objectives: PFS, Response Rates, Safety)	TMZ group: significant better scores for physical functioning, fatigue, insomnia. Similar results for responder subgroup analysis between groups. TMZ group: significant more patients with maintenance or improvement of physical and cognitive functioning	QoL data are not shown in detail Sample size seems to be too small for responder subgroup analysis (exact numbers not indicated, DTIC group: QoL Scores available n=31 of 149, responders n=18 of 149)	1b
Sigurdardottier et al. 1996	to describe QoL of patients with advanced melanoma during chemotherapy and to compare the clinical outcome variables and patients' self-assessed QoL	Longitudinal QoL study QoL Instruments: - EORTC QLQ-C36 - study-specific melanoma module - Hospital Anxiety and Depression (HAD) scale Treatment: DTIC	95 patients with advanced melanoma (73 patients of a randomized clinical trial, 22 non-randomized patients with chemotherapy)	QoL -score differences between baseline and week 9	- significant deterioration in all QoL measurements, with the exception of pain and emotional functioning at week 9	No randomized design	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		plus vindesine with or without cisplatin					
Thomson et al. 1993	To describe the prognostic associations of QL scores obtained during a multicentre randomised clinical trial comparing DTIC plus recombinant interferon-alfa 2a versus DTIC alone for patients with metastatic malignant melanoma.	<p>QoL assessment within a Phase III study</p> <p>QoL instrument: linear analog self assessment (LASA) scales, GLQ-8 by physician: QL Index questionnaire</p> <p>Time points: Baseline, week 12</p> <p>Treatment: Group 1: DTIC Group 2 DTIC + IFN-alpha-2a</p>	<p>176 advanced melanoma patients</p> <p>Number of QoL data not indicated</p>	QoL (Response rate, Response duration, Time to disease progression, Toxicity, Overall Survival)	Quality of life was not significantly different in either group, except that fatigue, as measured at week 12 by LASA scales, and activity, as measured by the functional living index, were both improved in the combination	QoL data not presented in detail. Not clear, if score changes between baseline and week 12 or if absolute scores at week 12 are compared between the groups. Number of received questionnaires not mentioned.	2b poor quality

6.6.4.2. Aktualisierungsrecherche 2015
Palliative Therapiestudien die QoL als Endpunkt enthalten

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Grob et al. 2014	To compare the change in QoL relative to baseline in BRAF V600E mutation-positive advanced and metastatic melanoma patients using the EORTC-QLQ-C30	<p>QoL evaluation within a phase III trial</p> <p>QoL instrument: EORTC QLQ-C30</p> <p>Time points: baseline, at week 6, week 12, and week 15 during treatment, upon progression, and 4 weeks after progression was first determined. (before any study drug was administered)</p> <p>Treatment: Group 1: Dabrafenib 150mg/bid po Group 2: DTIC 1000mg/m² iv q21</p>	<p>Dabrafenib, n=1 87 DTIC, n=63</p> <p>All required assessments 57 vs. 7 pts No baseline assessment 16 vs. 6 pts.</p> <p>No postbaseline assessments 8 vs. 10 pts.</p> <p>One or two missing postbaseline assessments 96 vs. 33 pts</p> <p>Three or more missing postbaseline assessments 10 vs. 7 pts</p>	HRQOL at week 6	<p>For DTIC, all functional dimensions except role dimension worsened from baseline at follow-up.</p> <p>For dabrafenib, all functionality dimensions remained stable relative to baseline or improved at week 6; In the DTIC arm, symptom dimensions were unchanged or worsened from baseline for all symptoms except pain (week 6), with the greatest exacerbations observed for fatigue and nausea and vomiting. Mixed-model-</p>	BREAK-3 was not powered to find a pre-specified difference between the two treatment arms for any symptom or functional dimension of QoL. QoL data	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					repeated measures analyses showed significant ($P < 0.05$) and/or clinically meaningful improvements from baseline in favour of dabrafenib for emotional and social functioning, nausea and vomiting, appetite loss, diarrhoea, fatigue, dyspnoea, and insomnia at weeks 6 and/or 12. After crossing over to dabrafenib upon progression		
Hatswell et al. 2014	To report and compare pre- and post-progression health state utilities in advanced melanoma, when generated using different methods -	QoL data extracted from the clinical database of the phase III trial MDX010-20 Patients were asked to complete both the EORTC	EORTC QLQ-C30 was completed by 616 patients (1,237 observations) SF-36 was completed by 599 patients (1,205	Analyses by progression status and time to death on the patient-level data using generalised estimating equations fitted, and to analyse the	Mean utility showed a decrease on disease progression in both the EORTC-8D and the SF-6D. Whilst higher utilities were obtained using the	Not comparing QoL between treatment groups but between questionnaires and methods.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<p>via the EORTC QLQ-C30 and the SF-36</p> <p>To explore the validity, in advanced melanoma, of progression-based health-state utility modelling compared to modelling based upon time to death health states.</p>	<p>QLQ-C30 and SF-36v2 questionnaires on receipt of the first dose of treatment, at the end of treatment and 12 weeks after treatment.</p> <p>Treatment: 676 patients randomized 3:1:1 to ipilimumab + gp100, ipilimumab only, or gp100 only.</p>	<p>observations).</p>	<p>predictive abilities of the two approaches.</p>	<p>EORTC-8D, the relative decrease in utility on progression was similar between measures. When analysed by time to death, both EORTC-8D and SF-6D showed a large decrease in utility in the 180 days prior to death. Compared to progression status alone, the use of time to death gave similar or better estimates of the original data when used to predict patient utility. Including both progression status and time to death further improved model fit. Utilities seen in MDX010-20 were also broadly comparable with</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					those seen in the literature.		
Revicki et al. 2014	To analyse the HRQL outcomes during the 12 week treatment induction period in comparison to baseline data of the ipilimumab Phase III clinical trial (MDX010-20).	QoL data from the phase III trial MDX010-20 Treatment: 676 patients randomized 3:1:1 to ipilimumab + gp100, ipilimumab only, or gp100 only.	EORTC QLQ-C30 data was available in 95% of the patients; Week 12 assessments were available for 236 (62%), 85 (65%), and 80 (61%) of the patients treated with ipilimumab plus gp100, ipilimumab alone, and gp100 alone, respectively.	QoL changes at week 12 compared to baseline.	In the ipilimumab plus gp100 and ipilimumab alone groups, mean changes from baseline to Week 12 generally indicated “no change” or “a little” impairment across EORTC QLQ-C30 global health status, function, and symptom subscales. Significant differences in constipation, favouring ipilimumab, were observed (p<0.05). For ipilimumab alone arm, subscales with no or a little impairment were physical,		1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					emotional, cognitive, social function, global health, nausea, pain, dyspnoea, constipation, and diarrhoea subscales. For the gp100 alone group, the observed changes were moderate to large for global health, role function, fatigue, and for pain.		
Schadendorf et al. 2014	To evaluate the impact of the MEKi, trametinib, on patients' QOL versus chemotherapy.	QoL evaluation within a phase III trial QoL instrument: EORTC QLQ-C30 Treatment: Patients randomized 2:1 to trametinib 2mg/d po or DTIC 1000mg/m ² iv q21	EORTC QLQ-C30 data was available in n=178 of the patients receiving trametinib and n=95 of the patients receiving chemotherapy	QoL changes at week 6 and 12 compared to baseline.	In the primary efficacy population from baseline to weeks 6 and 12, patients' global health status scores worsened by 4-5 points with chemotherapy but improved by 2-3 points with trametinib. Rapid and substantive reductions in QOL		1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>functionality (e.g. role functioning, 8–11 points at weeks 6 and 12) and symptom exacerbation (e.g. fatigue, 4–8 points; nausea and vomiting, 5 points, both at weeks 6 and 12) were observed in chemotherapy-treated patients. In contrast, trametinib-treated patients reported small improvements or slight worsening from baseline at week 12, depending on the functional dimension and symptom.</p>		
Schadendorf et al. 2015	To compare the effect of dabrafenib plus trametinib versus	QoL evaluation within a phase III trial	EORTC QLQ-C30 data was available in n=204 of the patients receiving	QoL changes at week 8, 16, 24, 32, 40 and at time point of	Baseline scores across both arms were comparable for all dimensions.		1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<p>dabrafenib alone on HRQoL and symptoms (improvement or delay in worsening) in patients with BRAF V600E or V600K mutation-positive metastatic melanoma enrolled in the COMBI-d trial.</p>	<p>QoL instrument: EORTC QLQ-C30</p> <p>Treatment: Patients randomized 1:1 to receive either a combination of oral dabrafenib (150 mg twice daily) and oral trametinib (2 mg once daily) or a combination of oral dabrafenib (150 mg twice daily) and placebo.</p>	<p>dabrafenib and trametinib and n=202 of the patients Dabrafenib and placebo at baseline >85% at week 40 and >70% at disease progression. Measurement was performed every 8 weeks.</p>	<p>progressive disease compared to baseline.</p>	<p>Global health dimension scores were significantly better at weeks 8, 16 and 24 for patients receiving the combination during treatment and at progression. The majority of functional dimension scores (physical, social, role, emotional and cognitive functioning) trended in favour of the combination. Pain scores were significantly improved and clinically meaningful (6-13 point difference) for patients receiving the combination for all follow-up assessments</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					versus those receiving dabrafenib monotherapy. For other symptom dimensions (nausea and vomiting, diarrhoea, dyspnoea, and constipation), scores trended in favour of dabrafenib monotherapy.		

Ausgeschlossene Studien

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Adamina et al. 2008	To assess the safety and immunogenicity of heterologous prime-boost immunotherapy of melanoma patients with Influenza	multi-centre phase I/II open labeled study LQ instrument: FACT-BRM 4 questionnaire	20 resected AJCC stages IIb-IV melanoma patients			QoL data are not presented excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<i>virosomes, and recombinant Vaccinia virus. Quality of life will be assessed with a dedicated FACT-BRM 4 questionnaire</i>						
<i>Beguerie et al. 2010</i>	<i>Tamoxifen vs. non-tamoxifen treatment for advanced melanoma: a meta-analysis</i>	<i>metaanalysis</i>	<i>9 randomized controlled trials</i>	<i>Secondary outcome quality of life (Response, mortality, toxicity, treatment-related mortality)</i>	<i>None of the trials reported QoL</i>	<i>excluded</i>	
<i>Noorda et al. 2007</i>	<i>To assess the long-term health-related quality of life (HRQL) of melanoma survivors who had undergone isolated limb perfusion (ILP) of the extremities, and to identify the patient-, tumour- and ILP-related factors associated</i>	<i>Comparative Study QoL Instrument: mailed questionnaire SF-36 Time point: after ILP, at least 6 months disease free Comparison: normative sample</i>	<i>QoL assessment n=51 (89%) of 51 patients after isolated limb perfusion median follow up after ILP 14 years (range 3-25 years)</i>	<i>SF-36 scores</i>	<i>SF-36 scores of the patient group were equal to or better than that of the general population, significantly for bodily pain, general health perceptions, and the physical and mental health component scores</i>	<i>Assessment after therapy, no baseline data Study excluded</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<i>most strongly with the patients' self-reported HRQL.</i>	<i>of the Dutch general population of SF-36 scores</i>					
<i>Petrella et al. 2007</i>	<i>To determine the role of single-agent interleukin-2 in the treatment of adults with metastatic melanoma. Outcomes: objective and complete response rates, duration of response, toxicity and quality of life</i>	<i>systematic review</i>	<i>1 systematic review, 5 RCTs, 12 Phase II trials, 1 QoL report</i>			<i>excluded (only 1 QoL report)</i>	
<i>Quirt et al. 2007</i>	<i>To examine the role of temozolomide in patients with metastatic melanoma. Outcomes: response rate, progression-free survival, overall survival, quality of life, and adverse effects</i>	<i>systematic review</i>	<i>Two randomized phase III trials and three randomized phase II trials</i>		<i>only 2 studies with QoL data</i>	<i>excluded</i>	

<i>Study</i>	<i>Aims</i>	<i>Design</i>	<i>Population</i>	<i>Outcomes</i>	<i>Results</i>	<i>Comments</i>	<i>LoE</i>
<i>Schallreuter et al. 1991</i>	<i>A quite promising clinical trial was conducted using the new nitrosourea fotemustine</i>	<i>phase II study</i>	<i>19 patients</i>		<i>quality of life of the patients during and after chemotherapy was not severely affected</i>	<i>no QoL assessment study excluded</i>	
<i>Verma et al. 2006</i>	<i>To examine the role of systemic adjuvant therapy in patients with high-risk, resected, primary melanoma Outcomes: overall survival, disease-free survival, adverse effects, and quality of life</i>	<i>systematic review</i>	<i>37 randomized controlled trials, 2 meta-analyses, and 1 systematic review were identified that investigated interferon, levamisole, vaccine, or chemotherapy as adjuvant therapy</i>			<i>only Q-TWiST data, no QoL data presented study excluded</i>	
<i>Sigurdardottir et al. 1993</i>	<i>To assess the QoL of patients with melanoma before the start of treatment</i>	<i>quality of life (QoL) study QoL instruments: - EORTC QLQ-C36 - study-specific melanoma (MM) module -Hospital Anxiety and Depression (HAD) scale</i>	<i>89 patients</i>		<i>Before treatment the patients reported a relatively low symptom burden, good physical and social functioning, moderate psychological distress and a high overall QoL rating</i>	<i>No assessment under therapy study excluded</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					during the past week		
Coates 1993	To measure aspects of quality of life (QL) prospectively by patients using linear analogue self assessment (LASA) scales including the GLQ-8 and by doctors using Spitzer's QL Index within a clinical trial comparing dacarbazine (DTIC) plus recombinant interferon-alfa2a (IFN) versus DTIC alone	QoL evaluation within a phase III study QoL instruments: patients: 5 linear analog self assessment (LASA) scales, GLQ-8 physician: Spitzer's QL Index Treatment: DTIC plus interferon-alfa2a versus DTIC alone	Baseline QoL data available of 152 patients	Prognostic value of Quality of Life Scores at Baseline	In univariate analyses, Spitzer QL Index assessed by the doctor and LASA scores for physical wellbeing (PWB), mood, pain, appetite, nausea and vomiting, GLQ-8 total and overall QL were significant (P < 0.01) predictors of subsequent survival	Only baseline QoL data Study excluded	
Kilbridge et al. 2002	To analyse quality-of-life-adjusted survival of the high-dose adjuvant interferon alpha-2b regimen	A quality-of-life--adjusted survival (QAS) analysis of two cooperative group phase III trials, E1684 and E1690, was performed			E1684: increase in QAS for all sets of patient utilities, significant for 16% E1690: increase in QAS 77%, decrease 23%, not significant	Utility weights were obtained in a separate study of 95 low-risk melanoma patients and were combined with survival and	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						<p><i>toxicity data of E1684 and E1690</i></p> <p><i>QoL data of the trials are not presented</i></p> <p><i>Study excluded</i></p>	

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6.6.6. Übersicht Fragebögen zur Erhebung der Lebensqualität

EORTC QLQ-C30 (Version 3.0 is currently the standard version of the QLQ-C30)

The QLQ-C30 is a questionnaire for patient self-completion, composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting and pain) and a global health status/QOL scale and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea and financial difficulties).

(<http://groups.eortc.be/qol/index.htm>)

EORTC QLQ-C36

first generation core questionnaire. The 36-item questionnaire was designed 1987 to be (1) cancer specific, (2) multidimensional in structure, (3) appropriate for self-administration (i.e. brief and easy to complete), and (4) applicable across a range of cultural settings.

(<http://groups.eortc.be/qol/index.htm>)

HADE Scale

Dimensionen: Angst, Depressivität; je 7 Items.

SF-36 (Short Form (36) Health Survey)

Entwickelt in den USA, Kurzform eines ursprünglich aus 149 Items bestehenden Fragebogens, der in den 60er und 70er-Jahren entwickelt wurde.

Deutsche Übersetzung durch M. Bullinger, I. Kirchberger, Hogrefe Verlag, Göttingen

Krankheitsübergreifendes Meßinstrument zur Erfassung der gesundheitsbezogenen Lebensqualität von Patienten.

2 Bereiche: körperliche Gesundheit und psychische Gesundheit

8 Dimensionen: Körperliche Funktionsfähigkeit, Körperliche Rollenfunktion, Körperliche Schmerzen, Allgemeine Gesundheitswahrnehmung, Vitalität, Soziale Funktionsfähigkeit, Emotionale Rollenfunktion und Psychisches Wohlbefinden.

QWB-SA

The Quality of Well-Being Scale (QWB) has been used in numerous clinical trials and studies over the years to evaluate medical and surgical therapies in conditions such as chronic obstructive pulmonary disease, HIV, cystic fibrosis, diabetes mellitus, atrial fibrillation, lung transplantation, arthritis, end stage renal disease, cancer, depression, and several other conditions. Further, the instrument has been used for health resource allocation modeling and served as the basis for an innovative experiment in the allocation of health care by the State of

Oregon. Studies have also demonstrated that the QWB is responsive to clinical change derived from surgery or medical conditions such as rheumatoid arthritis, AIDS, and cystic fibrosis.

The self-administered form of the QWB (QWB-SA) was developed more recently. It has been shown to be highly correlated with the interviewer-administered QWB and to retain its psychometric properties. The QWB-SA combines preference-weighted values for symptoms and functioning. Symptoms are assessed by questions that ask about the presence or absence of different symptoms or conditions. Functioning is assessed by a series of questions designed to record functional limitations over the previous three days, within three separate domains (mobility, physical activity, and social activity). The four domain scores are combined into a total score that provides a numerical point-in-time expression of well-being that ranges from zero (0) for death to one (1.0) for asymptomatic optimum functioning.

<http://www.healthmeasurement.org/Measures.html>

GLQ-8

To measure quality of life in cancer patients receiving chemotherapy

Number of items: 8 plus one optional write-in

Administration mode: Self-administered

Author: Coates Alan S

http://www.proqolid.org/instruments/glq_8_glq_8

LASA scale

5 linear analog self assessment (LASA) scales, measuring physical wellbeing, mood, pain, nausea and vomiting and appetite

IES (Impact of Event Scale)

a 15-item, self-report scale that assesses two categories of cognitive responses to stressful events: intrusion (intrusively experienced ideas, images, feelings or bad dreams) and avoidance (consciously recognized avoidance of certain ideas, feelings or situations). The scale was originally developed to assess current distress associated with a specific trauma. Patients in the present study were asked to rate the frequency

of intrusive thoughts and avoidance behaviours in relation to their current health status using a 4-point scale (0, 'not at all'; 1, 'rarely'; 2, 'sometimes'; 3, 'often'), with higher scores representing worse functioning. The IES total score is the sum of the two subscale scores.

6.7. Frage V.9. Medikamentöse Therapie Hirnmetastasen – De novo Recherche

6.7.1. PICO, Suchwörter

PICO – Schema			
Population	Intervention	Comparison	Outcome
Melanoma patients with brain metastases	Systemic treatment	Observation, other systemic treatments	Survival, progression free survival, Quality of Life

Suchwörter				
Stichwort	melanoma	Therapy	brain	Temo*, fotemustin
Synonyme		treatment	Cerebral, CNS	
Mesh Term				

6.7.2. Datenbanken, Suchstrategien, Trefferzahlen

6.7.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1.Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (treatment[tiab] OR therapy[tiab] OR	30.05.11	1553 (Auswahl 19)

Datenbank	Suchstrategie	Datum	Treffer
	therapy[MeSH] OR temo*[tiab] OR fotemustin[tiab]) AND (brain[tiab] OR cerebral[tiab] OR CNS[tiab] or Brain Neoplasms[MeSH])		
Embase	(melanoma and (treatment or therapy) and (brain or cerebral or CNS)).ti,ab.	11.05.11	1247 (Dedubliziert: 346, 0 dazu)
Cochrane Library	(melanoma and (treatment or therapy) and (brain or cerebral or CNS)).ti,ab.	20.05.11	28 (Auswahl 3 Dubletten, 0 dazu)
Update Suche			
Medline	s.o.	31.01.12	1625 (1 dazu , Weber et al. 2011)
Embase	s.o.	23.01.12	1349 (1 dazu, Heller et al. 2011-Abstrakt)
Cochrane Library	s.o.	31.01.12	31 (0 dazu)

6.7.2.2. Aktualisierungsrecherche 2015

Datenbank	Suchstrategie	Datum	Treffer
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (treatment[tiab] OR therapy[tiab] OR therapy[MeSH] OR temo*[tiab] OR fotemustin[tiab]) AND (brain[tiab] OR cerebral[tiab] OR CNS[tiab] or Brain Neoplasms[MeSH])	15.10.2015	587
Cochrane Library	(melanoma and (treatment or therapy) and (brain or cerebral or CNS)).ti,ab.	15.10.2015	45

6.7.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	3005
Einschlusskriterien	Systematische Reviews oder klinische Studien zur medikamentösen Therapie bei Melanompatienten mit Hirnmetastasen RCT´s die Patienten mit Hirnmetastasen eingeschlossen haben Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitäten Kombination mit Radiotherapie
Anzahl nach Abstractscreening, vorgesehen für Bewertung	22
Anzahl ausgewählter Studien nach Handsuche (Durchsicht der Literaturlisten)	0
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	9
Anzahl ausgewählter Volltexte	13 (davon 1 Asco Abstract)

Auswahl der Literatur	
Gesamttreffer	632
Einschlusskriterien	Systematische Reviews oder klinische Studien zur medikamentösen Therapie bei Melanompatienten mit Hirnmetastasen RCT´s die Patienten mit Hirnmetastasen eingeschlossen haben Sprachen: e,dt
Ausschlusskriterien	Case Reports

Auswahl der Literatur	
	Nicht systematische Reviews Kollektive mit gemischten Tumorentitäten Kombination mit Radiotherapie RCT's, in denen Patienten mit Hirnmetastasen lediglich ein Subkollektiv waren
Anzahl nach Abstractscreening, vorgesehen für Bewertung	133
Anzahl ausgewählter Volltexte	5

6.7.4. Evidenztabelle

6.7.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hodi et al. 2010	To compare ipilimumab, administered with or without a glycoprotein 100 (gp100) peptide vaccine with gp100 alone in patients with previously treated metastatic melanoma	RCT Treatment: Group A ipilimumab plus gp100 (n=403) Group B ipilimumab alone (n=137) Group C gp100	676 HLA-A*0201-positive patients with previously treated unresectable stage III or IV melanoma 82 patients with brain metastases	Median Overall survival	All patients (ipilimumab +gp100 vs. ipilimumab vs. gp100) 10.0 months vs. 10.1 months vs. 6.4 months, sign., (hazard ratio for death, 0.68;	Outcomes of patients with brain metastases not reported separately	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		alone (n=136)		Overall Response Rate	p<0.001). 5.7% (n=23) vs. 11% (n=15) vs. 1.5% (n=2), sign., p=0.04		
Avril et al. 2004	To compare fotemustine and dacarbazine (DTIC) in in patients with disseminated cutaneous melanoma	RCT Treatent: Arm A: Fotemustine Arm B: DTIC	229 patients with metastatic melanoma 43 patients with brain metastases (Arm A n=22, Arm B n=21)	Response	Patients with brain metastases n=43 Arm A Fotemustin vs. Arm B DTIC CR n=0 versus n=0 PR n=1 versus n=1 SD not reported PD not reported	Outcomes of patients with brain metastases not reported in detail. Author contacted, no reply	4
Weber et al. 2011	To further evaluate the efficacy and safety of ipilimumab at 10 mg/kg in melanoma patients with stable brain metastases.	Retrospective analysis of data from a phase II study	12 patients with stable brain metastases	Response Survival	PR n=2 of 12 SD n=3 of 12 Median OS: 14 months Both patients with a partial response and one with stable disease were alive at the last follow-up, with survival time of	Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					more than 4 years		
Amaravadi et al. 2009	To evaluate the combination of the oral alkylating agent temozolomide and the oral multikinase inhibitor sorafenib in advanced melanoma patients	Phase II study Treatment: Sorafenib 400mg twice daily + temozolomide	167 patients with metastatic melanoma 53 patients with brain metastases (Arm D)	Response rates 6-month PFS rate Median PFS Median OS	Evaluable patients (Arm D with brain metastases) n=52 CR rate: 0% PR rate: 15% SD rate: 48% PD rate: 37% 23% 3.5 months 8 months	Response assessed according RECIST criteria, CT every 8 weeks Lack of control group	4
Vestermark et al. 2008	To evaluate single agent antitumour activity and toxicity of Thalidomide in a phase II setting in patients with brain metastases associated with metastatic melanoma	Phase II study Treatment: thalidomide	36 patients with brain metastases	CNS Response CR+PR SD PD Median PFS Median OS	Evaluable patients: n=35 n=0 n=5 n=30 1.7 months 3.1 months	Response assessed according RECIST criteria, CT or MRI every 3 months Lack of control group	4
Larkin et al. 2007	To assess the maximum-tolerated dose (MTD), safety and	Phase I/II study Treatment: temozolomide +	26 patients with brain metastases	CNS Response CR+PR	Evaluable patients: n=20 n=0	Response assessed according WHO criteria, CT or MRI after 3.+ 6. cycle	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	efficacy of the combination of temozolomide and lomustine in melanoma metastatic to the brain	lomustine		SD PD Median OS	n=10, 50% n=10, 50% 2 months	(28days/cycle) only 10% of patients received more than 2 cycles of therapy Lack of control group	
Schadendorf et al. 2006	To test a dose-intensified regimen of temozolomide in melanoma patients with brain metastases in a prospective, open-label, multicentre phase II trial	Phase II study Treatment: temozolomide	45 patients with asymptomatic brain metastases	CNS Response CR PR SD PD Median OS	Evaluable patients: n=40 (5 missing patients: no clinical response) n=0 n=2, 4.4% n=5 n=33 4.1 months	Response assessed according RECIST criteria, CT or MRI, week 8 and week 20, responses were confirmed 4 weeks later. Lack of control group	4
Hwu et al. 2005	To examine the efficacy and safety of temozolomide plus thalidomide in chemotherapy-naive patients with brain metastases	Phase II study Treatment: temozolomide + thalidomide	26 patients with brain metastases, 16 with symptomatic brain metastases	CNS Response CR PR SD PD Median OS	Evaluable patients: n=14 n=2 n=1 n=7 n=4 5 months	Response assessed according WHO criteria, CT or MRI every 8 weeks 11 patients did not complete first cycle	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Lack of control group	
Bafaloukos et al. 2004	To evaluate the efficacy and toxicity of temozolomide-based chemotherapy in patients with cerebral metastases from melanoma.	Analyses of patients with brain metastases within 2 Phase II studies Treatment: temozolomide + docetaxel n=10, temozolomide + cisplatin n=9, temozolomide alone n=6	25 patients with brain metastases	CNS Response CR PR SD PD Median OS 1-year survival rate	Evaluable patients: n=24 n=0 n=6 n=5 n=13 4.7 months 20.9%	Response assessed according WHO criteria, CT or MRI every second cycle (28 days/cycle) Lack of control group	4
Agarwala et al. 2004	To assess the safety and efficacy of temozolomide in patients with brain metastases from metastatic melanoma	Phase II study Treatment: temozolomide	151 patients with brain metastases n=117 no prior chemotherapy n=34 prior chemotherapy	CNS Response CR PR SD PD Median OS	Evaluable patients: n=132 n=1 n=8 n=40 n=73 all patients (n=151) 3.2 months	Large study Response assessed according WHO criteria, gadolinium-enhanced MRI every second cycle (28 days/cycle), responses were confirmed 4 weeks later. Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Chang et al. 1994	To investigate the sequential administration of dacarbazine and fotemustine in the treatment of cerebral metastases from malignant melanoma	Phase II study Treatment: DTIC + fotemustine	34 patients with brain metastases	Response CR PR SD Median OS	Evaluable patients: n=34 n=2 n=2 n=9 duration of complete response: 12, 36+ months 4.5 months	Tumour response was defined according to World Health Organisation criteria Lack of control group	4
Jacquillat et al. 1990	To investigate the activity of fotemustine against cerebral metastases of disseminated malignant melanoma	Phase II study Treatment: fotemustine	42 patients with brain metastases 16 patients with only brain metastases, 23 patients with brain + extracerebral metastases	Response CR PR SD PD Median OS 1-year survival	Evaluable patients: n=39 n=2 n=9 n=9 n=19 26 weeks (6 months) 21%	Tumor assessment according WHO criteria Lack of control groups	4
Heller et al. 2011	To report safety and efficacy data of treatment with ipilimumab in patients with brain	open-label study Treatment: ipilimumab 3 or 10 mg/kg	165 with brain metastases at baseline (of 869 patients)	Toxicity	drug-related serious adverse events of any grade: 26.1% (similar rate to pts	only asco abstract available	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<i>metastases</i>			<i>1 year survival</i>	<i>without brain metastases) 20%</i>		

6.7.4.2. Aktualisierungsrecherche 2015

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ajithkumar et al. 2015	To review the present understanding and evolving multimodal management of melanoma brain metastases, and the challenges of how best to integrate new systemic therapies	Systematic review Categorized according to treatment modality	Patients suffering from brain metastases of melanoma	Not defined	“For patients with BRAF-mutant melanoma, BRAF-targeted agents could be used preferentially to radiotherapy while the potential benefits and risks of the combination of radiotherapy and immunotherapy are still being studied“	Only descriptive information provided	3a
Dummer et al. 2013	To study the safety, tolerability and efficacy of Vemurafenib for	Open-label, single-arm, two-centre, study designed	Patients with BRAFV600 mutation-positive metastatic	Safety	23 of 24 patients reported at least one adverse event (AE). Grade 3	Funding: Roche	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with advanced melanoma and symptomatic brain metastases	Vemurafenib (960 mg bid) n=24	melanoma with non-resectable, previously treated brain metastases.	Best overall response rate (BORR)	AEs were reported in 4 (17%; 95% confidence interval [CI], 4.7-37.4%) patients and included cutaneous squamous cell carcinoma in 4 patients		
				Progression-free survival (PFS)	Overall partial response (PR) at both intracranial and extracranial sites was achieved in 10 of 24 (42%; 95% CI, 22.1-63.4) evaluable patients, with stable disease in nine		
				Overall survival (OS)	Median PFS was 3.9 (95% CI, 3.0-5.5) months		
					Median OS was 5.3 (95% CI, 3.9-6.6) months		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Goyal et al. 2015	To review the current evidence regarding the treatment of multiple brain metastases from melanoma.	Systematic review	2006 pts. treated with radiotherapy; 642 treated with chemotherapy; description of non-RCTs for Ipilimumab	Rate of Intracranial Failure, % Overall Intracranial Response Rate, % Median Overall Survival, mo Progression-Free Survival or Median Time to Progression	8-48% for SRS(+/-WBRT), 29-100% for WBRT 7-47% for CTX 6.5-7.5m for WBRT, 5.7-15.2m for SRS(+/-WBRT) 0-47monts for chemotherapy (+/-WBRT/SRS) 4.7-21.3m for ipilimumab (+/-Chemo/WBRT/SRS) 1.2-5m for chemotherapy (+/-WBRT/SRS) 2.7m-9.5m for Ipilimumab (+/-Chemo/WBRT/SRS)	“At this time, the standard management for patients with MBM from melanoma includes SRS, WBRT, or a combination of both“	2a
Long et al. 2012	To confirm the activity of dabrafenib in brain metastases, we assessed dabrafenib in	Multicentre, open-label, phase 2 trial with 2 cohorts: Cohort A had not received	Patients with BRAFV600 mutation-positive metastatic melanoma who had or had not	Overall intracranial response (CR or PR)	Cohort A (Val600Glu-Mutated) 29/74 pts. (39.2%, 95% CI 28.0-51.2) (Val600Lys-	Funding: GSK	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with Val600Glu or Val600Lys BRAF-mutant melanoma and at least one brain metastasis who were either previously untreated for brain metastases or who had progressive metastases after previous local treatments.	<p>previous local treatment for brain metastases (n=89)</p> <p>Cohort B had progressive brain metastases after previous local treatments (n=83)</p> <p>Patients in both cohorts received 150 mg oral Dabrafenib twice a day</p>	received previous local treatment for brain metastases	Safety	<p>Mutated) 1/15 pts. (6.7%, 0.2–31.9)</p> <p>Cohort B (Val600Glu-Mutated) 20/65 pts. (30.8%, 19.9–43.4) (Val600Lys-Mutated) 4/18 pts. (22.2%, 6.4–47.6)</p> <p>Treatment-related AEs of grade 3 or worse occurred in 38 (22%) patients. Four grade 4 treatment-related AEs occurred in cohort A. Two grade 4 events occurred in cohort B. 51 (30%) patients had a serious adverse event.</p>		
Margolin et al.	To assess efficacy and safety of ipi-	Open-label, phase 2 trial with two	Patients had to have at least one	Proportion of patients with	9/51 patients in cohort A	Funding: BMS	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
2012	limumab specifically in patients with melanoma and brain metastases in a prospective clinical trial	parallel cohorts Cohort A Neurologically asymptomatic; not receiving corticosteroid treatment at study entry (n=51) Cohort B symptomatic; stable dose of corticosteroids (n=21) Ipilimumab 10mg/kg iv q21 for four doses	measurable index brain metastasis of 0.5–3 cm in diameter, or two measurable lesions larger than 0.3 cm visible on contrast MRI, or both.	disease control, defined as CR, PR, or stable disease after 12 weeks Proportion of patients with an objective response (CR/PR) Median PFS Overall survival Safety & Tolerability	exhibited disease control (18%, 95% CI 8–31) 1/21 patients in cohort B exhibited disease control (5%, 0.1–24). Cohort A: OR: 5/51 (10%, 3–21) Cohort B: OR: 1/21 (5%, 0.1–24) Cohort A: 1.4 (1.2–2.6) months Cohort B: 1.2 (1.2–1.3) months Cohort A: 7.0 (95% CI 4.1–10.8) months Cohort B: 3.7 (95% CI 1.6–7.3) months Most common AEs in both cohorts: Fatigue, diarrhoea, nausea, headache,		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>rash, and pruritus. Most common grade 3 events overall: diarrhoea, fatigue, dehydration, hyperglycaemia, and increased concentrations of serum aspartate aminotransferase. One patient in each cohort experienced grade 4 confusion. 3 patients in cohort A had brain oedema (one grade 1 and two grade 2).</p> <p>A man in cohort A died for reasons related to the study drug 24 days after his second dose of ipilimumab because of gangrenous colitis, despite treatment with</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>corticosteroids.</p> <p>15 pts. in cohort A completed induction. 28 pts. had discontinued treatment because of early progression of disease or death, five requested discontinuation without documented progression, three had adverse events.</p> <p>5 patients in cohort B completed induction. 11 had discontinued treatment because of disease progression or death, 3 requested discontinuation, and 2 had AEs.</p>		

6.7.5. Literatur

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7. AG Radiotherapie

7.1. Frage VI.1. Radiotherapie Primärtumor

Frage VI.1. Hat eine Radiotherapie von inoperablen Primärtumoren oder eine postoperative Radiotherapie nach R1 oder R2-Resektion von Primärtumoren bzw. bei Vorhandensein anderer Risikofaktoren (nicht einhaltbare Sicherheitsabstände) einen Einfluss auf das progressionsfreie Überleben oder Gesamtüberleben?

7.1.1. PICO, Suchwörter

PICO - Schema			
Population	Intervention	Comparison	Outcome
Melanoma patients with primary tumor, prior or after (partial) resection	radiotherapy	no radiotherapy	PFS, OS

Suchwörter				
Stichwort	melanoma	radiotherapy	primary	margin
Synonyme		Radiation, irradiation		
Ober-/Unterbegriffe	Lentigo maligna, cutaneous, skin			Resection, R1, R2, inoperable, unresectable, adjuvant, postoperative
Mesh Term	melanoma	radiotherapy, radiation		

7.1.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH]) AND (primary OR "lentigo maligna" OR margin* OR resection OR R1 OR R2 OR inoperab* OR unresectab*) NOT (uvea*[ti] OR anorectal[ti] OR mucosal[ti])	20.04.11	1836 (Auswahl 22 Studien)
Medline -Erweiterte Suchstrategie	(melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH] OR irradiation) AND (skin OR cutaneous OR primary OR "lentigo maligna" OR margin* OR resection OR R1 OR R2 OR postoperative OR inoperab* OR unresectab*) NOT (uvea*[ti] OR anorectal[ti] OR mucosal[ti])	16.05.11	5435 (Auswahl 8 Studien)
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation) and (skin or cutaneous or primary or "lentigo maligna" or margin* or resection or R1 or R2 or adjuvant or postoperative or inoperab* or unresectab*) not (uvea* or anorectal or mucosal)).ti,ab.	20.04.11	42 (0)
Embase	(melanoma and (radiotherapy or radiation or irradiation) and (skin or cutaneous or primary or "lentigo maligna" or margin* or resection or R1 or R2 or adjuvant or postoperative or inoperab* or unresectab*) not (uvea* or anorectal or mucosal)).ti,ab.	11.05.11	3272 (Auswahl 3 Studien)
Update Suche			
Medline	s.o.	31.01.12	5613 (1 Studie dazu, Hedblad et al. 2011)
Cochrane Library	s.o.	31.01.12	42 (0 dazu)
Embase	s.o.	23.01.12	3475 (0 dazu)

7.1.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	8721
Einschlusskriterien	Mangels RCT´s Einschluss von Kohortenstudien und Fallserien ab 20 Patienten Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kombinationstherapien Arbeiten zu RT von nicht invasiven Melanomen (Melanoma in situ/Lentigo maligna) Kollektive mit gemischten Tumorentitäten Arbeiten älter als 1980
Anzahl nach Abstractscreening, vorgesehen für Bewertung	34
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	19
Anzahl ausgewählter Volltexte	15

7.1.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Wasif et al. 2011	To study the surgical management of desmoplastic melanoma (DM), identify prognostic	Retrospective cohort study	1735 patients with desmoplastic melanoma 143 (8%) of patients in the	survival	adjuvant radiation therapy: negative impact on survival [HR 1.65 (95% CI 1.17-2.31)]	Adverse impact of RT probably reflects selection bias	3b Cohort study with imbalance of groups

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	factors, and impact of treatment options		cohort received adjuvant radiotherapy				
Chen et al. 2008	To describe the clinicopathologic features of desmoplastic neurotropic melanoma (DNM), to update outcomes, and to explore the role of adjuvant radiation treatment in the management of this entity	Retrospective cohort study Treatment: Surgery + different RT modalities and schedules	128 patients with DNM 27 patients received radiotherapy after local excision	Local recurrence Prognostic factors	RT group, N=27: n=2 (7.4%) Surgery only, N=101: n=6 (5.9%) significant predictors of local recurrence: -a positive margin (P < .001) -head and neck location (P = .03)	Imbalance of groups: RT group included more patients with worse prognostic factors (closer excision margin, higher tumor thickness, more head and neck tumors)	3b Cohort study with imbalance of groups
Hedblad et al. 2011	To evaluate Grenz ray treatment in a structured way for treatment of Lentigo maligna melanoma as an alternative to surgery	Retrospective cohort study Treatment: Grenz ray treatment	593 patients with Lentigo maligna or early lentigo maligna melanoma	Complete clearance	88%	Lack of control group	4
Vongtama et al. 2003	To address the role of radiation therapy in local control of	Retrospective cohort study (1976 - 1999)	44 patients with DMM 14 patients with postoperative RT	Local recurrence Local control in recurrent DMM	Overall: n=21 (48%) Surgery +RT (15	Possible selection bias, Imbalance of groups, small sample size	4 Cohort study with imbalance

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	desmoplastic malignant melanoma (DMM)	Treatment: Surgery alone Surgery + RT, median dose 50 Gy	after local recurrence 1 patient with preoperative RT	Distant metastasis	pts) n=15 Surgery alone (7pts) n=3 nonirradiated patients 35% irradiated patients 40%		of groups and small sample size
Foote et al. 2008	To address the role of radiotherapy in the local control of desmoplastic melanoma	Retrospective evaluation Treatment: Surgery + wide field radiotherapy with a 3- to 4-cm margin	24 patients with DM received surgical excision as initial treatment followed by postoperative radiotherapy	3-year in-field relapse-free survival 3-year relapse-free survival 3-year overall survival	91% (95% confidence interval 68.1–97.6%) 86% (95% confidence interval 63.2–95.4%) 83% (95% confidence interval 54.9–94.3%).	Lack of control group	4
Arora et al. 2005	To determine local recurrence rates for patients with desmoplastic melanoma who underwent wide excision alone	Retrospective evaluation Treatment: surgery alone	65 Patients with DM received surgical excision alone	Local recurrence rate	n=2 (4%) of 49 patients with minimum of 2 years of follow-up	Lack of control group	4
Farshad et al.	To perform a	Retrospective	150 patients with	Local recurrence	n=7 (7%)	Lack of control	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
2002	retrospective study of 150 patients with lentigo maligna (LM) and lentigo maligna melanoma (LMM) treated with radiotherapy using Grenz or soft X-rays.	evaluation Treatment: Grenzrays (12 kV) X-rays (20 or 30 kV) LM: 10-12 Gy x 10 fractions LMM 7-9 Gy x 6 fractions	LM or LMM treated at the skin cancer unit of the Department of Dermatology, University of Zurich (Switzerland) between 1950 and 2000	rate	of 101 patients followed up for at least 2 years	group	
Schmid-Wendtner et al. 2000	To present the results of a fractionated radiation therapy (modified Miescher's technique) in 64 patients with LM or LMM treated between 1987 and 1998.	Retrospective evaluation Treatment: superficial x-ray unit (Dermopan, Siemens, Erlangen, Germany) 100 Gy applied in 10 fractions, safety margin: 0.5 - 2.0 cm	64 patients with LM (n =42) and LMM (n= 22)	Local recurrence rate	LM n=0 (0%) of 42 patients LMM n=2 (9%) of 22 patients median follow up 15 months	Lack of control group	4
Stevens et al. 2000	To assess local recurrence and survival of patients treated with surgery and postoperative	Retrospective evaluation Treatment: TD 30-36 grays (Gy), 5-7 fractions,	174 Stage I-III melanoma patients received postoperative radiation therapy	Local recurrence rate 3-years metastasis free survival	n=20 (11%) (Group A and B) 60% (Group A)	Lack of control group No baseline characteristics presented	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	hypofractionated radiation therapy	twice weekly	Group A n=32: primary tumor site (Group B n=142: lymph node involvement)				
Panizzon et al. 1999	To report radiation treatment results of 129 patients with the precursor lesion lentigo maligna and 27 patients with lentigo maligna melanoma	Retrospective evaluation Treatment: RT alone	27 patients with lentigo maligna melanoma	Complete response	n=25 (92.8%)	Lack of control group	4
Ang et al. 1994	To assess the efficacy and toxicity of elective-adjunctive radiotherapy given in five 6-Gy fractions to patients with cutaneous melanoma of the head and neck at high risk for local-regional relapse	Retrospective evaluation Treatment: (most patients) electrons, mostly 9-12 MeV, 6-Gy dose per fraction, twice a week, total dose 30Gy	174 melanoma patients Group 1 (n=79) RT after wide excision Group 2 (n=32) RT+limited neck dissection Group 3 (n=63) RT after neck resection for nodal relapse	5-year local-regional control Survival Pattern of failure (after median follow-up of 35 months)	88% (all patients) 87% (Group 1) 47% (all patients) 62% (Group 1) Group 1 NED n=51 Dermal recurrence N=2 Nodal relapse n=2 D+N n=1 Distant met. N=21	Lack of control group	4
Storper et al. 1993	To elucidate the	Retrospective	44 melanoma	Survival	SE 19%	Imbalance of	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	efficacy of external beam irradiation in the treatment of head and neck malignant melanoma, in comparison with the efficacy of surgical excision and the efficacy of surgical excision combined with external beam irradiation	evaluation Treatment: -surgery (SE), n=26 -primary external beam irradiation (XRT), n=10 -adjuvant external beam irradiation (SE+XRT), n=8	patients with recurrent disease		XRT 20% SE+XRT 37%	prognostic factors between groups Site of RT not mentioned	
Phipps et al. 1992	To examine the effect of immediately preoperative adjuvant radiotherapy in the surgical treatment of primary cutaneous malignant melanoma	Retrospective evaluation (1958-1970) Treatment: All patients: 400 cGy external beam radiotherapy, 52 patients additional single-fraction 2000 cGy Surgery within 24h	77 melanoma patients, clinical Stage I	5-years survival 10-year survival Local recurrence	68% 57% 14% Follow-up minimum 10 years	Lack of control group Tumor thickness not mentioned	4
Elsmann et al. 1991	To facilitate clinical decisions the authors report on	Retrospective evaluation (1974-1989)	83 melanoma patients LMM n=64	Local recurrence	n=1 (skin metastasis) RT after total	Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	their results using soft X-ray therapy of primary melanomas	Treatment: Soft X-ray 30 - 100kV TD 48 - 105 Gy, fraction size 3.5 - 7 Gy after total excision n=23 after partial excision n=41 without prior excision n=19	SSM n=8 NMM n=6 Not classified n=5 pT1 n=17 pT2 n=13 pT3 n=19 pT4 n=13 pT classification not available n=2 not biopsied n=19	Survival	excision n=1 (recurrent tumor nodule) RT without total excision 60%, (melanoma deaths 9.6%, other diseases 30.1%) Follow-up median 42 months		
Harwood et al. 1983	To review the results of radiation treatment of 51 patients with LM and LMM.	Retrospective evaluation (1958-1982) Treatment: LMM 125, 140 or 175 KEV	28 patients with Lentigo maligna melanoma	Local recurrence or residual tumor No local recurrence Not assessable	n=2 (7%) n=23 (82%) n=3 (11%)	Lack of control group	4

Ausgeschlossene Studien

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Zygiogianni et al. 2011	To assess the potential impact of radiotherapy (RT) on local control, quality of life and	Review	Pubmed 1978 - 2010			Non systematic Review, excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	overall survival						
Newlin et al. 2005	To report our experience with neurotropic melanoma	Case Series Treatment: Surgery + x-rays (6 MV)	3 patients with neurotropic melanoma received RT after incomplete excision (n=2) and adjuvant RT after complete excision (n=1)	Local control	1 patient: recurrence in a regional lymph node after 30 months 2 patients disease-free (after 34 and 14 months)	<20 patients, study excluded	
Cooper et al. 2001	To report our initial results with elective radiation therapy after definitive surgery for selected patients who have high-risk malignant melanomas.	Retrospective evaluation Treatment: Surgery + 6Gy per fraction, 5 or 6 fractions	40 patients with high-risk malignant melanomas 29 patients with recurrent primary or regional disease 9 patients: close or microscopically involved surgical margins	5-year local-regional control rate	84%	majority of patients received RT for recurrent disease. Analyses were performed together for the very heterogenous group, study excluded	
Seegenschmiedt et al. 1999	To analyze relevant endpoints (tumor response, local tumor control, survival) and to identify prognostic factors for achievement of	Retrospective evaluation Treatment: linac 6–10 MV photons or 4–18 MeV electrons	2 917 melanoma patients 121 received RT, thereof 11 patients with relapsed/residual MM (UICC IIB)	Response at 3 months Recurrence rate In-field local relapse	CR n=7 (64%) PR n=4 (36%) n=3 (27%) n=2 (18%) n=1 (9%)	<20 patients RT primary tumor, study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<i>these endpoints in long-term follow-up (FU)</i>			<i>Regional in-transit metastases</i>	<i>of 11 patients</i>		
<i>Tsang et al.</i>	<i>To report the experience with radiotherapy for lentigo maligna</i>	<i>Retrospective evaluation</i>	<i>54 patients with lentigo maligna</i>			<i>No patients with lentigo maligna melanoma study excluded</i>	<i>4</i>
<i>Umebayashi et al 1995</i>	<i>To answer whether or not the proton beam can provide useful treatment for cutaneous melanoma</i>	<i>Case series</i> <i>Treatment: proton beam, total dose of around 100 Gy, fractionated into single doses of approximately 10 Gy</i>	<i>7 patients</i> <i>with 5 primary melanomas and 3 metastatic lymph nodes</i>	<i>Regression primary melanoma</i>	<i>100% n=1 90% n=2 80% n=1 85% n=1</i>	<i><20 patients, study excluded</i>	
<i>Rounsaville et al. 1988</i>	<i>Radiotherapy in the management of cutaneous melanoma: effect of time, dose, and fractionation</i>	<i>Review</i>				<i>Non systematic Review, excluded</i>	
<i>Von Rottkay et al. 1987</i>	<i>Radiation therapy in malignant melanoma using accelerated fractionation. Remission and</i>	<i>Retrospective evaluation (1982-1985)</i>	<i>14 patients at different clinical stages</i>			<i><20 patients, different stages, study excluded</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<i>preliminary results of local tumor control</i>						
<i>Blake et al. 1985</i>	<i>To report the results of treatment of malignant melanoma by fast neutrons</i>	<i>Retrospective evaluation Treatment: 1560cGy in 12 fractions (4 weeks) or 1395cGy in 6 fractions (2 weeks)</i>	<i>7 patients with primary melanomas (of 48 melanoma patients with 87 tumors)</i>	<i>Response</i>	<i>CR n=6 (86%) of 7 primary melanomas</i>	<i><20 patients, study excluded</i>	
<i>Overgaard et al. 1980</i>	<i>Radiation Treatment of malignant melanoma</i>	<i>Retrospective evaluation (1970-1980) Treatment: Different fractions and dose schedules</i>	<i>36 patients with 24 skin lesions and 25 lymph node metastases</i>	<i>Response CR PR No response Progression CR PR No response Progression</i>	<i>skin lesions n=24 n=7 n=10 n=6 n=1 lymph node metastases n=25 n=5 n=10 n=8 n=2</i>	<i>Baseline characteristics missing primary melanomas and skin metastases are not distinguished study excluded</i>	
<i>Tonak et al. 1976</i>	<i>To present the treatment results of 195 melanoma patients (clinical stages I and II)</i>					<i>published before 1980, study excluded</i>	
<i>Von Lieven et al.</i>	<i>To investigate the</i>					<i>published before</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
1976	<i>correlation between the total dose needed for a local healing and the period of treatment</i>					<i>1980, study excluded</i>	
König et al. 1970	<i>Problems in the radiological treatment of malignant melanomas of the skin. Report on 136 patients followed-up over long period of time</i>					<i>published before 1980, study excluded</i>	
Stein et al. 1965	<i>The avoiding of a combination-effect in combined surgical-radiological treatment of malignant skin tumors</i>					<i>published before 1980, study excluded</i>	
Hellriegel et al. 1963	<i>To present radiotherapeutic improvements and results in malignant melanomas</i>					<i>published before 1980, study excluded</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Wernsdoerfer et al. 1960	On the treatment and prophylaxis of malignant melanoma skin tumors					published before 1980, study excluded	
Spoljar et al. 1959	The treatment of malignant melanoma					published before 1980, study excluded	
Nitter et al. 1956	The treatment of malignant melanoma with special reference to the possible effect of radiotherapy					published before 1980, study excluded	
Greve et al. 1952	Roentgen irradiation of skin tumors					published before 1980, study excluded	

7.1.5. Literatur

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7.2. Frage VI.2. und VI.3. Radiotherapie Intransit- und Fernmetastasen

Frage VI.3. Welche Radiotherapie-Indikationen bestehen im Stadium der Fernmetastasierung?

Frage VI.2. Hat eine Radiotherapie von Satelliten- und In-transit-Metastasen einen Einfluss auf das Progressionsfreie Überleben oder Gesamtüberleben?

7.2.1. PICO, Suchwörter

PICO – Schema (Intransitmetastasen)

Population	Intervention	Comparison	Outcome
Melanoma patients with satellite or intransit metastases	radiotherapy	no radiotherapy	PFS, OS

Suchwörter (Intransitmetastasen)				
Stichwort	Melanoma	radiotherapy	Satellite metastases	salvage
Synonyme		Radiation, irradiation	Satellite metastasis, In-transit metastases, In-transit metastasis, Intransit metastases, Intransit metastasis	
Ober-/Unterbegriffe	cutaneous, skin, subcutaneous		Local recurrence, Locoregional recurrence, Locoregional spread, Locoregional metastases, Locoregional metastasis, relapse	relapse
Mesh Term	melanoma	radiotherapy, radiation	Neoplasm Recurrence, Local	

PICO - Schema (Fernmetastasen)			
Population	Intervention	Comparison	Outcome
Melanoma patients with distant metastases, Stage IV	radiotherapy	no radiotherapy	Lesion response, overall response, survival, toxicity, quality of life

Suchwörter (Fernmetastasen)				
Stichwort	melanoma	radiotherapy	Postoperative palliative	metastases
Synonyme		Radiation, irradiation		Stage IV
Ober-/Unterbegriffe		radiosurgery		lung, pulmonal bone spinal cord spine liver, hepatic visceral skin, dermal
Mesh Term	melanoma			

7.2.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie (Intransitmetastasen)	Datum	Treffer
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH]) AND ("Satellite metastases" OR "Satellite metastasis" OR "In-transit metastases" OR "In-transit metastasis" OR "Intransit metastases" OR "Intransit metastasis" OR "Local recurrence" OR "Locoregional recurrence" OR "Locoregional spread" OR "Locoregional metastases" OR "Locoregional metastasis" OR "Neoplasm Recurrence, Local"[MeSH]) NOT (uvea*[ti] OR anorectal[ti] OR mucosal[ti])	14.04.11	477

Datenbank	Suchstrategie (Intransitmetastasen)	Datum	Treffer
Medline – erweiterte Suchstrategie	(melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH] OR irradiation) AND (skin OR cutaneous OR subcutaneous OR "Satellite metastases" OR "Satellite metastasis" OR "In-transit metastases" OR "In-transit metastasis" OR "Intransit metastases" OR "Intransit metastasis" OR "Local recurrence" OR "Locoregional recurrence" OR "Locoregional spread" OR "Locoregional metastases" OR "Locoregional metastasis" OR "Neoplasm Recurrence, Local"[MeSH] OR salvage OR relapse) NOT (uvea*[ti] OR anorectal[ti] OR mucosal[ti])	04.07.11	4872
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation) and (skin or cutaneous or subcutaneous or Satellite metastases or Intransit metastases or Locoregional metastases or salvage or relapse or recurrence or locoregional spread)).ti,ab.	10.06.11	33
Embase	(melanoma and (radiotherapy or radiation or irradiation) and (skin or cutaneous or subcutaneous or Satellite metastases or Intransit metastases or Locoregional metastases or salvage or relapse or recurrence or locoregional spread)).ti,ab.	11.05.11	2710
Update Suche			
Medline	s.o.	31.01.12	4980 (0 dazu)
Cochrane Library	s.o.	31.01.12	33 (0 dazu)
Embase	s.o.	23.01.12	2889 (0 dazu)
Gesamttreffer			7902

Datenbank	Suchstrategie (Fernmetastasen)	Datum	Treffer
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiation[MeSH] OR radiosurgery[tiab] OR irradiation[tiab]) AND (postoperative[tiab] OR palliative[tiab] OR metastas*[tiab] OR "stage IV"[tiab] OR lung[tiab] OR pulmonal[tiab] OR bone[tiab] OR "spinal cord"[tiab] OR "spine"[tiab] OR liver[tiab] OR hepatic[tiab] OR visceral[tiab] OR skin[tiab] OR dermal[tiab])	16.05.11	3273
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation or radiosurgery) and (postoperative or palliative or metastasases or "stage IV" or lung or pulmonal or bone or "spinal cord" or "spine" or liver or hepatic or visceral or skin or dermal)).ti,ab.	19.05.11	28
Embase	(melanoma and (radiotherapy or radiation or irradiation or radiosurgery) and (postoperative or palliative or metastasases or "stage IV" or lung or pulmonal or bone or "spinal cord" or "spine" or liver or hepatic or visceral or skin or dermal)).ti,ab.	11.05.11	2915
Update Suche			
Medline	s.o.	31.01.12	3359 (0 dazu)
Cochrane Library	s.o.	31.01.12	28 (0 dazu)
Embase	s.o.	23.01.12	3032 (0 dazu)
Gesamttreffer			6419

7.2.3. Auswahlkriterien

Auswahl der Literatur (Intransit- und Fernmetastasen)	
Gesamttreffer (Intransit- und Fernmetastasen)	14321
Einschlusskriterien	Arbeiten die die Radiotherapie von Fern- und Intransitmetastasen bei Patienten mit metastasiertem Melanom beschreiben Mangels RCT´s Einschluss von Kohortenstudien und Fallserien ab 20 Patienten, bzw. ab 20 Läsionen (bei Angabe von läsionsbezogenen Responsedaten) Sprachen: e,dt
Ausschlusskriterien	ausschliesslich ZNS Metastasen (siehe Frage VI.4.) Kollektive mit gemischten Tumorentitäten Nicht systematischer Review Publikation vor 1980
Anzahl ausgewählter Volltexte	23
Bemerkungen: Da zum Thema keine randomisierten Studien existieren, wurden Fallberichte aufgenommen (Level 4). Kollektive mit ausschliesslicher ZNS Metastasierung wurden ausgeschlossen. Arbeiten mit historischen Verfahren (Bremer et al. 1999) wurden ausgeschlossen. Aufgrund der Überlappung der gefundenen Arbeiten aus beiden Suchen wurden diese in einer gemeinsamen Evidenztabelle zusammengefasst	

7.2.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Overgaard et al. 2009 (original publication 1996)	To investigate the value of hyperthermia as an adjuvant to radiotherapy in	RCT Treatment RT vs RT+Hyperthermia	70 patients, 134 lesions, skin lesions: n=93	Response	128 evaluable tumors, RT vs RT + HT CR: 35% vs 62% ,	Randomisation based on lesions, not on patients Response assessment was	4 1b (question RT vs RT + HT)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	treatment of malignant melanoma	(HT) RT; high voltage photons or electrons		Overall 5-year Survival Rate	sign., p=0.003 PR: 37% vs 27% n.s. NR: 28% vs 11% n.s. 68 evaluable patients: 19%	not blinded response was not analyzed separately for node and cutaneous lesions	
Richtig et al. 2005	To evaluate the organ-specific response rate, local response rate of each therapeutic measure and survival of 68 patients with stage IV disease	Retrospective evaluation Treatment: RT: TD 30 - 50 Gy, fraction size 2 - 4 Gy Gama knife Surgery Local hyperthermia Chemotherapy	68 patients with unresectable stage IV disease 46 treatment periods radiotherapy (total: 410 treatment periods)	Response	CR+PR (in regard to treatment periods): Total 12/46 (26%) Lymph Node 3/9 Bone 0/10 Cutaneous / subcutaneous 2/3 Other 2/3 Brain 5/21	No patient related response data available	4
Kirova et al. 1999	To assess the response rate and efficacy of palliative radiation therapy in patients with metastatic melanoma	Retrospective evaluation Treatment (most patients): TD 30 or 20 Gy, fraction size 3 or 4 Gy	28 patients, 35 sites, bone and soft tissue metastases n=20, brain metastases n=8	Response	Clinical response bone metastases 67%	Response was defined as relief of symptoms Lack of response and survival data	4
Seegenschmiedt et al. 1999	To analyze different endpoints	Retrospective evaluation	121 patients of a melanoma registry	Response	Stage IV (n=53), at 3 months	Detailed analyses, large cohort,	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	and prognostic factors in patients with locally advanced, recurrent or metastatic melanoma	Treatment: median TD 48 (range 20 - 66) Gy, fraction size 2-6 Gy	with 2,917 patients Stage IV n=53 (distant LN, SK, ST mets n=7, visceral organ mets n=46)	Suvival Rate (mean follow up 7.8 years)	CR n=9 (17%) PR n=17 (32%) NC n=12 (23%) PD n=15(28%) Stage III (n= 57) CR n=25 (44%) PR n=19 (33%) NC n=5 (9%) PD n=8 (14%) Stage IV 6% Stage III 30%)	Results are reported separately for different stages, stage III includes lymph node and intransit-metastases response was not analyzed separately for node and cutaneous lesions	
Engin et al. 1993	To present the experience with hyperthermia combined with radiation in advanced melanoma patients between 1980-1988	Retrospective evaluation Treatment: RT mean TD 37 (range 13 - 66) Gy, mean fraction size 3.6 Gy (range 2 - 5.5) combined with hyperthermia	40 melanoma patients with 48 lesions, Stage IV lesions n=26	Response	Evaluable lesions (n=33) CR n=12 (36%) PR n=17 (52%)	WHO/UICC criteria were used to assess tumor response	4
Pyrhönen et al. 1992	To present 15 patients with histologically proven recurrent or metastatic	Case Series Treatment: Electron beams at appropriate	15 melanoma patients, 89 treated lesions skin n=68 (76%) transplanted skin	Response	Evaluable lesions (n=89) CR n=61 (69%) PR n=25 (28%)		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cutaneous melanomas treated with large fractions between April 1987 and May 1991	energies (6-15 MeV). A total dose of 40 Gy was given in 8 fractions (fraction size 5 Gy) over 23 days.	n=3 (3 %) subcutaneous n=11 (12%) lymph nodes n=7 (8%)		No response n=3 (3%)		
Herbert et al. 1991	To evaluate the efficacy of palliative radiation therapy in the treatment of spinal cord and cauda equina compression due to metastatic malignant melanoma	Retrospective evaluation Treatment: RT (all patients), decompressive laminectomy (n=11), steroids (n=32) RT: cobalt-60, 6 or 15 MV, median TD 2850 cGy (range, 500 to 4000 cGy), fraction size 200-800 cGy	35 patients with spinal cord and cauda equina compression, 38 sites treated	Response Median Overall Survival (OS)	28 sites (in 26 patients) evaluable CR 11 sites (39%) PR 13 sites (46%) ORR 24 sites (86%) OS all patients: 11 weeks (range 4 - 35 weeks)	multivariate analysis performed but not presented in detail, small sample size	4
Chadha et al. 1990	To evaluate the role of brachytherapy in the management of locally advanced malignant melanoma.	Retrospective evaluation (1979-1986) Treatment: brachytherapy, temporary and	33 melanoma patients with locally advanced disease with/without nodal disease or distant metastases	Local control/Implant site:	33 patients 80% at 6 months 42% at 1 year Extremity vs. Intrathoracic and	Baseline characteristics are not presented in detail, clinical stages not indicated	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		permanent implants, different doses			chest wall vs. Gynecologic & intra-abdominal vs. Head and neck n=13 of 14 vs. n=4 of 9 vs. n=3 of 7 vs. n=0 of 2		
Konefal et al. 1988	To see if the use of larger dose fractions increased the rate of palliation of visceral melanoma metastases	Retrospective evaluation Treatment: TD range <2000 - 5000 cGy, fraction size < 200 to > 600	63 patients, 89 visceral metastases treated, 65 evaluable	Response	40 of 65 lesions (62%) 19 of 28 bone metastases (68%)	response was defined as the significant relief from symptoms for at least 2 months	4
Rate et al. 1988	To present the experience with palliative radiotherapy for malignant melanoma metastatic to brain, to bone, or with spinal cord compression.	Retrospective evaluation Treatment: TD 1100 - 4000 cGy, fraction size 115 cGy - 1100 cGy	26 patients with 39 bone metastases, 17 patients with spinal cord compression	Response	Bone: 33 of 39 lesions (85%) Spinal cord compression: (8/17) 47% Partial palliation 24% (4/17).	response was defined as pain relief	4
Rounsaville et al. 1988	To review the experience of	Retrospective evaluation	81 patients 29 patients (51	Response	Measurable tumor: CR 4 of 51 sites	Definition response in bone	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	three San Francisco radiation oncology departments	Treatment: TD range 600 – 7700 cGy, fraction size 180 - 1000	sites) with measurable tumor (Lymph node, skin, liver, mucosa, spleen) 15 patients (28 sites) with bone metastases		(8%) PR 22 of 51 sites (43%) Bone metastases: 24 of 28 sites (86%)	metastases: marked regression or elimination of pain	
Mameghan et al. 1988	To assess the acute skin reaction after treatment and to measure the response of the melanoma	Case Series Treatment: Radiotherapy alone (15 lesions) Heat therapy alone (6 lesions) Combined radiation and heat therapy (11 lesions)	12 melanoma patients with 32 lesions subcutaneous tissue n=26 Lymph node n=5 Cheek n=1	Response	All lesions (n=32) CR n=14(44%) PR n=10(31%) No response n=2(6%) Not evaluable n=6 (19%) Lesions treated with radiotherapy alone (n=15) CR n=8 PR n=2 No response n=1 Not evaluable n=4		4
Konefal et al. 1987	To retrospectively analyze the results of 67 cutaneous or lymph node metastatic lesions,	Retrospective evaluation (1970-1985) Treatment:	35 melanoma patients with 67 cutaneous or lymph node metastatic lesions,	Response	All lesions (n=67) Overall Tumor Control n=14 CR n=16	Overall tumor control indicates that lesions were controlled at the time of patient´s	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	focusing on dosetime fractionation and tumor response	TD 18-66 Gy, fraction size 1.5 - 8 Gy, intervals daily to weekly	30 cutaneous lesions		PR n=23 No response n=28	death or at last follow-up PR was defined as >50% reduction of tumor size	
Overgaard et al. 1987	To present the experience with hyperthermia and radiotherapy in metastatic melanoma patients	Retrospective evaluation Treatment: - Radiation alone (TD 15-30 Gy) n=62 sites - Simultaneous heat plus radiation n=26 - Sequential radiation plus heat n=27 - heat alone n=3	36 patients, many patients with disseminated disease, 118 lymph node and cutaneous metastases	Response	102 lesions evaluable CR n=57 (56%) PR n=32 (31%) NR n=13 (13%)	Patient baseline characteristics are missing, no response data available for tumors treated with radiation alone. PR was defined as >50% reduction of tumor size	4
Overgaard et al. 1986	Some factors of importance in the radiation treatment of malignant melanoma	Retrospective evaluation Treatment: TD median 40 Gy, range 8-77, fraction size median 5 Gy, range 2 - 11, number of	204 cutaneous or lymph node lesions in 114 patients with recurrent or metastatic melanoma, 45 patients with only local or regional disease	Local tumor control 3 year survival	45 patients with regional disease n=26 of 45 (58%) 56%	Baseline characteristics are not presented in detail, clinical stages not indicated, response for node and cutaneous lesions was not analyzed	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		fractions median 10, range 1-27.				separately	
Blake et al. 1985	Treatment of malignant melanoma by fast neutrons	Retrospective evaluation Treatment: 75 MeV neutron beam, TD 1560 or 1395 cGy in 12 or 6 fractions	48 patients, 87 primary, recurrent or metastatic tumors	Response Recurrence Complications	All sites n= 87 CR n=62 (71%) n=8 (9%) n=19 (22%)	Baseline characteristics are not presented in detail, clinical stages not indicated, response for primary, recurrent or metastatic lesions was not analyzed separately	4
Khan et al. 1984	To evaluate the results of different modes of treatment the records of 182 melanoma patients, referred to the Regional Radiotherapy Centre, Newcastle upon Tyne between January 1975 and December 1980	Retrospective evaluation Treatment: external beam radiotherapy (collimated beam from cobalt-60 and caesium-137 teletherapy units, or 100-250 keV or 4-8 MeV X-rays) different fractionation	63 melanoma patients (42 Stage 2, 21 Stage 3) with 74 sites of disease (skin and lymph nodes, 58; bone, 8; brain, 8)	Response Duration of remission	Overall response rate 73% CR 47% PR 26% Sites with skin and lymph node metastases (58): CR 35 (60%) PR 8 (14%) Bone metastases (8): CR 0		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	have been reviewed	regimes and tumor doses			PR 6 (75%) Median duration of remission 7 months (range 1-72)		
Johanson et al. 1983	To report the the experience of the Princess Margaret Hospital with large dose per fraction (800 rad) radiotherapy in the curative and palliative treatment of nodular melanoma	Retrospective evaluation (1975-1980) Treatment: TD 2400 rad, fraction size 800 rad, given on day 0, day 7, and day 21	23 patients with recurrent melanoma	Response	n= 23 patients CR, no local recurrence n=7 CR, local recurrence n=2 PR n=5 SD n=3 no response n=6	clinical stages not indicated, response was not analyzed separately	4
Doss et al. 1982	To review the institutional experience	Retrospective evaluation Treatment: TD range 500 to <4500 cGy, fraction size 100 - 1250	27 patients, 41 lesions	Response	CR 15/41 (37%)	Definition complete response: disappearance of measurable lesions, symptoms ceased within 2 months after RT	4
Adam et al. 1982	Response rate of malignant melanoma to large		22 patients, 24 sites, visceral sites n=2				

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	fraction irradiation						
Katz et al. 1981	To determine if results in the irradiation of soft tissue, visceral, and bone metastases were comparable to those previously reported in the literature	Retrospective evaluation Treatment: TD range 1000 to 6000 rad, fraction size 200 - 1000 rad	86 patients 16 patients with visceral metastases (20 lesions) 32 patients with bone metastases (48 lesions) 8 patients with skin metastases (14 lesions)	Response	Visceral lesions 13 of 20 lesions (65%) Bone lesions 37 of 48 lesions (77%)	Definition response: subjective decrease in bone pain, reduction in size to a degree which significantly relieved the local tumor-associated symptoms	4
Lobo et al. 1981	To evaluate the experience in the radiotherapeutic management of patients with malignant melanoma	Retrospective evaluation Treatment: (bone lesions) TD range 2700-3000 rad, fraction size 300 rad	45 patients, 69 lesions Bone n=22, lung n=3, liver n=3	Response	bone: 15 of 22 (68%) lung: 1 of 3 liver 0 of 3	Response was defined as improvement of symptoms	4
Strauss et al. 1981	To evaluate clinical responses of metastatic melanoma to four radiation dose fractionation	Retrospective evaluation Treatment: fraction size 180 rad to 800 rad	48 patients, 83 sites	Response	Soft tissue: 29 of 46 sites (63%) Bone: 7 of 9 sites	Response was defined as improvement of symptoms	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	schemes.						

7.2.5. Literatur

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7.3. Frage VI.4. Radiotherapie und Chirurgie Hirnmetastasen

Frage VI.4. Wie ist der Einfluss unterschiedlicher Behandlungsmodalitäten und deren Kombinationen (Operation, Ganzhirnbestrahlung, Einzeitbestrahlung) auf das Gesamtüberleben, die lokale Kontrolle, die intrakranielle Kontrolle, Verlängerung der symptomfreien Zeit und Lebensqualität bei Patienten mit cerebralen Metastasen?

7.3.1. PICO, Suchwörter

PICO - Schema

Population	Intervention	Comparison	Outcome
Melanoma patients with cerebral metastases	Radiotherapy, surgery, stereotactic radiosurgery, combinations	no therapy	OS, local control, time without symptoms, QoL

Suchwörter

Stichwort	Melanoma	radiotherapy	surgery	brain
Synonyme		Radiation, irradiation	resection, excision	Cerebral CNS Central Nervous System
Ober-/Unterbegriffe		Stereotactic radiosurgery		
Mesh Term	melanoma	radiotherapy, radiation		

7.3.2. Datenbanken, Suchstrategien, Trefferzahlen

7.3.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH] OR "Irradiation"[tiab] OR Stereotatic[tiab] OR radiosurgery[tiab] OR surgery[tiab] OR resection[tiab] OR excision[tiab]) AND (brain[tiab] OR cerebral[tiab] OR CNS[tiab] OR "Central Nervous System"[tiab])	19.09.11	874 (Auswahl 64)
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation or stereotatic or radiosurgery or surgery or resection or excision) and (brain or cerebral or CNS)).ti,ab.	19.09.11	10 (Auswahl: Mornex, Dublette, zusätzliche Auswahl 0)
Embase	(melanoma and (radiotherapy or radiation or irradiation or stereotatic or radiosurgery or surgery or resection or excision) and (brain or cerebral or CNS)).ti,ab.	10.05.11	823 (zusätzliche Auswahl 0)
Update Suche			
Medline	s.o.	31.01.12	889 (0 dazu)
Cochrane Library	s.o.	31.01.12	10 (0 dazu)
Embase	s.o.	23.01.12	903 (0 dazu)

7.3.2.2. Aktualisierungsrecherche 2015

Datenbank	Suchstrategie	Datum	Treffer
Medline	((((melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH] OR "Irradiation"[tiab] OR Stereotatic[tiab] OR radiosurgery[tiab] OR surgery[tiab] OR resection[tiab] OR excision[tiab]) AND (brain[tiab] OR cerebral[tiab] OR CNS[tiab] OR "Central Nervous System"[tiab]))) AND ("2011.09.20"[Date - Publication] : "2015.09.16"[Date - Publication]))	16.09.2015	246
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation or stereotatic or radiosurgery or surgery or resection or excision) and (brain or cerebral or CNS)).ti,ab.	16.09.2015	39

7.3.3. Auswahlkriterien

7.3.3.1. Primärrecherche 2012

Auswahl der Literatur		
Gesamttreffer		1802
Einschlusskriterien	Studien, die mind. einen der Parameter Gesamtüberleben, lokale Kontrolle, symptomfreie Zeit oder Lebensqualität bei Melanompatienten nach Radiotherapie oder Operation von Hirnmetastasen beschreiben Sprachen: e,dt	
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitäten	
Erweitertes Ausschlusskriterium	Studien ohne Vergleichsgruppe Retrospektive Kohortenstudie ohne Multivariatanalyse Publikation vor 1980	
Anzahl nach Abstractscreening, vorgesehen für Bewertung		64

Auswahl der Literatur	
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	57
Anzahl ausgewählter Volltexte	7

7.3.3.2. Aktualisierungsrecherche 2015

Auswahl der Literatur	
Gesamttreffer	285
Einschlusskriterien	Studien, die mind. einen der Parameter Gesamtüberleben, lokale Kontrolle, symptomfreie Zeit oder Lebensqualität bei Melanompatienten nach Radiotherapie oder Operation von Hirnmetastasen beschreiben RCTs Systemische Reviews Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitäten Non-RCTs
Erweitertes Ausschlusskriterium	Studien ohne Vergleichsgruppe Retrospektive Kohortenstudie ohne Multivariatanalyse Publikation vor 1980
Anzahl nach Abstractscreening, vorgesehen für Bewertung	64
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	57
Anzahl ausgewählter Volltexte	3

7.3.4. Evidenztabelle

7.3.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Eigentler et al. 2011	To identify prognostic factors in patients with brain metastases (BM) from malignant melanoma	Retrospective survival analysis Treatment: SRS + Surgery (n=122) WBRT + Chemotherapy (n=92)	692 patients	Median Survival (from date of diagnosis of brain metastases)	Entire cohort (n=672) 5 months SRS + Surgery vs. WBRT + Chemotherapy Single BM: 9 vs. 6 months, p=0.036 <3 BM: 6 vs. 7 months, p=0.448 <u>multivariate analysis</u> independent prognostic factors - entire cohort: single vs. multiple BM, HR 1.6, 95% CI 1.3-2.7, p=0.002 LDH not elevated vs. elevated, HR	Retrospective study large cohort SRS vs. Surgery was not compared Funding: in part by an educational grant from Essex/Schering-Plough.	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					1.6, 95% CI 1.1-2.4, p=0.01 - Single BM: SRS or surgery vs. WBRT and/or chemotherapy, HR 1.5, 95% CI 1.1-1.9, p=0.0061		
Staudt et al. 2010	To identify prognostic factors in patients with brain metastases from cutaneous melanoma	Retrospective survival analysis Treatment: Surgery (n=63) SRS (n=31) WBRT (n=122) chemotherapy (n=28) no therapy (n=12)	265 patients 36.7% had local treatment (neurosurgery or stereotactic radiosurgery (SRS))	Median Survival (from date of diagnosis of brain metastases)	Entire cohort (n=265) 5 months, 95% CI 4.3-5.7 months surgery vs. SRS vs. WBRT vs. chemotherapy vs. no therapy 9 vs. 9 vs. 4 vs. 3 vs. 1 month(s) <u>multivariate analysis</u> independent favourable prognostic factors: LDH level, type of therapy, number of brain metastases, presence of bone	Retrospective study detailed data, few missing cases follow up time not mentioned (but at time of analysis already 253 deaths) Funding: not mentioned	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastasis surgery (n=63) vs. SRS (n=31): HR 1.0, 95% CI 0.6 - 1.8		
Raizer et al. 2008	To gain a better understanding of patient and disease characteristics that have the greatest impact on overall survival in melanoma patients with brain metastases	Retrospective survival analysis Treatment: Surgery (n=126) SRS (n=78) Temozolomide (n=113) WBRT (n=190)	355 patients	Median Survival (from date of diagnosis of brain metastases)	Entire cohort (n=335) 5.2 months (range 0.1 - 155 months) surgery vs. SRS vs. Temozolomide vs. WBRT 9.3 vs. 10.0 vs. 7.9 vs. 6.1 months <u>multivariate analysis</u> surgery: RR 0.56, 95% CI 0.43 - 0.75 SRS: RR 0.69, 95% CI 0.50 - 0.94	Retrospective study Median follow up among surviving patients 18.4 months Funding: Schering-Plough International	3b
Fife et al. 2004	To analyze prognostic factors, effects of treatment, and survival for patients with	Retrospective survival analysis Treatment: surgery+RT (n=158)	1137 patients with cerebral metastases; 686 with therapy	Median survival (from date of diagnosis of brain metastases)	Entire cohort (n=1137) 4.1 months (range, 0 to 17.2 years) Surgery+RT vs.	Retrospective study Large cohort results of univariate analyses not shown, only 578 of 686	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cerebral metastases from melanoma.	surgery (n=47) radiotherapy (n=236) supportive care alone (n=210)			surgery vs. RT vs. supp.care 8.9 vs. 8.7 vs. 3.4 vs. 2.1 months <u>multivariate analysis</u> Prognostic factors: surgical treatment (p<0.0001), no concurrent extracerebral metastases (p<0.0001), younger age (p=0.0007), longer disease-free interval (p=0.036)	patients included missing data not addressed Funding: Supported by the Melanoma Foundation of the University of Sydney and the Melanoma and Skin Cancer Research Institute	
Mornex et al. 2003	To compare a combined regimen of fotemustine plus whole brain irradiation with fotemustine alone	RCT Treatment: Group A: Fotemustine (n = 39) Group B: fotemustine + WBRT (n = 37)	76 patients	Median survival cerebral response after 7 weeks	Group A vs. B (ITT population) 86 days (2.8 months) vs. 105 days (3.4 months) n.s. 5.1% (95% CI 1-17%) vs. 8.1% (95% CI 2-22%), p=0.60	Early termination of study, small sample size Independent tumor assessment Funding: not mentioned	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				control rates (objective responses + stable disease) after 7 weeks	23.1% (95% CI 10-36%) vs. 37.8% (95% CI 22-54%), p=0.16		
				time to cerebral progression	49 days (1.6 months) vs. 80 days (2.6 months), p=0.030		
Wronski et al. 2000	To review the surgical experience in a series of patients with brain metastases from primary melanoma	Retrospective survival analysis Treatment: Surgery alone (n=29) Surgery + WBRT (n=49)	91 patients	Median survival following craniotomy survival rates 1 year 2 years 3 years 5 years	Entire cohort (n=91) 6.7 months 36.3% 18.7% 13.2% 6.6% Surgery alone (n=29) vs. Surgery+WBRT (n=49) 8.3 vs. 9.5 months, p = 0.67 <u>multivariate</u>	Retrospective study, small sample size, results of multivariate analyses not presented in detail Funding: not mentioned	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<u>analysis</u> negative impact on survival: lack of resection of recurrent brain tumor (p =0.0003) and infratentorial location of brain metastases (p = 0.0013)		
Stevens et al. 1992	To analyze factors affecting survival in 129 patients with cerebral metastases from malignant melanoma	Retrospective survival analysis Treatment: Radiotherapy (n=74) Surgery + Radiotherapy (n=45)	129 patients	Median survival after detection of cerebral metastases	Entire cohort (n=127) 5 months Radiotherapy vs. Surgery + Radiotherapy 4 vs. 9 months (p<0.001) <u>multivariate analysis</u> Independently associated with a prolonged survival: Surgery, p=0.004	Retrospective study, multivariate analysis not presented in detail Funding: not mentioned	3b

Ausgeschlossene Studien

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Lonser et al. 2011	to determine the effectiveness of resection and the effects of immunotherapy on brain metastasis management	Retrospective analyses Treatment: Surgery, Immunotherapy, whole brain radiation	41 patients		Duration of survival from brain metastasis diagnosis was not significantly different between patients who received WBRT (mean 24.9 months) and those who did not (mean 23.3 months) ($p > 0.05$)	Combination with Immunotherapy → study excluded	
Salvati et al. 2011	To report on 84 patients with single melanoma brain metastasis surgically treated from 1997 to 2007	Retrospective analysis Treatment: Surgery	84 patients with single melanoma brain metastasis	1-year survival rate 2 years survival rate	52% (32 patients) 14% (12 patients)	Lack of comparison group → study excluded	
Skeie et al. 2011	To review a series of patients who underwent Gamma Knife surgery (GKS)	Retrospective analysis Treatment: Gamma Knife	77 patients with a total of 143 metastases	Growth control median survival after GKS	59 of 70 (84.3%) patients 7 months (range 0-73 months)	Lack of comparison group → study excluded	
Rades et al. 2010	To investigate a potential benefit from escalation of	Retrospective analysis, Cohort study	51 patients		Standard vs. high dose	Lack of comparison group → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<i>the whole-brain radiotherapy (WBRT) dose beyond the "standard" regimen 30 Gy in 10 fractions</i>	<i>Treatment: WBRT 10x3 Gy (n = 33) 40 Gy/20 fractions (n = 11) 45 Gy/15 fractions (n = 7)</i>		<i>6 months survival (OS) 12 months OS 6 months local (intracerebral) control (LC) 12 months LC</i>	<i>27% vs. 50% (p = 0.009) 4% vs. 20% 23% vs. 50% 0% vs. 13%.</i>		
<i>Redmond et al. 2008</i>	<i>To investigate which patient- or treatment-specific factors influence survival of patients with melanoma brain metastases</i>	<i>Retrospective analysis, Prognosis study Treatment: GKS</i>	<i>59 patients</i>		<i>Survival was significantly better in patients with solitary metastasis (p = 0.04), lesions without evidence of pre-GKS hemorrhage (p = 0.004), and in patients with total tumor volume treated < 4 cm(3) (p = 0.02)</i>	<i>Lack of comparison group → study excluded</i>	
<i>Mathieu et al. 2007</i>	<i>to assess clinical outcomes and identify prognostic factors for survival and cerebral disease control after Gamma knife</i>	<i>Retrospective analysis, Prognosis study Treatment: GKS</i>	<i>244 patients</i>	<i>median survival Sustained local control</i>	<i>5.3 months 86.2% of tumors</i>	<i>Lack of comparison group → study excluded</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	radiosurgery						
Hofmann et al. 2007	To examine prognostic factors and the evaluation of different treatment options	Retrospective survival analysis Treatment: Surgery (n=34) SRS (n=43) WBRT (n=33) corticosteroids (n=63)	133 patients	Median Survival (from date of diagnosis of brain metastases)	Entire cohort (n=133) 24 weeks (5.1 months) (range 1-196 weeks) surgery vs. SRS vs. WBRT vs. corticosteroids: 57 vs. 40 vs. 24 vs. 17 weeks	univariate analysis is missing, small sample size → study excluded	
Samlowski et al. 2007	To report a retrospective analysis of our institutional experience of multimodality treatment utilizing linear accelerator (Linac)-based stereotactic radiosurgery (SRS)	Retrospective analysis Treatment: stereotactic radiosurgery (SRS)	44 patients	median survival with brain metastases 1-year survival 2-year survival	11.1 months (95% confidence interval [CI]: 8.2-14.9 months) from diagnosis 47.7% 17.7% Addition of WBRT to maintain control of brain metastases in a subset of patients did not improve survival	Lack of comparison group → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
<i>Christopoulou et al. 2006</i>	<i>To investigate the effect of gamma knife surgery on the local control of cerebral metastases from melanoma and to assess survival</i>	<i>Retrospective analysis Treatment: GKS</i>	<i>29 patients</i>	<i>local control median survival from gamma knife surgery</i>	<i>61.5% of 96 metastases regressed by more than 50% of the pretreatment volume, 25% regressing by more than 90% and 13.5% completely</i>	<i>Lack of comparison group → study excluded</i>	
<i>Gaudy-Marqueste et al. 2006</i>	<i>To assess retrospectively a strategy that uses Gamma-Knife radiosurgery in the management of patients with brain metastases of malignant melanoma</i>	<i>Retrospective analysis Treatment: GKS</i>	<i>106 patients, 221 brain metastases</i>	<i>Median survival from the time of GKR Control rate complete response partial response stabilization</i>	<i>5.09 months 83.7% 14% (14 BMs) 42% (41 BMs) 43% (43 BMs)</i>	<i>Lack of comparison group → study excluded</i>	
<i>Koc et al. 2005</i>	<i>To evaluate retrospectively the effectiveness of Gamma Knife radiosurgery for intracranial metastatic</i>	<i>Retrospective analysis Treatment: GKS</i>	<i>26 patients, 72 brain metastases</i>	<i>Overall median survival after GKS 1-year survival</i>	<i>6 months 25%</i>	<i>Lack of comparison group → study excluded</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<i>melanoma and to identify prognostic factors related to survival</i>						
<i>Meier et al. 2004</i>	<i>to determine the factors influencing survival in a retrospective review of patients with melanoma brain metastases to permit more specific recommendations regarding therapy</i>	<i>Retrospective survival analysis Treatment: WBRT (n=54) surgery (n=37) SRS (n=17) chemotherapy (n=38)</i>	<i>100 patients</i>	<i>median overall survival 6-month survival 1-year survival 2-year survival</i>	<i>Entire cohort (n=100) 4.8 months 36% 14% 5% WBRT vs. surgery vs. radiosurgery vs. chemotherapy vs. temozolomide 5.5 vs. 10.6 vs. 10.3 vs. 6.6 vs. 10.1 months</i>	<i>< 20 patients in one of the treatment groups → study excluded Only 63 patients included in multivariate analysis due to missing data</i>	
<i>Morris et al. 2004</i>	<i>To determine the outcome of patients with metastatic malignant melanoma (MMM) treated with palliative whole brain radiotherapy</i>	<i>Retrospective analysis Treatment: WBRT</i>	<i>112 patients</i>	<i>median survival after WBRT</i>	<i>51 days (range 3-1386)</i>	<i>Lack of comparison group → study excluded</i>	

<i>Study</i>	<i>Aims</i>	<i>Design</i>	<i>Population</i>	<i>Outcomes</i>	<i>Results</i>	<i>Comments</i>	<i>LoE</i>
	(WBRT)						
<i>Radbill et al. 2004</i>	<i>To identify associated prognostic indicators for patients receiving gamma knife (GK) radiosurgery in the initial treatment of intracranial melanoma metastases</i>	<i>Retrospective analysis Treatment: GKS</i>	<i>51 patients, 188 brain metastases</i>	<i>median overall survival from time of GKS</i>	<i>26 weeks Subgroup analysis: 77 weeks for patients presenting with a single lesion, compared with 20 weeks for patients presenting with multiple lesions (P = 0.003)</i>	<i>Lack of comparison group → study excluded</i>	
<i>Stone et al. 2004</i>	<i>To evaluate overall survival in patients with brain metastases from malignant melanoma</i>	<i>Retrospective survival analysis Treatment: SRS+WBRT (n=8) Surgery + WBRT (n=16) WBRT (n=59)</i>	<i>91 patients</i>	<i>Overall Survival</i>	<i>A survival benefit of 7.3 months (p = 0.05) was found to be associated with gamma knife radiosurgery or surgical excision plus radiation therapy over radiation therapy alone after controlling for differences in age, number of brain lesions, and presence of symptoms.</i>	<i>< 20 patients in one of the treatment groups → study excluded</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Selek et al. 2004	To report on the outcome of patients with melanoma brain metastases treated with stereotactic radiosurgery (SRS)	Retrospective analysis Treatment: SRS alone (61 patients), SRS + whole-brain radiotherapy (WBRT) (12 patients), and salvage SRS after WBRT (30 patients)	103 patients, 153 intracranial melanoma metastases	1-year local control (LC) for all patients treated with SRS	49%	< 20 patients in one of the treatment groups → study excluded	
Herfarth et al. 2003	Stereotactic radiosurgery is an alternative option to neurosurgical excision in the management of patients with brain metastases.	Retrospective analysis Treatment: Stereotactic radiosurgery	64 patients, 122 brain metastases	Median survival 1 year local control	10.6 months 81%	Lack of comparison group → study excluded	
Buchsbaum et al. 2002	To determine whether various therapies provided any benefit at all in a population of patients with brain metastases from melanoma	Retrospective analysis Treatment: surgical resection, WBRT, stereotactic radiosurgery, or WBRT combined with local therapy	74 patients with brain metastases	median survival was for all patients	5.5 months combined treatment offered significantly better survival ($P < 0.0001$; combined vs. other)	< 20 patients in one of the treatment groups → study excluded	

<i>Study</i>	<i>Aims</i>	<i>Design</i>	<i>Population</i>	<i>Outcomes</i>	<i>Results</i>	<i>Comments</i>	<i>LoE</i>
					<p><i>median survival was 8.8 months (range, 1.8-99.2 months) for the combined therapy group, 4.8 months (range, 1.2-27.8 months) for the local therapy alone group, 2.3 months (range, 0.2-9.6 months) for the WBRT alone group, and 1.1 months (0.1-3.0 months) for the group that received no therapy</i></p>		
<i>Gonzales-Martinez et al. 2002</i>	<p><i>to evaluate retrospectively the effectiveness of stereotactic radiosurgery for intracranial metastatic melanoma and to identify prognostic factors</i></p>	<p><i>Retrospective analysis</i></p> <p><i>Treatment: stereotactic radio surgery</i></p>	<p><i>24 patients, 115 lesions</i></p>	<p><i>mean survival after radiosurgery</i></p>	<p><i>5.5 months</i></p> <p><i>no difference in terms of survival between patients who underwent WBRT or chemotherapy and those who did not</i></p> <p><i>significant difference ($p <$</i></p>	<p><i>Lack of comparison group → study excluded</i></p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					0.05) in mean survival was observed between patients receiving immunotherapy or those with a Karnofsky Performance Scale (KPS) score of greater than 90		
Mingione et al. 2002	To evaluate the usefulness and limitations of gamma surgery in the treatment of brain metastases from melanoma.	Retrospective analysis Treatment: GKS	45 patients, 92 brain metastases	Follow-up imaging studies available: 35 patients, 66 lesions	24% percent of the lesions disappeared, 35% shrank, 23% remained unchanged, and 18% increased in size.	Lack of comparison group → study excluded	
Noel et al. 2002	To evaluate the efficacy and toxicity of stereotactic radiotherapy in the treatment of brain metastases of melanoma.	Retrospective analysis Treatment: stereotactic radiotherapy	25 patients, 61 metastases	Median survival overall survival rates 3- month 6- month 12-month Progression local control rates	8 months 75 +/- 9% 53 +/- 10% 29 +/- 10% n=5 (9.8%) 95 +/- 3%	Lack of comparison group → study excluded	

<i>Study</i>	<i>Aims</i>	<i>Design</i>	<i>Population</i>	<i>Outcomes</i>	<i>Results</i>	<i>Comments</i>	<i>LoE</i>
				3- month 6- month 12-month	90 +/- 5% 84 +/- 7%		
<i>Yu et al. 2002</i>	<i>To identify important prognostic factors predictive of survival and tumor control in patients with metastatic melanoma to the brain who underwent gamma knife radiosurgery</i>	<i>Retrospective analysis</i> <i>Treatment: GKS</i>	<i>122 patients, 332 intracranial melanoma metastases</i>	<i>median overall survival from time of radiosurgery</i>	<i>7.0 months</i>	<i>Lack of comparison group → study excluded</i>	
<i>Zacest et al. 2002</i>	<i>to review the outcome of patients who underwent surgery for treatment of cerebral metastatic melanoma</i>	<i>Retrospective analysis</i> <i>Treatment: surgery</i>	<i>147 patients</i>	<i>median survival from the time of surgery</i>	<i>8.5 months</i>	<i>Lack of comparison group → study excluded</i>	
<i>Ellerhorst et al. 2001</i>	<i>To obtain a description of the population offered WBRT</i>	<i>Retrospective analysis</i> <i>Treatment: WBRT</i>	<i>87 patients</i>	<i>median survival</i>	<i>19 weeks</i>	<i>Lack of comparison group → study excluded</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
<i>Konstadoulakis et al. 2000</i>	<i>To evaluate the prognostic parameters and treatment modalities of malignant melanoma patients with brain metastases</i>	<i>Retrospective analysis Treatment: Surgery surgery + radiotherapy (n=2) surgery + chemotherapy (n=17)</i>	<i>136 patients</i>	<i>1-year survival rate</i>	<i>surgery 28.3% radiotherapy and/or chemotherapy 6.67% no treatment 3.45% (p=0.006)</i>	<i>Subgroups < 20 patients → study excluded</i>	
<i>Lavine et al. 1999</i>	<i>To analyze the effectiveness of Leksell gamma unit therapy for metastatic melanoma to the brain</i>	<i>Retrospective analysis Treatment: GKS</i>	<i>45 patients, 59 Leksell gamma unit treatment sessions</i>	<i>Median overall survival from the time of gamma knife treatment improved or stable neurological symptomatology local tumor control rate</i>	<i>8 months (range, 1-20 months) 78% 97%</i>	<i>Lack of comparison group → study excluded</i>	
<i>Friehs et al. 1998</i>	<i>To determine the effectiveness of gamma knife radiosurgery in patients with malignant melanoma metastases</i>	<i>prospective multicenter study Treatment: GKS</i>	<i>45 patients, 96 lesions</i>	<i>median overall survival tumor control</i>	<i>4.2 months 86% of lesions</i>	<i>Lack of comparison group → study excluded</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
<i>Sampson et al. 1998</i>	<i>To identify demographic factors associated with the development of clinically significant brain metastases in 702 of these patients and to determine the factors influencing the prognosis of this population to permit more informed recommendations regarding surgical therapy</i>	<i>Retrospective survival analysis Treatment: Surgery (n=52) Surgery+WBRT (n=87) WBRT (n=180) Chemotherapy (n=205) Symptomatic treatment (n=178)</i>	<i>702 patients</i>	<i>median overall survival</i>	<i>Entire cohort (n=702) 3.7 months surgery vs. surgery+WBRT vs. WBRT vs. chemotherapy: 8.8 vs. 6.4 vs. 3.9 vs. 1.3 months</i>	<i>no multivariate analysis included → study excluded</i>	
<i>Fletcher et al. 1998</i>	<i>To reviewe the results of surgical resection</i>	<i>Retrospective analysis Treatment: surgery</i>	<i>77 patients, different sites, brain n = 12</i>			<i><20 patients with brain metastases → study excluded</i>	
<i>Grob et al. 1998</i>	<i>To evaluate the effectiveness of radiosurgery without whole brain radiotherapy</i>	<i>Retrospective analysis Treatment: radiosurgery</i>	<i>35 patients</i>	<i>Median overall survival</i>	<i>22 months (solitary brain metastasis) 7.5 months (single brain metastasis +</i>	<i>Lack of comparison group → study excluded</i>	

<i>Study</i>	<i>Aims</i>	<i>Design</i>	<i>Population</i>	<i>Outcomes</i>	<i>Results</i>	<i>Comments</i>	<i>LoE</i>
	<i>in the palliative treatment of melanoma brain metastases</i>			<i>local control rate at 3 months</i>	<i>metastases elsewhere) 4 months (multiple brain metastases) 98.2% (55/56 metastases)</i>		
<i>Mori et al. 1998</i>	<i>To evaluate results after stereotactic radiosurgery (SR) for patients with metastatic melanoma to identify patient outcomes and factors for survival</i>	<i>Retrospective analysis Treatment: SR alone n=9 SR+WBRT n=51</i>	<i>60, 118 melanoma brain metastases</i>	<i>Median survival after SR local control rate of evaluable tumors (n = 72) disappearance shrinkage stable</i>	<i>7 months 90% 11% 44% 35%</i>	<i>< 20 patients in one of the treatment groups → study excluded</i>	
<i>Seung et al. 1998</i>	<i>To evaluate the efficacy and toxicity of gamma knife radiosurgery in the treatment of melanoma metastases to the brain</i>	<i>Retrospective analysis Treatment: GKS</i>	<i>55 patients, 140 lesions</i>	<i>median overall survival</i>	<i>35 weeks 35 weeks for patients with solitary metastases versus 33 weeks for those with multiple metastases</i>	<i>Lack of comparison group → study excluded</i>	
<i>Gupta et al. 1997</i>	<i>To report the experience of 31 patients who</i>	<i>Retrospective analysis</i>	<i>31 patients</i>	<i>median overall survival</i>	<i>4 months</i>	<i>< 20 patients in one of the treatment groups</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	presented with cerebral metastasis of cutaneous melanoma	Treatment: Surgery (n=17) Surgery + radiotherapy (n=6)				→ study excluded	
Gieger et al. 1997	to determine the radiographic response of intracranial metastatic melanomas to SRS	Retrospective analysis Treatment: stereotactic radiosurgery	12 patients with 21 intracranial melanoma metastases			Lack of comparison group → study excluded	
Isokangas et al. 1996	To report the long-term results of the irradiation of intracranial malignant melanoma	Retrospective analysis Treatment: Radiotherapy TD 40 Gy vs. normalized TD at 3 Gy (NTD3Gy) with 30 Gy as cutpoints	60 patients	median survival	4.1 months Those with higher total doses to the tumour area had significantly better (P = 0.0006) survival	Lack of comparison group → study excluded	
Skibber et al. 1996	To evaluate postoperative adjunctive cranial irradiation in 34 patients with solitary brain	Retrospective analysis Treatment: Surgery alone n=12	34 patients, 34 brain metastases		Overall survival was significantly improved in the 22 patients who received adjunctive cranial irradiation	< 20 patients in one of the treatment groups → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastases	Surgery + WBRT n=22			versus that in the 12 patients who had surgery alone		
Willner et al. 1995	To show treatment results and to define prognostic subgroups in patients undergoing radiotherapy for brain metastases from malignant melanoma	Retrospective analysis Treatment: Radiotherapy	30 patients	Overall survival rate 6 months 1 year	39% 23%	Lack of comparison group → study excluded	
Somaza et al. 1993	To determine local tumor control rates and survival of patients with melanoma metastases to the brain	Retrospective analysis Treatment: stereotactic radiosurgery + WBRT	23 patients, 32 tumors	median survival period after diagnosis local tumor control rate	9 months (range 3 to 38 months) 97%	Lack of comparison group → study excluded	
Davey et al. 1991	To determine how many patients might be candidates for radiosurgery, a retrospective analysis of computed		41 patients			No survival + efficacy data → study excluded	

<i>Study</i>	<i>Aims</i>	<i>Design</i>	<i>Population</i>	<i>Outcomes</i>	<i>Results</i>	<i>Comments</i>	<i>LoE</i>
	<i>tomographic brain scans performed on 41 patients with cerebral metastases from malignant melanoma was undertaken</i>						
<i>Hagen et al. 1990</i>	<i>To report treatment results of patients with brain metastasis from melanoma</i>	<i>Retrospective analysis</i> <i>Treatment: Surgery + postoperative radiation n=19</i> <i>Surgery alone n=16</i>	<i>35 patients</i>		<i>Group A had a longer interval to CNS relapse compared with group B, but survival was similar.</i>	<i>< 20 patients in one of the treatment groups → study excluded</i>	
<i>Oredsson et al. 1990</i>		<i>Retrospective analysis</i> <i>Treatment: Surgery</i>	<i>40 patients</i>	<i>median survival</i> <i>3-year survival</i> <i>5-year survival</i> <i>Neurological improvement</i> <i>surgical mortality rate</i>	<i>8 months</i> <i>25%</i> <i>15%</i> <i>25 patients</i> <i>less than 5%</i>	<i>Lack of comparison group → study excluded</i>	

<i>Study</i>	<i>Aims</i>	<i>Design</i>	<i>Population</i>	<i>Outcomes</i>	<i>Results</i>	<i>Comments</i>	<i>LoE</i>
					<i>Quality of life as judged by Karnofsky index was improved after surgery and maintained on an acceptable level for the remaining time of survival</i>		
<i>Guazzo et al. 1989</i>		<i>Retrospective analysis</i> <i>Treatment: Surgery</i>	<i>31 patients</i>	<i>Significant and life-threatening complications</i> <i>relief of symptoms:</i>	<i>5 patients (17%)</i> <i>64% had complete remission of symptoms while a further 20% were substantially improved</i>	<i>Lack of comparison group → study excluded</i>	
<i>Mendez et al. 1988</i>		<i>Retrospective analysis</i> <i>Treatment: Surgery, Radiotherapy</i>	<i>55 patients with neurological signs and symptoms secondary to metastases to the brain</i>	<i>6 month survival</i>	<i>58% if surgical excision was possible</i>	<i>< 20 patients in one of the treatment groups → study excluded</i>	
<i>Rate et al. 1988</i>	<i>To review the records of all patients receiving</i>	<i>Retrospective analysis</i>	<i>77 patients with brain metastases</i>	<i>median survival from the initiation of radiotherapy</i>	<i>14 week</i>	<i>Lack of comparison group → study excluded</i>	

<i>Study</i>	<i>Aims</i>	<i>Design</i>	<i>Population</i>	<i>Outcomes</i>	<i>Results</i>	<i>Comments</i>	<i>LoE</i>
	<i>palliative radiotherapy for malignant melanoma metastatic to brain, to bone, or with spinal cord compression</i>	<i>Treatment: Radiotherapy</i>					
<i>Retsas et al. 1988</i>		<i>Retrospective analysis</i> <i>Treatment: Different treatments</i>	<i>100 patients</i>	<i>Median survival</i>	<i>2.5 months</i>	<i>Lack of comparison group → study excluded</i>	
<i>Wornom et al. 1986</i>		<i>Retrospective analysis</i> <i>Treatment: surgery</i>	<i>65 patients, 94 metastatic lesions (brain, lung, abdomen, distant subcutaneous sites, and distant lymph nodes)</i>	<i>Median survival after excision of brain metastases</i> <i>Relief of symptoms</i>	<i>8 months</i> <i>77% of brain metastases</i>	<i>Lack of comparison group → study excluded</i>	
<i>Ziegler et al. 1986</i>	<i>To examine the records of 72 patients who received various regimens of radiotherapy for cerebral</i>	<i>Retrospective analysis</i> <i>Treatment: WBRT 300 cGy (conventional</i>	<i>72 patients</i>		<i>No difference in response could be attributed to dose schedules, either overall or in the subgroups of patients who had</i>	<i>Lack of comparison between different treatments → study excluded</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<i>metastases from malignant melanoma</i>	<i>fractionation, CF) vs. 500-600 cGy (high-dose-per-fraction, HDF) to a total of 3000 cGy</i>			<i>solitary or multiple brain metastases</i>		
<i>Choi et al. 1985</i>		<i>Retrospective analysis Treatment: WBRT</i>	<i>194 patients with intracranial metastatic melanoma</i>			<i>Lack of comparison group → study excluded</i>	
<i>Stridsklev et al. 1984</i>	<i>To analyze patients who completed whole-brain irradiation treatment for brain metastases from malignant melanoma</i>	<i>Retrospective analysis Treatment: WBRT</i>	<i>39 patients</i>	<i>Median survival clinical improvement objective regression of the brain metastases</i>	<i>2 months n=21 (53.8%) 6 of 15 evaluable patients (40%)</i>	<i>Lack of comparison group → study excluded</i>	
<i>Madajewicz et al. 1984</i>	<i>To review 8 years of Roswell Park Memorial Institute's (RPMI) experience with the management of malignant melanoma CNS</i>	<i>Retrospective analysis Treatment: None (n=15) Steroids (n=17) radiotherapy</i>	<i>125 patients with brain metastases (73% multiple metastases)</i>	<i>median survival</i>	<i>The median survival of the untreated group of patients was 3 weeks as compared with that of 6 weeks for the patients</i>	<i>< 20 patients in one of the treatment groups, no multivariate analysis → study excluded</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastases (1972-1980)	(n=23) surgery (n=20) chemotherapy				maintained on steroids only, 9 weeks for those who received radiotherapy, 11 weeks for the patients treated with intraarterial chemotherapy, and 26 weeks for the patients who underwent successful surgical excision of a solitary lesion.	
Byrne et al. 1983		Retrospective analysis Treatment: Group 1, multiple brain metastases treated with radiation therapy (RT) (n = 49) Group 2, single brain metastasis treated with RT (n = 17)	81 patients with brain metastasis	Median survival	Groups 1 vs 2 vs 3 11, 9 and 41 weeks	No multivariate analysis included → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Group 3, single brain metastasis treated with surgery with or without RT (n = 9).					
Vlock et al. 1982	To examine the results in 46 patients treated with high- or low-dose fractions for intracranial metastases	Retrospective analysis Treatment: 26 patients received high-dose fraction therapy, generally 600 rad/fraction/week to 2400--3600 rad; 20 patients received low-dose fraction radiotherapy with 125--400 rad/fraction daily	46 patients	Median survival Improvement Stability deterioration	high-dose fraction group vs. low-dose fraction group 3 months vs. 2 1/2 months 38 vs. 35% 23 vs. 25% 38 vs. 40%	Lack of comparison between different treatments → study excluded	
Katz et al. 1981	To records of all patients who received radiotherapy for melanoma metastatic to brain (63 patients)	Retrospective analysis Treatment: corticosteroids, radiotherapy, surgery (n=8)	63 patients	Response	73% to corticosteroids 42% to radiotherapy	< 20 patients in one of the treatment groups → study excluded	

<i>Study</i>	<i>Aims</i>	<i>Design</i>	<i>Population</i>	<i>Outcomes</i>	<i>Results</i>	<i>Comments</i>	<i>LoE</i>
<i>Carella et al. 1980</i>	<i>To determine the response to whole brain irradiation</i>	<i>Retrospective analysis</i> <i>Treatment: WBRT</i>	<i>60 patients</i>	<i>Median survival</i>	<i>Study I patients 10 weeks (range 1-200) vs. Study II patients 14 weeks (range 1-76)</i> <i>significant benefit from radiation therapy in terms of symptomatic and neurologic function improvement. Symptomatic improvement was observed in 76%, with 31% completely improved</i>	<i>Lack of comparison group → study excluded</i>	
<i>Cooper et al. 1980</i>		<i>Retrospective analysis</i> <i>Treatment: WBRT</i>	<i>30 patients, 35 courses</i>		<i>Marked improvement in neurologic status occurred in approximately 35%. Slight to moderate improvement was evident in an additional 35%.</i>	<i>Lack of comparison group → study excluded</i>	
<i>Hafstrom et al.</i>		<i>Retrospective</i>	<i>25 patients</i>	<i>median survival</i>	<i>5 months</i>	<i>Lack of</i>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
1980		analysis Treatment: Surgery				comparison group → study excluded	
Pennington et al. 1975		Retrospective analysis Treatment: Radiotherapy, chemotherapy, surgery and immunotherapy	57 patients			Publication <1980 → study excluded	

7.3.4.2. Aktualisierungsrecherche 2015

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Fogarty et al. 2015	To analyze the distant intracranial failure on magnetic resonance imaging (MRI) within twelve months of randomization for pts. receiving WBRT vs. observation after	Randomized controlled trial Treatment: WBRT with at least 30Gy in 10 fractions Vs.	200 pts randomized to WBRT or observation	Proportion of patients with distant intracranial failure as determined by magnetic resonance imaging (MRI) assessment within twelve months of	Only data quality of the first 100 pts reported so far.	Only data quality of the first 100 pts reported so far.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	local treatment of brain mets.	Observation		<p>randomization</p> <p>Time to intracranial failure (local, distant and overall) as determined by MRI</p> <p>Quality of life as measured by EORTC QLQ-C30 and BN-20</p> <p>Neurocognitive function as measured by Hopkins Verbal Learning Test, Controlled Oral Word Association Test, Trail Making Test Part A & B, Stroop - Colour and Word Test and Digit Span (Forwards and Backwards).</p> <p>Overall survival</p> <p>ECOG Performance</p>			

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				status			
Goyal et al. 2015	To review the current evidence regarding the treatment of multiple brain metastases from melanoma.	Systematic review	2006 pts. treated with radiotherapy; 642 treated with chemotherapy; description of non-RCTs for Ipilimumab	Rate of Intracranial Failure, % Overall Intracranial Response Rate, % Median Overall Survival, mo Progression-Free Survival or Median Time to Progression	8-48% for SRS(+/-WBRT), 29-100% for WBRT 7-47% for CTX 6.5-7.5m for WBRT, 5.7-15.2m for SRS(+/-WBRT) 0-47monts for chemotherapy (+/-WBRT/SRS) 4.7-21.3m for ipilimumab (+/-Chemo/WBRT/SRS) 1.2-5m for chemotherapy (+/-WBRT/SRS) 2.7m-9.5m for Ipilimumab (+/-Chemo/WBRT/SRS)	“At this time, the standard management for patients with MBM from melanoma includes SRS, WBRT, or a combination of both“	1a
Hauswald et al. 2013	To exploratory investigate the treatment response to	Randomized controlled trial Treatment:	50 pts randomized 1:1 to WBRT or WBHT+ integrated boost	Toxicity (frequency and intensity according to CTCAE Ver. 4)		No results published so far	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	conventional whole brain radiotherapy applying 30 Gy in 10 fractions versus whole brain helical tomotherapy applying 30 Gy in 10 fractions with an integrated boost of 50 Gy to the brain metastases as well as hippocampal-sparing in patients with brain metastases from malignant melanoma	WBRT 30 Gy in 10 fractions Vs. WBHT applying 30 Gy in 10 fractions with an integrated boost of 50 Gy to the brain metastases as well as hippocampal-sparing		every 2 months for one year			

7.3.5. Literatur

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7.4. Frage VI.5. Adjuvante Radiotherapie Regionale Lymphknotenstation

Frage VI.5. Beeinflusst eine adjuvante Radiotherapie der Lymphknotenstation das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?

7.4.1. PICO, Suchwörter

PICO – Schema

Population	Intervention	Comparison	Outcome
melanoma patients after nodal surgery	radiotherapy	no radiotherapy	Overall survival, progression free survival

Suchwörter				
Stichwort	melanoma	adjuvant radiotherapy	postoperative	lymph node lymph nodes
Synonyme		radiation		nodal
Ober-/Unterbegriffe				
Mesh Term	melanoma	adjuvant radiotherapy		lymphoid tissue

7.4.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	("melanoma"[tiab] OR "melanoma"[MeSH]) AND ("adjuvant radiotherapy"[tiab] OR "Radiation"[tiab] OR "postoperative"[tiab] OR adjuvant radiotherapy[MeSH Terms]) AND ("lymph node"[tiab] OR "lymph nodes"[tiab] OR "nodal "[tiab] OR "lymphoid tissue"[MeSH])	04.11.11	455
Cochrane Library	(melanoma and ("adjuvant radiotherapy" or radiation) and lymph*).ti,ab	07.11.11	7
Embase	(melanoma and ("adjuvant radiotherapy" or radiation) and lymph*).ti,ab	12.10.10	475
Update Suche			
Medline	s.o.	31.01.12	459 (0 dazu)
Cochrane Library	s.o.	31.01.12	7 (0 dazu)
Embase	s.o.	23.01.12	590 (0 dazu)

7.4.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	1056
Einschlusskriterien	Studien, die das Outcome (regionale Kontrollrate, Gesamtüberleben) einer adjuvanten Radiotherapie nach erfolgter Lymphknotendissektion beschreiben Mangels RCT´s Einschluss von Kohortenstudien ab 20 Patienten Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitäten Publikationen vor 1980
Anzahl nach Abstractscreening, vorgesehen für Bewertung	32
Anzahl ausgewählte Volltexte	11

7.4.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Burmeister et al. 2012	To compare adjuvant radiotherapy with observation alone in patients at high	Multicenter randomized study Treatment: Group A: surgery	250 patients after lymphadenectomy	Lymph node field relapse	Surgery alone vs. Surgery + RT 34 patients vs. 20 patients relapsed	Jadad Score 3 Limitations: high number of ineligible patients	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	risk of lymph-node field relapse who had undergone therapeutic lymphadenectomy for metastatic melanoma in regional lymph nodes	alone n=127 Group B: surgery + RT (TD 48Gy, 20 fractions) after lymphadenectomy , n=123		Relapse-free survival Overall survival	(HR 0.56, 95% CI 0.32 – 0.98, p=0.041) 73 vs. 70 events, n.s. (HR 0.91, 95% CI 0.65 – 1.26, p=0.56) 47 vs. 59 deaths, n.s. (HR 1.37, 95% CI 0.94 – 2.01, p=0.12)	Funding: National Health and Medical Research Council of Australia, Cancer Australia, Melanoma Insitute Australia and the Cancer Council of South Australia	
Gojkovic-Horvat et al. 2011	To determine the efficacy of and criteria for postoperative radiotherapy (PORT) in patients with palpable melanoma metastases to the groin	Retrospective cohort study Treatment: Group A: surgery alone, n=64 Group B: surgery + RT (TD range 50 - 72 Gy, fraction size 2 - 3 Gy),	101 patients, 103 nodal dissections	Recurrence 2-year regional	Surgery alone vs. Surgery + RT 14 of 66 dissections (21.2%; 95% CI, 12.1-33.0%) vs. 5 of 37 (13.5%; 95% CI, 4.5-28.8%) (p=0.431)	retrospective study, Imbalance of prognostic factors between the groups: worse prognostic factors in the surgery + RT group	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		n=37		control rates 2 years overall survival	86% (95% CI, 76-95%) and 91% (95% CI, 81-100%), respectively (p=0.395) 56% (95% CI, 44-68%) vs. 56% (95% CI, 39-72%), (p=0.813)		
Bibault et al. 2011	To analyze the outcome after adjuvant radiation therapy with standard fractionation regimen in metastatic lymph nodes (LN) from cutaneous melanoma	Retrospective cohort study Treatment: Group A: surgery alone, n=26 Group B: surgery + RT (median TD 50Gy, range 30-70 Gy, fraction size 2 - Gy), n=60	86 patients with lymphadenectomy Indications for radiation therapy: >= 4 involved LNs, extracapsular extension, LN size > 3 cm	Regional control Overall survival	Surgery alone vs. Surgery + RT No improvement of regional control (p=0.17) or overall survival (p=0.18) Subgroup RT > 50 Gy (n=30) vs. no RT (n=26): better regional control p=0.004, better survival p=0.005 control rates / regions: Axillary 90 vs. 70%	retrospective study, Imbalance of groups: worse prognostic factors in the surgery + RT group (Ulceration, number of positive LN, extracapsular extension)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>inguinal 80 vs. 72% cervical 85 vs. 50%</p> <p>Subgroup extracapsular extension: RT <50Gy vs. RT <50Gy 5 year regional control 80 vs. 35%, p=0.03</p>		
Strojan et al. 2010	To review experiences in the treatment of regionally advanced melanoma to the neck and/or parotid with adjuvant radiotherapy.	<p>Retrospective cohort study</p> <p>Treatment: Group A: surgery alone, n=40</p> <p>Group B: surgery + RT (median eqTD2 60 Gy, range 47.8–78.8, fraction size 5 Gy, range 2–6 Gy), n=43</p>	83 patients after surgery on metastases to the neck and/or parotid gland lymph nodes, no distant metastases	<p>2-year regional control rates</p> <p>2-year distant metastasis-free survival rates</p> <p>2-year survival rates (all deaths considered as events)</p>	<p>Surgery alone vs. Surgery + RT 56% (CI 40–72%) vs. 78% (CI 63–92%) (p =0.015)</p> <p>55% (CI 40–70%) vs. 40% (CI 25–56%), n.s.</p> <p>51% (CI 36–66%) vs. 58% (CI 42–73%), n.s.</p>	retrospective study. Due to imbalance of groups (irradiated patients had more extensive surgery, a significantly higher median number of involved nodes, more frequently extracapsular tumor extension, nonradical surgery, less systemic immunotherapy with interferon) a risk factor score was used for	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						retrospective grouping of patients.	
Agrawal et al. 2009	To evaluate the impact of adjuvant radiation therapy (RT) on regional recurrence and survival after therapeutic lymphadenectomy	Retrospective cohort study Treatment: Group A: surgery alone, n=106 Group B: surgery + RT (most patients: TD 30 Gy, fraction size 6 Gy, 2.5 weeks), n=509	615 patients after lymphadenectomy (cervical, axillary, inguinal)	Recurrence (at a median follow-up 60 months) 5-year regional control rate	Surgery alone vs. Surgery + RT Regional recurrence: 43 of 106 pts (40.6%) vs. 52 of 509 pts (10.2%) distant recurrence: 73.6% (78 of 106 pts) vs. 55.4% (282 of 509 pts) all sites 52 vs. 87%, p<0.0001 cervical 43 vs. 93%, p<0.0001 axillary 48 vs. 91%, p<0.0001 inguinal 69 vs. 69%, n.s. <u>multivariate analysis</u> : DMFS and DSS both were influenced by the	retrospective study, large series. P-values for recurrence missing. data for overall survival not compared between groups	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					number of positive lymph nodes and the number of lymph nodes removed. In addition, DSS was influenced by primary tumor thickness and the receipt of adjuvant RT. The most common complication was symptomatic lymphedema		
Hamming et al. 2009	To examine the effect of adjuvant radiotherapy on regional control of melanoma neck node metastasis.	Retrospective cohort study Treatment: Group A: surgery alone, n=24 Group B: surgery + RT (TD 24 - 36 Gy, fraction size 6 Gy) n=40	64 patients with melanoma neck node metastasis	2-year ipsilateral regional recurrence rate	Surgery alone vs. Surgery + RT 46% vs. 18%, n.s. (p=0.16) <u>multivariate analysis:</u> significant reduction of the RR rate after correction for the number of involved nodes	retrospective study, short median follow-up (2.5 years), small sample size,- Imbalance of prognostic factors between the groups	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				2-year disease-free survival (DFS) 2-year overall survival (OS).	(p=0.04) 29% vs. 18%, n.s. (p=0.30) 58% vs. 26%, n.s. (p=0.07)		
Moncrieff et al. 2008	To examine the effectiveness of adjuvant radiotherapy in controlling regional disease in high-risk patients	Retrospective cohort study Treatment: Group A: surgery alone, n=587 Group B: surgery + RT (median TD 33 (range 30 - 60 Gy, most patients: fraction size 5.5 Gy, 2x/week) n=129	716 patients after cervical lymph node surgery	6 years regional recurrence rate Overall survival	Surgery alone vs. Surgery + RT 6.1% vs. 10.1%, n.s. no benefit to patients with adjuvant radiotherapy <u>multivariate analysis</u> : ulceration in the primary tumor: only significant independent predictor of regional recurrence (p =	retrospective study, large series, imbalance of groups: the surgery plus RT group includes significantly less patients with microscopic than macroscopic disease and significantly more patients with extensive surgery	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					0.005; hazard ratio, 5.60; 95% confidence interval, 1.7-18.4) nodal status, extracapsular spread and ulceration of the primary tumor: significant independent predictors of survival (p = 0.001, p = 0.014, and p = 0.003)		
Fuhrmann et al. 2001	To evaluate the usefulness of adjuvant radiotherapy following resection of lymph node metastases	Retrospective cohort study Treatment: Group A: surgery alone, n=58 Group B: surgery + RT (most patients TD 50-65 Gy, fraction size 2 - 3.8 Gy) n=58	116 patients, Stage III after resection of lymph node metastases	Local recurrence rate Overall survival (after a follow up of 12-14 years)	Surgery alone vs. Surgery + RT 79% vs. 84%, n.s. 26% vs. 17% , n.s.	retrospective study, Imbalance of groups: pairs were only matched for gender and number of tumour-bearing lymph nodes. Group B includes more head and neck melanomas and thicker tumours.	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Groups were treated in 2 different german centres using the same follow up schedule. missing data, e.g. median follow up, p-values	
Shen et al. 2000	To examine the incidence of cervical recurrence among patients who did not receive postoperative radiotherapy after surgical management of nodepositive head and neck melanoma	Retrospective cohort study Treatment: Group A: surgery alone, n=196 Group B: surgery + RT (treatment Schedule not indicated) n=21	217 patients with head and neck melanoma after regional lymph node dissection	Cervical recurrence rate 5 years overall survival 5 years disease free survival	Surgery alone vs. Surgery + RT 14% (25/183) vs. 15% (2/13), n.s. 32% 21% <u>multivariate analysis:</u> extranodal disease: only independent predictor for cervical recurrence	Baseline characteristics for the surgery+RT group were not indicated, no statistical analyses for this group due to small sample size, retrospective study	3b
O'Brien et al. 1997	To analyze the	retrospective	143 patients after		Surgery alone vs.	retrospective	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	influence of the number of positive nodes, extracapsular spread, and the use of adjuvant radiotherapy on regional control and survival	cohort study Treatment: Group A: surgery alone, n=107 (sites) Group B: surgery + RT (TD 33 Gy, fraction size 5.5 Gy, 3 weeks) n=45 (sites)	neck or parotid dissection, 152 lymphadenectomy sites	Local recurrence 5 years survival	Surgery + RT 18.7% (20 of 107) vs. 6.5% (3 of 45), p=0.055 35% vs. 40%, n.s.	study, imbalance of groups, difficult to compare data for recurrence with other studies as they do not refer to patients but to irradiated sites.	
Creagan et al. 1978	To assess the role of postoperative radiation therapy directed to the regional node area in patients undergoing lymphadenectomy for metastatic melanoma	RCT Treatment: Group A: surgery alone, n=29 Group B: surgery + RT (TD 5000 rad, fraction size 2500 rad) n=27	56 patients after lymphadenectomy	Time to recurrence Survival	Surgery alone vs. Surgery + RT 9 months vs. 20 months, n.s. (p=0.07) 22 months vs. 33 months, n.s. (p=0.09)	Limitations: randomization scheme not appropriate (group assignment predictable), small sample size, Imbalance of groups (more younger patients and more patients with only one positive node in the RT group)	2b poor quality RCT

7.4.5. Literatur

- Agrawal S, Kane JM, 3rd, Guadagnolo BA, et al. The benefits of adjuvant radiation therapy after therapeutic lymphadenectomy for clinically advanced, high-risk, lymph node-metastatic melanoma. *Cancer* 2009;115:5836-5844
- Bibault JE, Dewas S, Mirabel X, et al. Adjuvant radiation therapy in metastatic lymph nodes from melanoma. *Radiat Oncol* 2011;6:12
- Creagan ET, Cupps RE, Ivins JC, et al. Adjuvant radiation therapy for regional nodal metastases from malignant melanoma: a randomized, prospective study. *Cancer* 1978;42:2206-2210
- Burmeister BH, Henderson MA, Ainslie J, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. *Lancet Oncol* 2012; 13: 589-597
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- Gojkovic-Horvat A, Jancar B, Blas M, et al. Adjuvant Radiotherapy for Palpable Melanoma Metastases to the Groin: When to Irradiate? *Int J Radiat Oncol Biol Phys* 2011
- Hamming-Vrieze O, Balm AJ, Heemsbergen WD, et al. Regional control of melanoma neck node metastasis after selective neck dissection with or without adjuvant radiotherapy. *Arch Otolaryngol Head Neck Surg* 2009;135:795-800
- Henderson MA, Burmeister B, Thompson JF, et al. Adjuvant radiotherapy and regional lymph node field control in melanoma patients after lymphadenectomy: Results of an intergroup randomized trial (ANZMTG 01.02/TROG 02.01). *J Clin Oncol (Meeting Abstracts)* 2009;27:LBA9084
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7.5. Frage VI.6. Fraktionierung

Frage VI.6. Hat das Fraktionierungsschema einen Einfluss auf die Effektivität der Radiotherapie bei Melanompatienten?

7.5.1. PICO, Suchwörter

PICO - Schema

Population	Intervention	Comparison	Outcome
melanoma patients	Radiotherapy high dose per fraction	Radiotherapy low dose per fraction	effectiveness

Suchwörter				
Stichwort	Melanoma	radiotherapy	fraction	
Synonyme		Radiation, irradiation	dose	
Ober-/Unterbegriffe				
Mesh Term	melanoma	radiotherapy, radiation		

7.5.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	((melanoma[ti] OR melanoma[MeSH]) AND (radiotherapy[ti] OR radiotherapy[MeSH] OR radiation[MeSH] OR radiation[ti] or irradiation[ti]) AND (fraction*[ti] OR dose[ti]))	14.07.1 1	216 (Auswahl 9)
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation) and fraction*).ti.	14.07.1 1	3 (Overgaard, Chang, Sause – alles Dubletten, 0 dazu)
Embase	(melanoma and (radiotherapy or radiation or irradiation) and fraction*).ti.	11.05.1 1	49 (Katz - Dublette)
Update Suche			
Medline	s.o.	31.01.1 2	221 (0 dazu)

Cochrane Library	s.o.	31.01.1 2	3 (0 dazu)
Embase	s.o.	23.01.1 2	52 (0 dazu)

7.5.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	276
Einschlusskriterien	RCT´s Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kombinationstherapien Kollektive mit gemischten Tumorentitäten Arbeiten älter als 1980
Anzahl nach Abstractscreening, vorgesehen für Bewertung	9
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	7
Anzahl ausgewählter Volltexte	2

7.5.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Sause et al. 1991	To evaluate the effectiveness of high dose per fraction irradiation in the treatment of melanoma	RCT Treatment: Group A: 4 fractions, 8.0 Gy, days 0, 7, 12 and 21 Group B: 20 fractions, 2.5 Gy, 5 days a week	137 patients with skin, soft tissue and nodal lesions Group A n=67 patients Group B n=70 patients	Response	Group A vs. Group B: no significant differences CR 24.2% vs. 23.4% PR 35.5% vs. 34.4% NC 33.9% vs. 39.1% PD 6.5% vs. 3.1%	Randomization scheme not described assessment not blinded	1b
Overgaard et al. 1985	To compare two high-dose per fraction radiation schedules in recurrent or metastatic malignant melanoma	RCT Treatment: Group A: 9 Gy X 3, 2 fractions per week Group B: 5 Gy X 8, 2 fractions per week	14 patients, 35 skin and lymph node metastases	Response	Group A vs. Group B: no significant differences CR n=11 (65%) vs. n=13 (72%) PR n=5 (29%) vs. n=5 (28%) NC n=1 (6%) vs. n=0 (0%)	Randomization scheme not described, assessment not blinded, lesions not patients were randomized, very heterogeneous population, small sample size	2b low quality RCT

7.5.5. Literatur

Overgaard J, von der Maase H, Overgaard M. A randomized study comparing two high-dose per fraction radiation schedules in recurrent or metastatic malignant melanoma. Int J Radiat Oncol Biol Phys 1985;11:1837-1839

Sause WT, Cooper JS, Rush S, et al. Fraction size in external beam radiation therapy in the treatment of melanoma. Int J Radiat Oncol Biol Phys 1991;20:429-432

8. AG Nachsorge

8.1. Frage VII.3. Selbstuntersuchung im Rahmen der Nachsorge - Adaptation

Frage VII.3. Sollte die Selbstuntersuchung ein Bestandteil der Nachsorge sein?

8.1.1. Synopse (kurz)

Thema/Fragestellung	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
3. Sollte die Selbstuntersuchung ein Bestandteil der Nachsorge sein?	Notwendiger Bestandteil der Nachsorge (C)	Bestandteil der Nachsorge für jeden Patienten, lebenslang; Durchführung von Schulungen zur Selbstuntersuchung durch Ärzte oder Pflegekräfte	LL Frankreich French National Authority for Health 2005	nur relevant für medikamentöse Therapien

8.1.2. Empfehlung, Hintergrundtext und Literatur australischen und französischen Quell-Leitlinien

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
Schlüsselempfehlungen	<p>S. 122</p> <p>1. Self-examination by patients is essential and they should be taught the process. Routine follow-up by the patient's preferred health professional may be appropriate to emphasise sun smart behaviour and perform skin checks Grade of Recommendation: C</p>	<p>Empfehlungen zur Selbstuntersuchung in der NICE Guideline beziehen sich nur auf SCC und BCC, daher werden hier die Angaben aus dem Guideline Evidence Review wiedergegeben:</p>	<p>S. 51</p> <p>Suivi Stade I AJCC Standards [...] ■ éducation du patient à 'autodépistage d'un nouveau mélanome et à l'autodétection d'une récurrence. <i>Nachsorge Stadium I nach AJCC Standards [...]</i> ■ Anleitung des Patienten zur Selbstuntersuchung auf ein neues Melanom und zur selbständigen Erkennung eines Rezidivs.</p> <p>Stades IIA et IIB AJCC Standards [...] ■ éducation du patient à l'autodépistage d'un nouveau mélanome et à l'autodétection d'une récurrence. <i>Stadien IIA und IIB Standards</i></p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
			<p>[...]</p> <ul style="list-style-type: none"> ■ <i>Anleitung des Patienten zur Selbstuntersuchung auf ein neues Melanom und zur selbständigen Erkennung eines Rezidivs.</i> <p>Stades IIC et III AJCC Standards [...]</p> <ul style="list-style-type: none"> ■ <i>éducation du patient à l'autodépistage d'un nouveau mélanome et à l'autodétection d'une récurrence.</i> <p><i>Stades IIC et III AJCC Standards [...]</i></p> <ul style="list-style-type: none"> ■ <i>Anleitung des Patienten zur Selbstuntersuchung auf ein neues Melanom und zur selbständigen Erkennung eines Rezidivs.</i>
Hintergrundtexte	<p>S. 121 – 122</p> <p>19.2 Undertaking follow-up Current guidelines world-wide do not specify where routine follow-up should take place or who should do it. [6,7] However, it is becoming accepted by most [8-10] but not all [11-13] that patients themselves rather than doctors</p>	<p>S. 370 (Guideline Evidence Review)</p> <p>Patient self examination</p> <p>The questions <i>In the follow-up of patients with skin cancer, what is the usefulness of education for self examination?</i></p>	<p>S. 51</p> <p>JUGEMENT ARGUMENTÉ DES EXPERTS [...] Face à l'ensemble de ces considérations, il semble raisonnable d'envisager une surveillance minimale, à savoir basée essentiellement sur l'examen clinique et l'éducation du patient à l'autodépistage.</p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
	<p>are likely to detect their own recurrence. Those studies reporting a high patient-detection rate attribute this to patients receiving thorough explanations of the signs and symptoms of recurrences and new primary melanomas. Despite such explanations, it is obvious that the ability of individual patients to detect recurrence varies. Some can identify recurrences that are not discernible to doctors, while others can be unaware of a large tumour mass. The existence of these latter patients perhaps explains the reticence of some centres to forego routine follow-up.</p> <p>In Australia, with its heightened awareness of the disease, up to 75% of patients detect their own recurrences. [14] World-wide the mean percentage is 62%. [1]</p> <p>The UK Medical Research Council has designed a 'framework for the design of an integrated follow-up program'. [15] One technique employed was to interview patients to determine their preferred follow-up requirements. Most supported follow-up by general practitioners, and felt that the main purpose of follow-up was reassurance. However, there was</p>	<p>The nature of the evidence Twelve papers were identified representing eleven studies (with one RCT reported at two stages of follow-up) as follows:</p> <ul style="list-style-type: none"> · One RCT of good quality · One systematic review of good quality · One case control study of good quality · Eight observational studies, four of good quality, one of fair quality and three of poor quality <p>Only one study originates from the UK. Seven studies are from the US, one study is from Australia and two studies are from Italy. Generalisability to the UK is therefore limited.</p> <p>Seven studies are of patients at risk of melanoma based upon family history or presence of naevi. Three studies are of screened populations and two studies are of patients with proven melanoma.</p> <p>Summary of the supporting evidence for the recommendations</p> <p>Self examination (SE) versus physician examination There is consistent evidence that expert physician examination has greater</p>	<p>Pour les mélanomes de stade I AJCC qui présentent globalement un faible risque de récurrence, l'examen clinique annuel ou biennuel aura pour objectif la détection d'un éventuel second mélanome. Pour les patients de stades II et III AJCC, une échographie ganglionnaire de la zone de drainage peut être envisagée en option (accord d'experts).</p> <p>Les autres examens d'imagerie (à la recherche de métastases à distance) n'ont pas apporté la preuve qu'ils pouvaient influencer sur la survie en partie du fait de l'absence de thérapeutique efficace à ce stade.</p> <p>En l'absence d'études portant spécifiquement sur l'intérêt de la surveillance et de son rythme, il n'est pas apparu possible de formuler des conclusions <i>evidence-based</i> à partir de la littérature. De ce fait, les recommandations qui seront établies ne pourront reposer que sur des accords d'experts et seront le reflet d'un consensus pour un protocole de surveillance minimum basé sur l'examen clinique complet et l'éducation du patient à 'autodépistage.</p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
	<p>concern over travelling times, costs, brevity of consultations, and poor continuity.</p> <p>Nearly all queried the experience and skill of the general practitioners and said training would be vital, with rapid access to specialist advice if necessary. Total skin examination, instruction in self-examination and the provision of more information were seen as desirable at visits to general practitioners. Other studies assessing patients' opinions of the value of follow-up [6,16] found that most considered routine follow-up worthwhile, with only a few considering that it was not. While favouring follow-up, more than half the patients in these studies reported anxiety before each visit.</p> <p>Evidence summary</p> <p>There is a consensus that the majority of patients detect their own recurrence if they have received a thorough explanation of the signs and symptoms of recurrences and new primary melanomas</p> <p>LoE: IV</p>	<p>reliability than SE in detecting melanoma. Systematic review evidence suggests that melanoma lesions detected by physicians are thinner than those detected by patients. Observational study evidence suggests that detection by dermatologist is associated with earlier melanoma diagnosis and that input by physicians is the strongest single determinant of SE, although there is little evidence for improved survival arising from recurrences of melanoma diagnosed by patients compared to recurrences diagnosed by hospital doctors. The same level of evidence suggests that SE based on naevi count has poor concordance with dermatological assessment for risk of melanoma and is not reliable.</p> <p>Factors affecting SE</p> <p>Studies have identified a number of patient characteristics and also events which are associated with SE. Systematic review evidence suggests that elderly men have lower rates of SE. There is observational study evidence that factors associated with greater likelihood of patients performing self skin</p>	<p>CONFRONTATION</p> <p>Les nouvelles données identifiées convergent globalement avec les données présentées dans les documents initiaux de 1995 et 1998 et apportent de nouveaux éléments, notamment concernant l'échographie ganglionnaire qui peut être proposée pour le suivi des patients opérés de stades II et III AJCC (option, accord d'experts). L'examen clinique complet et l'éducation à l'autodépistage du patient restent le standard.</p> <p>La fréquence est à adapter au stade du patient : une à deux fois par an pour les patients atteints d'un mélanome de stade I et tous les 3 mois pour les autres stades.</p> <p>S. 51</p> <p><i>BEGRÜNDETES URTEIL DER EXPERTEN</i> [...] <i>Im Angesicht dieser Überlegungen scheint es vernünftig, eine minimale Überwachung in Erwägung zu ziehen, das heißt im Prinzip basierend auf der klinischen Untersuchung und der Anleitung des Patienten zur</i></p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
	<p>References: 14–16</p> <p>Self-examination may be combined, if appropriate, with routine follow-up by the patient's preferred health professional</p> <p>LoE: IV</p> <p>References: 14–16</p>	<p>examination are:</p> <ul style="list-style-type: none"> · skin awareness · habitual sun protection · previous benign skin biopsy · family cancer history · personal history of skin cancer · physician or nurse examination or recommendation · help from a spouse (especially wives assisting husbands) · presence of a wall mirror · age <50 years <p>The same level of evidence suggests that older patients may be less likely to perform SE.</p> <p>Rates of SE</p> <p>Estimates of rates of SE vary widely within the studies identified, according to factors such as populations studied and different definitions of SE or questions used by researchers to ascertain rates of SE. Subsequently, estimates of rates of SE from observational studies have range 9% to 87%. A rate of 71.6% for SE performed within the preceding year, was reported amongst first degree relatives of melanoma patients by Manne et al., (2004). Systematic review evidence</p>	<p><i>Selbstuntersuchung.</i></p> <p><i>Bei Melanomen im Stadium I nach AJCC, die insgesamt ein geringes Rezidivrisiko haben, wird die jährliche oder zweijährliche klinische Untersuchung die Erkennung eines eventuellen zweiten Melanoms zum Ziel haben.</i></p> <p><i>Für Patienten in den Stadien II und III nach AJCC kann eine Lymphknoten-Sonographie des Abflussgebietes als Option ins Auge gefasst werden (Expertenmeinung).</i></p> <p><i>Andere bildgebende Verfahren (zur Suche nach Fernmetastasen) haben noch nicht den Beweis erbracht, dass sie das Überleben beeinflussen, zum Teil aufgrund einer fehlenden effektiven Therapie in diesem Stadium.</i></p> <p><i>Durch das Fehlen von Studien zum Thema Nachsorge und Nachsorge-Intervalle scheint es nicht möglich, aus der Literatur evidenzbasierte Schlussfolgerungen zu ziehen.</i></p> <p><i>Daher beruhen die gegebenen Empfehlungen nur auf Expertenmeinung und spiegeln einen Konsensus für eine minimale Nachsorge basierend auf vollständiger klinischer Untersuchung und Anleitung des Patienten zur</i></p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		<p>suggests that the effect of promoting SE cannot be distinguished from that of routine screening in patients seeing the physician for unrelated reasons. RCT and case control study evidence suggests that rates of SE can be significantly improved through educational interventions.</p> <p>Role of photography in SE Evidence from one RCT suggests that the use of photography as an adjunct to health education produces no short term (i.e. same day as intervention) difference in compliance above standard education for SE but the same level of evidence is suggestive of a four month follow-up advantage in terms of rate of SE through the use of photographs.</p> <p>Benefit of SE Case control study evidence suggests that SE is associated with a marginally significant reduced risk of melanoma incidence: OR 0.66 [95% CI 0.44-0.99] which is reportedly an inexpensive screening method. Observational study evidence suggests that female sex, high educational level</p>	<p><i>Selbstuntersuchung wider.</i></p> <p>GEGENÜBERSTELLUNG <i>Die neuen Daten deuten in die gleiche Richtung wie die Daten aus den ersten Dokumenten von 1995 bis 1998 und bringen neue Elemente ein, vor allem bezüglich der Lymphknoten-Sonographie, die für die Nachsorge von operierten Patienten der Stadien II und III empfohlen werden kann (Option, Expertenkonsens). Die vollständige klinische Untersuchung und die Anleitung zur Selbstuntersuchung des Patienten bleiben Standard.</i> <i>Die Nachsorgefrequenz ist an das Stadium des Patienten anzupassen: ein- bis zweimal für Patienten mit Melanom Stadium I und alle 3 Monate für Patienten der anderen Stadien.</i></p>

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		<p>and performance of SE are associated with thinner melanoma tumours.</p> <ul style="list-style-type: none"> · The prevalence study by Aitken et al. (2004) found that 25.9% of randomly selected adults reported whole body SE within the last 12 months and 1055 (33.9%) within the last 3 years and concluded that input by physicians is the strongest single determinant of SE. · The case control study by Berwick et al. (1996) found that SE was performed by 15% of all subjects (patients with melanoma and population matched controls) and was associated with a marginally significant reduced risk of melanoma in all subjects: OR 0.66 [95% CI 0.44-0.99]. · The qualitative study by Berwick et al. (2000) found that amongst a sample of patients with a history of melanoma and also lower risk patients without a history of melanoma, the rate of reported SE was 32% at baseline, rising to 64% after an educational intervention (p = 0.03). · The survey of patients referred by their GPs to a pigmented lesion clinic undertaken by Carli et al. (2002) found poor concordance between SE and 	

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		<p>dermatological assessment for both common and atypical naevi and concluded that SE of melanoma risk is not reliable.</p> <ul style="list-style-type: none"> · The case series study by Carli et al. (2003) found that 40.6% of patients with melanoma sampled self detected their melanoma tumour. Female sex (OR 0.70 [95% CI 0.50-0.97]), high educational level (0.44 [95% CI 0.24-0.79]) and performance of SE (0.65 [95% CI 0.45-0.93]) were factors associated with thinner tumours. 48% of patients performed SE, but only 20.4% regularly. · The systematic review by Helfan et al. (2001) found melanoma lesions detected by physicians to be thinner than those detected by patients. Elderly men had lower rates of SE and the authors recommended that physicians perform skin examination in these patients. The authors reported that the effect of promoting SE cannot be distinguished from that of routine screening in patients seeing the physician for unrelated reasons. · The qualitative survey of first degree 	

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		<p>relatives of patients with melanoma by Manne et al. (2004) found the rate of SE in the last year to be 71.6%. SE correlated closely with having received a clinical skin examination by a physician.</p> <ul style="list-style-type: none"> · The case series study of patients with metastatic melanoma by Odili and Evans (2001) found that 56% of cases of recurrent melanoma were patient detected and no significant difference in survival between recurrences diagnosed by SE and those diagnosed by hospital doctor were found. · The qualitative study by Oliveria et al. (1999) found that amongst a sample of Caucasian people without melanoma, skin awareness was a strong factor associated with SE whereas older age and higher education was associated with a decreased likelihood of performing SE. · The RCT by Phelan et al. (2003) compared nurse education for SE and provision of skin photographs with nurse education and provision of standard brochure in patients with 5 or more dysplastic naevi, with or without a history of melanoma. The mean group scores for knowledge, 	

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		<p>awareness and confidence increased in both groups at immediate follow-up ($p < 0.0001$) but there were no significant differences in scores between the photography group and the brochure group.</p> <ul style="list-style-type: none"> · The RCT of patients at high risk for melanoma based upon dysplastic naevi by Oliveria et al. (2004) provided further follow-up to the study by Phelan et al. (2003) and found that a teaching intervention with photo book demonstrated a 51% increase in 3 or more reported examinations at 4 month follow-up, compared to a 17.6% increase in the group which received teaching only [$p = 0.001$]. · The observational pilot study (as part of a subsequent trial) by Weinstock et al. (2004) found the rate of SE amongst patients attending for routine follow-up visits to be between 12% and 38%. Help from a partner and presence of a wall mirror were associated with higher rates of SE whereas visual impairment was found to be associated with lower rates of SE. 	
Bemerkungen		Diese Leitlinie bezieht sich auf MM und	Keine Literaturangaben zu Fragen der

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		auf NMSC.	Selbstuntersuchung; Angaben sind daher nur konsensbasiert.

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Siehe Evidence Table 5.3, S. 375 – 379 des Guideline Evidence Review

8.2. Frage VII.4., VII.5. und VII.6. Nachsorge-Dauer und -Intervalle – De-novo-Recherche

Frage VII.4. Wie lange sollte die Nachsorge von Melanompatienten erfolgen?

Frage VII.5. In welchen Intervallen sollte die Nachsorge erfolgen?

Frage VII.6. Welche Untersuchungen sind im Rahmen der Nachsorge bei asymptomatischen Patienten indiziert?

8.2.1. PICO, Suchwörter

Suchwörter			
Stichwort	melanoma	Surveillance	Relapse
Synonyme		Follow-up, After-care, aftercare, post-operative care	recurrence
Ober-/Unterbegriffe, Mesh Term	S. Suchstrategie (Kapitel 7.4.2. und Kapitel I.6.)		

8.2.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	"melanoma"[tiab] AND ("relapse"[tiab] OR "recurrence"[tiab] OR "surveillance"[tiab] OR "follow-up"[tiab] OR aftercare[tiab] OR "after-care"[tiab] OR "post-operative care")	23.01.2012	7047
Cochrane Library	(melanoma and (surveillance or "follow up")).ti.	23.01.2012	278

Datenbank	Suchstrategie	Datum	Treffer
Embase	(melanoma and (surveillance or "follow up")).ti.	23.01.2012	443
2. Suche	s. "Evidenztabelle I.6, I.7, I.8, VII.6", Kapitel I.6		
3. Suche/Ergänzungen	("second primary"[title] AND melanoma) OR "second melanoma"[title] OR ("multiple primary"[title] AND melanoma)	23.01.2012	186
<p>Bemerkungen: Datum der Erst-Recherche (1. Suche) für Medline und Cochrane war der 21.12.2010 bzw. für die Ergänzungs-Recherche (3. Suche) der 08.06.2011. Die erste EMBASE-Recherche erfolgte am 11.05.2011. Eine letzte Update-Recherche (initiale Suche, Ergänzungsrecherche) erfolgte am 23.01.2012 für EMBASE, am 26.01.2012 für Medline bzw. am 19.01.2012 für Cochrane. In den Tabellen angegeben sind die Zahlen der letzten Update-Recherche. Die Daten für die zweite Suche für die Frage VII.6 entnehmen Sie bitte der Tabelle „I.6, I.7, I.8, VII.6“ unter Kapitel I.6.</p>			

8.2.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	7954
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews, Bench Research
Anzahl nach Abstractscreening	163 (inkl. Dupletten)
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	59
<p>Bemerkungen Zum Thema "multiple melanomas" liegt ein Review von Francken et al. (2005) vor, das Studien bis Februar 2004 umfasst, das in diese Tabelle ebenfalls mit</p>	

Auswahl der Literatur

aufgenommen wurde.

Die Tabelle enthält alle relevanten Rechercheergebnisse für die Fragen VII.4., VII.5., VII.6.

Die Literatur wurde entsprechend der Fragestellungen zugeteilt, s. hierfür auch die Übersicht am Ende der Tabelle. Im Rahmen der AG-Treffen wurde durch die Experten eine konsensbasierte Beantwortung der Frage VII.5 entschieden. Da diese Entscheidung nach erfolgter Literatursuche getroffen wurde, sind die Ergebnisse der Frage VII.5 in dieser Tabelle aufgeführt. Auch die Nachsorgetabelle zu den verschiedenen Untersuchungen und Intervallen zu den jeweiligen Tumorstadien wurde konsensbasiert erstellt auf Basis der vorliegenden Literatur. Aufgrund der Studiendesigns und von thematischen Überschneidungen ist eine strikte Auftrennung der Literatur nach Fragestellung nicht möglich. Aus diesem Grund wurde die Literatur, bei gleicher Suchstrategie, in dieser Tabelle zusammengefaßt. Studien zu der Frage VII.6 zu der hier aufgeführten Suchstrategie befinden sich in dieser Tabelle. Weitere Studien zu der Frage VII.6, die im Rahmen der 2. Literaturrecherche/Ergänzungen (s.o.) identifiziert wurden, sind in der Tabelle „I.6, I.7, I.8, VII.6_kurz“ enthalten.

8.2.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Leiter et al. (2011)	To analyze stage- and time-dependent hazard rates (HR) and to discuss current surveillance recommendations.	Prognostic study	33,384 patients with CM stage I-III	Overall survival Relapse-free survival Hazard ratios (HRs) for recurrences and secondary melanoma	melanoma-specific 5- and 10-year survival: 91.9% and 87.2%, respectively Recurrences recorded in 4999 patients (15.3%; stage I, 7.1%; stage II, 32.5%; and stage III, 51.0%) median RFS time: 44 months	Very large and multi-center patient cohort	1b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>10-year recurrence-free survival was 78.9% (95% confidence interval 73.1-90.5); in stage I, 89.0%; stage II, 56.9%; and stage III, 36.0%.</p> <p>HR for recurrent CM:</p> <ul style="list-style-type: none"> - Stage IA: constantly low level HR \leq 1:125 per year - stage IB: higher HRs \geq 1:40 for the first 3 years and generally in stages II to III <p>From 3 years of follow-up onward, stage II and III CIs overlapped/ no significant differences for the development of recurrences. After 10 years of follow-</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>up HR of all 3 stages did not differ significantly.</p> <p>Of all patients 2.3% developed secondary melanomas, with a consistently low HR < 1:220 per year</p>		
Voit et al. (2001)	to evaluate whether early detection of metastases improves relapse-free and overall survival	Diagnostic study	829 consecutive macroscopically disease-free melanoma patients	<p>Sensitivity</p> <p>Specificity</p> <p>Positive predictive value (PPV)</p> <p>negative predictive value (NPV)</p> <p>Survival</p> <p>relapse-free survival</p> <p>overall survival</p> <p>2- and 4-year survival rates</p>	<p>Physical examination (PE): sensitivity 25.2%, (95% confidence interval [CI]: 19.9 – 31.2%), PPV 57.5%, (95% CI: 47.5–66.9%). specificity: 98,4%, NPV 93.8%.</p> <p>ultrasound B-scans (UBS): sensitivity 99.2%, 95% CI: 97.3–99.6%, specificity: 98.3% (95% CI: 97.7–98.7%), PPV: 83.3% (95% CI: 78.5–87.4%), NPV: 99.9% (95% CI: 99.6–</p>	No information about the examiner (blinded for the results of the other examination?)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>100.0%.</p> <p>B-scan was highly superior to physical examination (P = 0.001).</p> <p>Out of 242 proven melanoma metastases, 24.8% were detected by both methods simultaneously.</p> <p>Survival curves: see full-text</p>		
Francken et al. (2005)	To discuss frequency and duration of follow-up, type of health professional involved, optimum intensity of routine investigation, and patients' satisfaction with follow-up.	Systematic review (without meta-analysis)	<p>72 articles included</p> <p>Given separately for every included study (see original article)</p>	Various	<p>first recurrence:</p> <ul style="list-style-type: none"> - 20–28% local or in-transit recurrences - 26–60% regional recurrences - 15–50% distant metastases <p>Ultimately</p> <ul style="list-style-type: none"> - 3–5% local or in-transit recurrence - 5–13% regional 	Systematic literature search, but no meta-analysis (no summary of effect measures)	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>nodes - 3-10% distant metastases</p> <p>62% of patients detected their first recurrence themselves</p> <p>frequency of late recurrences (DFS>10 years) between 1% to 25%</p> <p>Incidence of subsequent PM: 2% to 7%</p> <p>Optimum frequency and length of follow-up services: no true evidence for follow-up surveillance in localised melanoma according to the articles In no study any benefit in DFS or OS associated</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					with follow-up surveillance		
Peric et al (2011)	determine whether regular measurements of serum S100B are a useful tool for discovering patients with CM metastases and to evaluate the diagnostic value of PET-CT during the follow-up	Diagnostic study	115 CM patients included in regular follow up (82 patients with clinical signs of disease progression, 33 (28.7%) asymptomatic patients with two subsequent elevated values of S100B)	Sensitivity Specificity PPV NPV	S100B: Sensitivity, specificity, PPV and NPV 33.8%, 90.9%, 96.0% and 17.5% respectively in patients with clinical signs of disease progression. Sensitivity and PPV of S100 in asymptomatic patients were 100.0% and 69.7%. PET-CT: sensitivity, specificity, PPV and NPV of PET-CT for symptomatic patients: 98.5%, 90.9%, 98.5% and 90.9% sensitivity, specificity, PPV and NPV of PET-CT for		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					asymptomatic patients: 100%, 90.0%, 95.8% and 100%		
Kruger et al. (2011)	to demonstrate the high efficacy of ultrasonography as a noninvasive technique for early detection of lymph node involvement during clinical follow-up, especially in patients with subclinical metastases.	Diagnostic study	433 melanoma patients with stage-dependent follow-up intervals of 3 to 12 months	Sensitivity Specificity	Sensitivity and specificity of combined clinical and sonographic investigations: 0.9394 (95% confidence interval: 0.7977-0.9926)] and 0.9808 (95% confidence interval: 0.9717-0.9875)] respectively. combinatorial approach was significantly superior with regard to detection of metastases compared with clinical investigations alone (P<0.0001)	Prospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Significant differences between clinical follow-up and sonographically assisted follow-up for stages I (P = 0.0389), III (P = 0.0101), and IV (P = 0.0016).		
Turner et al. (2011)	to relate the estimated delay in diagnosis of recurrence or SPM in patients with stage I or II melanoma to the number of visits needed by two different monitoring schedules. Secondly, to estimate the effect of prognostic factors on development of recurrence or SPM	Prognostic study	2,998 consecutive patients first diagnosed with stage I or II melanoma	Delay in diagnosis of recurrence predictors of developing new primary	small difference in modeled delay in diagnosis (extra 44.9 and 9.6 patients per 1,000 for recurrence and new primary, respectively, with delay >2 months) using a schedule that requires far fewer visits (3,000 fewer visits per 1,000 patients) than recommended by current guidelines. AJCC substage= predictor of	Big patient cohort	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					recurrence age and date of primary diagnosis=predictors of developing new primary		
Aukema TS et al. (2010)	to assess the clinical relevance of increased S-100B during follow up of high-risk melanoma patients and to determine the value of subsequent whole-body PET/CT and brain MRI.	Diagnostic study	46 melanoma patients who were found to have an elevated serum S-100B level during follow-up	survival Accuracy Sensitivity Specificity negative predictive value (NPV) positive predictive value (PPV) False-positives (FP) False negatives (FN)	Median of the elevated S-100B serum levels during follow-up: 0.14 µg/L, range 0.10-1.33 µg/L. PET/CT: hypermetabolic lesions in 27 of 46 patients (59%). FN: n=0 FP: n=4 by median follow-up of 1 year sensitivity: 100% specificity: 83% accuracy: 91% PPV: 85% NPV: 100%. MRI:	sensitivity of MRI not determined because of the low incidence of brain metastases. Small population	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>Brain metastases in 1 patient (2%). NPV: 100% specificity: 100%</p> <p>PPV of an elevated serum S-100B: 50% (S-100B level > 0.10 µg/L).</p> <p>Of the 23 patients with a true positive PET/CT scan, 6 (26%) received surgical treatment with curative intent; 17 (74%) received palliative treatment or supportive care.</p> <p>2-year-survival: 51.9% in patients with a positive PET/CT compared with 100% in the patients with normal PET/CT findings (P=0.002).</p>		
Brown RE et al.	to determine the	Diagnostic study	1,235 patients	Sensitivity	210 patients	post hoc analysis	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(2010)	clinical efficacy of routine CXR for recurrence surveillance in melanoma.		with invasive cutaneous melanoma ≥ 1.0 mm in Breslow thickness and without clinical evidence of regional or distant metastases	Specificity PPV NPV	(17.0%) had a recurrence: local or in-transit in 36,2%, distant (nonlung) metastases in 35,2%, lung-only metastases in 13,3%. 99% (n = 4,180) of CXR were read as either "normal" or falsely positive (FP). 0.9%(n = 38) of all CXR obtained were true positives (TP). Sensitivity and specificity: 7.7% and 96.5%, respectively.	on data from a prospective, randomized, multiinstitutional study on melanoma (Sunbelt Melanoma Trial) no information about reference standard	
Hohnheiser et al. (2010)	to identify factors that influence time to recurrence and survival after the first recurrence with a special interest in late recurrences.	Prognostic study	2487 patients with the first manifestation of a cutaneous malignant melanoma	Overall survival Time to first recurrence Prognostic factors	Significant independent prognostic factors for survival (Cox regression analysis): - patient's age - sex	Retrospective review (prospective database) Large patient cohort	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<ul style="list-style-type: none"> - tumor localization, - pT - pN. <p>median time to first recurrence: 24 months.</p> <p>5-recurrence-rate: 81.6%</p> <p>late recurrences-rate (>10-years): 6.5%</p> <p>independent factors for time to recurrence. (Cox regression analysis)</p> <ul style="list-style-type: none"> - age at primary - treatment - pT - pN - type of recurrence were found to be <p>independent factor influencing survival</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>after a first recurrence: - type of recurrence</p> <p>(advanced age at diagnosis of recurrence male sex marginally significant)</p>		
Leiter et al. (2010)	To investigate whether detection in an early phase is associated with prolonged survival and whether the observed longer survival times are a mere consequence of detection at an earlier time point (lead time bias).	Prognostic study	1969 patients with melanoma stage I - III, recurrences in 112 patients	<p>disease-specific mortality</p> <p>Overall survival (OS)</p> <p>Survival after recurrence (SAR)</p> <p>Adjusted survival time by using sojourn time</p>	<p>disease-specific mortality: 69.6% (n=78).</p> <p>Overall 10-year survival rate: 36.1%</p> <p>10-year SAR survival rate: 25.4%</p> <p>10-year OS probability for detection in early phase: 42.6% for early phase vs. 25.6% for advanced phase (P = 0.012)</p> <p>Adjustment for</p>	<p>Adjustment for important confounding factor</p> <p>Estimated sojourn time (no evidence base available)</p> <p>Missing data in 10 of 112 patients for Cox proportional hazard model</p>	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					lead time: 10-year OS probability: 40.5% (95 CI: 27.4, 53.6) for early phase recurrences vs. 25.6% (95% CI: 12.5, 38.7) for advanced phase metastases (P=0.021) independent prognostic factors (multivariate analysis): - detection of early phase metastases (P = 0.022) - stage at primary diagnosis (P <0.0001)		
Rueth et al. (2010)	To examine whether conditional survival (CS) is more accurate in predicting longterm melanoma survival.	Prognostic study	8647 T2-T4 patients patients who underwent surgical treatment for melanoma	cancer-specific survival 10-year-survival rate	At diagnosis: 10-year survival rates: low-risk: 79.6% high-risk: 41.2% P<0.001 initial predictors of	Very large patient cohort Only available study which gives data for this outcome (conditional	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>survival: age, gender, location, ulceration</p> <p>On CS analysis: - survival differences until 8 years after treatment - 10-year survival rates: low-risk :95.4% high-risk: 91.7% P = 0.51</p> <p>On Multivariate analysis: age, gender, location, ulceration: no longer predictive after 8 years</p>	<p>survival)</p> <p>CS is a function of the traditional survival estimates, adjusted to reflect the probability of survival conditioned on living to a certain point in follow-up</p> <p>the low-risk category: T2-T3, N0</p> <p>high-risk category T4N0 or T2-4N1-3</p>	
Murchie et al. (2010)	to evaluate the effects of GP-led melanoma follow-up on patient satisfaction, in comparison to hospital-led follow-up, follow-up guideline	RCT	142 melanoma patients free of recurrent disease	<p>Patient satisfaction measured by questionnaire</p> <p>Adherence to guidelines</p> <p>Health status measured by SF-36</p>	<p>cluster-adjusted mean summary satisfaction score: - at baseline no significant difference between groups - at follow-up significantly lower</p>	<p>Reliable randomization design; blinding not possible</p> <p>Study took place in Scotland; transferability to German health</p>	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	compliance, anxiety and depression, as well as health status.			Anxiety and depression measured by the Hospital Anxiety and Depression Scale HADS	<p>in the intervention group 26.4 (95% CI: 24.9–27.9) vs 33.5 (95% CI: 32.5–34.4),</p> <p>Adherence o guidelines: - in the year before the study: 84,9% in the intervention group and 85.4% of the control group - At follow-up: 98.1% in the intervention group and 80.9% of the control group</p> <p>SF-36 scores and HADS score: no statistically significant differences between groups at either baseline or follow-up.</p>	care system?	
Morton RL et al. (2009)	to evaluate the accuracy of	Diagnostic study	108 patients AJCC stage IIIA/B (N1a,	sensitivity	CXR: sensitivity, 48%; 95%	Not all patients receive verification	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	detecting asymptomatic pulmonary metastases by surveillance chest X-rays (CXRs) in melanoma patients with a positive SNB		N2a) disease	specificity time to diagnosis survival	confidence interval [95% CI], .27-.68) specificity, 78%; 95% CI, .77-.79 Additional metastatic disease was apparent in 18% of CXR-detected versus 76% of non-CXR-detected patients (p<0.05) median time to diagnosis of pulmonary metastases: 24 months (95% CI, 12-41) vs. 16 months (95% CI, 10-30, p = 0.30 log rank). median survival of 42 months (95% CI, 24-84)vs. 36 months (95% CI, 18-46, p = 0.53 log rank)	using a reference standard (only patients with positive CXR)	
Tarhini AA et al.	To asses the effect	Progostic study	Sera from 670	Overall survival	median OS time:	Patients were	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(2009)	of elevated serum S100B level at baseline and during therapy.		patients with high risk melanoma (\geq stage IIB disease) banked at baseline and 3 additional time points were tested for S100B	(OS) RFS	7.2 years (95% CI, 6.0 years to not reached). RFS time: 3.1 years (95% CI, 2.4 to 3.7 years). Multivariate analysis was performed adjusting for significant prognostic factors (ulceration and lymph node status) and treatment. Baseline S100B was a significant prognostic factor for survival (HR = 1.39; 95% CI, 1.01 to 1.92; P = 0.043) S100B values measured at later time points over 1 year were also demonstrated to be significant prognostic factors for RFS and OS. Lower S100B	included in an intergroup trial E1694 was a randomized comparison of heGM2ganglioside vaccine (GMK) versus HDI that accrued 880 patients. No information about staging	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					values at baseline and during follow-up were associated with longer survival.		
Leiter et al. (2009)	To develop an efficient and cost-effective surveillance strategies, dependent on tumor stage	Economic study	Same cohort as Leiter et al. (2010) and Garbe et al. (2003) 1969 patients	Total costs Costs per recurrence detection	Total costs for routine melanoma follow-up during this 2-year period: 236.30€patient. Costs for follow-up examinations in: - stage I: 307914€/887261 - stage II: 62673€/252292\$ - stage III: 89651€/352214\$ costs for the detection of one recurrence for physical examination and LN sonography: - stage 14289€/4391\$ and 18035€/131423\$	Retrospective analysis of prospective study data For detailed tables of costs, see original publication The calculation of costs was based on the 2004 GOÄ (Germany) and on the 2004 Medicare fee reimbursement schedule (USA)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>- stage II: 500€/512\$ and 1333€/9712\$</p> <p>- stage III: 168€/171\$ and 1250€/9112\$, respectively.</p> <p>Cost for CR to detect of one 1 recurrence: - stage I: 22886€/20 512\$) (stage II and III: see full-text)</p> <p>Total costs amounted to 990.8€/2208\$ per patient (stage I) and up to 1841€/ 4009\$ per patient (stage III)</p>		
Egberts et al. (2009)	to investigate whether a serial analysis of protein S-100B in serum with a luminescence immunoassay	Diagnostic study	97 patients with stage II/III disease treated within prospective randomized trials	Sensitivity Specificity PPV	sensitivity to detect metastasis: S-100B: 36.5% vs. LDH: 17,3%, (P=0.006). sensitivity in	Treatment bias: Patients were treated with different adjuvant therapies	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	compared with routine LDH assessment could be of value as an indicator of melanoma progression				<p>patients progressing to stage IV: S-100B: 53.8% vs. LDH: 23.1% (P=0.008)</p> <p>Specificity 98% for both S-100B and LDH</p> <p>PPV: S-100B% 73% vs. LDH: 64%</p>		
Moore Dalal et al. (2008)	to determine the effect of the method of detection of initial recurrences and timing of visit on post-recurrence survival in patients undergoing SLN biopsy	Prognostic study	198 Clinical stage I/II patients who developed recurrence after SLNB and who were evaluable for longterm follow-up	<p>Method of recurrence detection</p> <p>Prognistic factors of survival</p>	<p>Median follow-up after first recurrence: 17 months.</p> <p>Self-detection of recurrences in 55% of patients, 78% were seen earlier than their scheduled visit.</p> <p>Self-detected physical diseases: -24% in-transit -23% nodal</p>		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>Physician detection in 45%, in 46% by a scheduled radiographic test (CXR 16%; CT 29%; PET 1%).</p> <p>method of detection significantly predicted post-recurrence survival ($p < 0.05$)</p> <p>Multivariate analysis adjusted for worst site of recurrence, method of detection remained significantly associated with post-recurrence survival ($P = 0.02$) Timing of visit did not affect survival</p>		
Hengge et al. (2007)	to analyze the follow-up of	Economic analysis	526 melanoma patients stage I-III	Recurrence	Detection of 57 recurrences in	Retrospective data	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	<p>melanoma patients under clinical and economic aspects on an as-treated basis based on current recommendations of the AJCC/UICC 2002 and the German Dermatologic Society.</p>			<p>Method of examination</p> <p>Direct medical costs per metastasis</p> <p>QALYs</p>	<p>stages I-III (5-year follow-up period), 61% detected by physician and 39 % by patients. Detection of 25 SPM.</p> <p>The total costs for melanoma follow-up in stages I-III for the 5-year term at the tertiary care university center accounted for 725,095 € (\$870,114)</p> <ul style="list-style-type: none"> - Clinical examinations represented 21,437 € (\$145,724) - technical examinations accounted for 286,656 € (\$343,987) <p>laboratory costs totaled 317,002 € (\$380,402) respectively</p>	<p>Patients kept only about 75% of follow-up appointments (real costs possibly even higher)</p> <p>Costs were calculated according to standardized average fees (GOÄ 2004)</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ferrone et al. (2005)	To determine the incidence of multiple primary melanomas (MPM) from a prospective, single-institution, multidisciplinary database, and to describe the clinical and pathological characteristics and risk factors specific to these patients.	Prognostic study	4484 patients diagnosed with a first PM, 385 had \geq PM	Incidence of MPM Risk factors for MPM	For 74% of patients, the initial melanoma was the thickest tumor. estimated cumulative 5-year risk of: - a SPM for the whole cohort: 11.4%, with 5,5% occurring within the 1st year - a MPM for patients with a positive family history or dysplastic nevi: 19.1% and 23.7%, respectively. - a third PM from the date of the SPM: 30.9%, with 15.6% occurring within the 1st year	Retrospective design (prospective database)	2b
Machet et al. (2005)	to study the value of adding ultrasound lymph node examination	Diagnostic study	373 patients enrolled in a follow-up protocol	Sensitivity specificity	Sensitivity of clinical examination and ultrasound	No information about design (prospective/retrospective)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(7.5 MHz) to the routine clinical examination recommended by French guidelines in melanoma follow-up.				Examination: 71,4% [95% confidence interval (CI) 55.4-84.3] and 92.9 (95% CI 80.5-98.5), respectively. P=0.02). Specificity of clinical examination and ultrasound examination: 99.6% (95% CI 99.2-99.8) and 97.8% (95% CI 97.0-98.4), respectively.		
Goggins et Tsao (2003)	To examine how the risk of a SPM tumor varied with time from diagnosis of CM and examined the patient-specific factors that modify a CM patient's risk of developing a second primary tumor.	Prognostic study	61,245 melanoma patients, of whom 2.32% developed ≥ 1 additional primary CM	Incidence of additional primary CM Risk factors	≥ 1 additional CM in 2.32% of the 61,245 patients during follow-up, ca. 22% of these patients had 2 synchronous primary CMs. HRs correspond to mean rates of 271.3, 227.8, 229.3 and 224.4	Retrospective design Large patient cohort For cumulative risk and monthly hazard diagrams see original article	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>cases per 100,000 per year from 1–4 years, for 5–10 years, 10–15 years, and 15–20 years after diagnosis, respectively.</p> <p>presence of 1st CM on the face, neck, and trunk → increased risk for 2nd CM (in both univariate and multivariate models):</p> <p>stage IV disease → lower risk of 2nd CM</p>		
Garbe et al. (2003)	To prospectively examine and evaluate the results of follow-up procedures in a large cohort of cutaneous melanoma patients.	Prospective cohort study	2,008 patients with stage I-IV	<p>Recurrence detection</p> <p>Time to detection of recurrence</p> <p>Modes of detection</p>	<p>Detection of recurrences:</p> <ul style="list-style-type: none"> - in 71% on scheduled follow-up examinations - in 17% by patients themselves, in 13% of these recurrences 	<p>Descriptive study</p> <p>Standardized follow-up procedures</p> <p>Detailed description of procedures and of follow-up of study</p>	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>diagnosis was established during subsequent regular follow-up examinations</p> <ul style="list-style-type: none"> - in 12% by physicians not participating in the melanoma follow-up schedule <p>In 2,3% of patients, SPM were identified.</p> <p>Modes of detection: see full-text</p>	<p>drop-outs</p> <p>Data about yield of different imaging methods vs. physical examination not listed here (see original article)</p>	
Manola et al. (2000)	To identify factors that are prognostic for survival in patients with metastatic melanoma treated in eight Eastern Cooperative Oncology Group (ECOG) trials conducted over the past 25	Prognostic study	See fulltext	<p>Survival</p> <p>Relative risks</p>	<p>Median survival: 6.4 months (95% confidence interval, 6.1 to 6.9 months.) F</p> <p>factors conferring the greatest increased risk of death:</p> <ul style="list-style-type: none"> - number of metastatic sites 		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	years.				<p>(RR = 1.12)</p> <ul style="list-style-type: none"> - ECOG performance status ≥ 1 (RR = 1.49) - metastatic disease in the GIT (RR = 1.49), liver (RR = 1.44), pleura (RR = 1.35), or lung (RR = 1.19). <p>Prior immunotherapy (RR = 0.84) and female sex (RR = 0.87) were associated with prolonged survival.</p> <p>response to protocol treatment (RR = 0.57) was a significant prognostic factor:</p> <p>Prognostic for poorer survival:</p> <ul style="list-style-type: none"> - increased number of sites of metastasis (RR = 1.30) 		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<ul style="list-style-type: none"> - abnormal LDH (RR = 1.89) - abnormal alkaline phosphatase (RR = 1.76) - abnormal platelets (RR = 1.63) - GI metastases (RR = 1.66) 		
Schlagenhauff et al. (2000)	To evaluate the significance of serum protein S100 in screening for metastases during regular follow-up examinations of patients with malignant melanoma.	Diagnostic study	<p>411 melanoma patients with PM with a tumour thickness ≥ 1.5 mm</p> <p>(237 patients stage II, 148 patients stage III, 26 stage IV)</p>	<p>Sensitivity</p> <p>Specificity</p> <p>False-negatives (FN)</p> <p>True-negative (TN)</p> <p>True-positives (TP)</p> <p>False-positives (FP)</p> <p>Positive predictive value (PPV)</p> <p>Negative predictive value (NPV)</p> <p>efficiency of protein S100 as a diagnostic test</p>	<p>Serum protein S100 cut-off value at 0.13 $\mu\text{g/l}$:</p> <p>FN: n=28</p> <p>TN: n=355</p> <p>TP: n=13</p> <p>FP: n=15</p> <p>PPV: 46</p> <p>NPV: 93</p> <p>Test efficiency (< 2): 1.39. The protein S100 values of the metastasis group were significantly higher (P = 0.0.001).</p> <p>S100: sensitivity: 0.32,</p>	Interval between relapse and serum analysis of S100: up to 2 months (clinical situation may change during this interval)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>specificity: 0.96</p> <p>cut-off value of 0.08 µg/l (outcomes for this cut-off: see full-text): lower specificity, PPV and test efficiency</p> <p>sensitivity: 41%</p>		
Brobeil et al. (1997)	To determine the impact of an intensive follow-up protocol on the stage of disease at diagnosis of subsequent primary melanomas.	Prevalence study	101 patients with SPM (67 with synchronous and 44 with metachronous SPM)	Incidence of MPM Tumor thickness in primary and secondary lesions	<p>Of 2,600 patients: 4.3% of patients with SPM</p> <p>mean tumor thickness: 1,72 mm for PM vs. 0.58 mm for SPM</p> <p>mean thickness of metachronous melanoma: 2.27 (range 0.18-10.2) mm for PM vs. 0,90 (range 0.11-2.58) mm for SPM</p> <p>initial primary melanomas tended to be thicker (by an</p>	<p>Retrospective design</p> <p>Predominantly male patients</p>	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					average of 3.8 mm, p = 0.008).		
Basseres et al. (1995)	To assess the cost-effectiveness of surveillance in stage I melanoma.	Prevalence study	528 patients with melanoma stage I and Clark's level II or higher (214 males, 314 females)	Time to relapse	<p>115/528 patients had relapses.</p> <p>The rate of relapse and the mean time between initial resection and relapse: 9.6% and 37 months for melanoma < 1.5 mm, 34% and 24 months for melanoma of 1.5 to 3 mm, 47.7% and 17 months for melanoma > 3 mm.</p> <p>Time between relapse and last follow-up examination: ≤ 2 months in 9% of cases, ≤ 3 months in 23% and ≤ 4 months in 34%.</p>	<p>Retrospective design</p> <p>For cost analysis see full text of paper</p>	2b
De Giorgi et al. (2010)	To identify main risk factors	Prognostic study	40 patients with MPM	Thickness of SPM	Overall mean thickness of	Retrospective design	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	associated with MPM and to investigate the association between regular follow up and tumour thickness of a SPM			Odds ratio of having MPM	<p>melanoma: 0.517 mm for first melanoma and 0.64 mm for SPM (P = 0.12).</p> <p>Significant difference in mean tumour thickness in patients not attending follow up vs. patients adhered to follow up (1.22 mm vs. 0,36 mm)</p> <p>OR of having a diagnosis of MPM in comparison with SPM:</p> <ul style="list-style-type: none"> - female 1.94 (vs. male) - >/= 1 atypical nevi 4.18 - positive family history 2.18 	Small patient sample with secondary melanoma	
Bower et al. (2010)	To determine the outcome and incidence of multiple primary	Prognostic factors	41 melanoma patients with multiple melanoma and no evidence of	Disease-free-survival overall survival	Thickness of subsequent vs. primary melanomas:	Posthoc analysis from a multi-institutional prospective	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma (MPM) and other cancer types among patients with melanoma. The risk for secondary nonmelanoma malignancies was also assessed.		distant metastasis and no palpable nodal metastasis. (Patients with synchronous lesions not included)		<p>median 0,32 mm versus 1,50mm, $p < 0,0001$)</p> <p>Multivariant analysis: age ($p = 0,028$), lymphovascular invasion ($p = 0,010$) and SSM subtype of the original melanoma ($p = 0,024$) were associated with MPM.</p> <p>Patients with MPM vs. patients with single primary melanoma: - 5-year-DFS: 88,7 vs. 81.3%, $p = 0,380$ - 5-years-OS 95,3 vs. 80%, $p = 0,005$</p> <p>detection of secondary melanomas within the first year in</p>	<p>randomized trial</p> <p>Loss-to-follow-ups not commented</p> <p>Patients with melanoma <1 mm excluded</p>	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>29,3% of patients, detection of subsequent melanoma within 60 days in 9,8 % after primary melanoma.</p> <p>Median time to development of second primary: 29 months.</p> <p>Nonmelanoma malignancies in 6,1% of patients</p>		
Fusi et al. (1993)	To determine whether there are significant trends in the prognostic factors or in the timing and sites of recurrence.	Prognostic study	250 patients with recurrent malignant melanoma	<p>Time to recurrence</p> <p>Sites of recurrence</p> <p>Survival</p>	<p>Sites of first recurrence: 52% regional nodes, 17% local recurrences, 8% in-transit metastases, 23% to a distant organ.</p> <p>Diagnosis of recurrences: 67% within 24 months, 81% within 36 months</p>	<p>Retrospective design</p> <p>Population not described in detail</p>	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>Survival after the diagnosis of recurrence was independent of:</p> <ul style="list-style-type: none"> - thickness of the primary tumor - duration of DFI (local, in-transit or regional nodal) <p>diagnosis of distant organ metastasis: shorter survival</p> <p>local recurrence, in-transit metastasis, and regional nodal metastasis: comparable survivals</p>		
Romano et al. (2010)	implications for follow-up guidelines	Prognostic study	340 patients AJCC stage III who recurred	<p>Relapse-free survival</p> <p>Overall survival</p> <p>Mode of relapse detection</p>	<p>5-year RFS for stage IIIA, IIIB, and IIIC patients was 63%, 32%, and 11%, respectively</p> <p>Site of first relapse: - local/in-transit</p>	<p>Retrospective design</p> <p>estimated site-specific risk of first relapse for each substage</p>	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				5-year survivals	<p>28%</p> <ul style="list-style-type: none"> - regional nodal 21% - systemic 51% <p>1st relapses detected by patient or family, physician, or by screening radiologic tests in 47%, 21%, and 32% of patients, respectively.</p> <p>Factors associated for better OS (multivariate analysis):</p> <ul style="list-style-type: none"> - younger age - 1st relapse being local/in-transit or nodal, asymptomatic, or resectable. <p>estimated 5-year survivals for stages IIIA, IIIB, and IIIC from time of 1st</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					relapse: 20%, 20%, and, 11%, respectively. Survival curves showed a plateau at around 50 months in all substages.		
Stucky et al. (2010)	Understanding the risk factors for local and in-transit recurrences (LR/ITR) may help facilitate methods of prevention, early detection, and treatment.	Prognostic study	255 patients treated with surgical resection of a single melanoma and with at least 18 months of follow-up (26 patients with LR/ITR)	Time to recurrence Site of recurrence	average time to LR/ITR: 16.2 months (range, 4.2-82.4 mo). Within 12 months of follow-up: LR/ITR in 53% of the patients within 18 months of follow up: 78% of recurrences patients with LR/ITR (n=26): - 3% local recurrences - 5% in transit recurrence - 2% both LR/ITR	Retrospective design	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<ul style="list-style-type: none"> - 56% concurrent regional LN metastases. LR/ITR was associated with: <ul style="list-style-type: none"> - older age - thicker original tumor - presence of angiolymphatic invasion in the original melanoma 		
Meyers et al. (2009)	To determine the impact of routine imaging on the method of detection of first recurrence in patients with stage II and sentinel lymph node-positive stage III melanoma.	Prognostic study	118 patients with stage II or III	<ul style="list-style-type: none"> Mode of recurrence detection Time to recurrence Overall survival Costs 	<ul style="list-style-type: none"> Median time to recurrence: 14 months (range, 2-88 months) Types of recurrence: 9% local, 40% in transit, 16% regional lymph node basin, 35% distant Mode of detection: <ul style="list-style-type: none"> - self-detection in 37% asymptomatic patients 	<ul style="list-style-type: none"> Retrospective analysis of prospective database Small patient cohort 	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<ul style="list-style-type: none"> - 30% of patients with symptoms that led to detection of recurrence - in 23% by physician during routine follow-up examination - in 7% by routine follow-up imaging - in 3% by high LDH values <p>Median survival after recurrence: 22 months (locoregional disease) vs. 7 months (distant disease)</p> <p>no difference in survival among symptomatic vs. asymptomatic patients</p> <p>no significant difference in survival between a</p>		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					self-detected recurrence and recurrence detected by either a physician or by routine diagnostic scans.		
Francken et al. (2008)	To calculate recurrence rates and establish prognostic factors for recurrence to help redesign a follow-up schedule.	Prognostic study	4726 patients with a single invasive primary cutaneous melanoma and stage I or II disease	Recurrence rate Disease-free survival Disease-specific survival	Recurrence occurred in 18.9% (895 of 4748) of patients overall, 5.2% (95 of 1822) of those with stage IA disease, 18.4% (264 of 1436) with IB, 28.7% (215 of 750) with IIA, 40.6% (213 of 524) with IIB and 44.3% (86 of 194) with IIC disease. Overall, the median disease-free survival time was 2.6 years, but there were marked differences between AJCC subgroups. Primary tumour	Retrospective design Part of the cohort very old (starting 1959) For Kaplan-Meier curves for time to first recurrence see original article Time between relapse and last follow-up not measured	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					thickness, ulceration and tumour mitotic rate were important predictors of recurrence.		
Khan et al. (2006)	To help develop parameters for future trials, treatment history and	Prognostic study	212 patients with pathologically proven stage IV melanoma	survival	<p>median survival of stage M1c: 6.0 months. Survival was longer for stage M1a and M1b and shorter in older patients. No significant differences were found in survival based on gender.</p> <p>Patients with a normal LDH level survived almost twice as long (median survival, 12.0 months, [95% CI 8.85-15.15]) compared to those with an elevated LDH level (median survival 6.0</p>		2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months, [95% CI 3.51–8.49]); these were significantly different by the log-rank test ($\chi^2 = 5.88$, $P = .0154$).		
Martenson ED et al. (2001)	To evaluate whether S-100B protein in serum is an independent prognostic marker in malignant melanoma.	Prognostic study	1,007 consecutive patients for scheduled follow-up visits. (876 stage I, 35 stage II, 96 stage III)	Disease-specific survival	The mean serum concentration of S-100B protein was significantly related to clinical stage significant differences in disease-specific survival for patients with S-100B values $>$ and < 0.10 mg/L, both when analyzed in the whole group of patients and in the subset of patients with metastatic disease (clinical stages II to III) Significantly lower levels in patients in	Follow-up diagnostic procedures not stated in article Study included in Mocellin et al. 2008 The three-stage system for classification of malignant melanoma	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>whom the metastases had been resected compared with patients with subcutaneous and/or LN metastases (P=0,004) or disseminated metastases (P < 0,001).</p> <p>multivariant analysis: In clinical stages II and III, the S-100B protein level in serum was the strongest independent prognostic factor for melanoma survival (P<0,001)</p>		
Mruck et al. (1999)	To investigate the predictive value of the protein S100 as a tumor marker in the post-surgical follow-up staging of patients with	Diagnostic study	50 patients	<p>Sensitivity</p> <p>Specificity</p> <p>Predictive values</p>	<p>FDG-PET: Sensitivity=100%, specificity=95%</p> <p>Conventional imaging: Sensitivity=92%,</p>	<p>Selection criteria not described</p> <p>No information about time interval between blood sample and</p>	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	high risk melanomas (Clark levels IV/V, thickness>0,75 mm)				<p>specificity=82%</p> <p>S100 : Cut-off-levels were 0,1 µg/l and 0,2 µg/l: Sensitivity=85%, specificity=55% when measured by RIA, Sensitivity=77%, specificity=61% when measured by LIA</p> <p>NPV=91% (RIA) and 88% (LIA) PPV=39% (RIA), 40% (LIA)</p> <p>At a cut-off level of 4,0 µg/l, TK showed a sensitivity of 70% and a specificity of 41%.</p>	<p>imaging procedures</p> <p>Small patients cohort</p>	
Poo-Hwu et al. (1999)	To evaluate the follow-up protocol instituted in 1987 at the Yale	Retrospective prognostic study	373 patients followed according to the protocol schedule.	<p>Recurrence-free interval</p> <p>Overall survival</p>	<p>median time interval to recurrence: - stage I:22.0</p>	<p>Detailed follow-up procedure given</p> <p>Retrospective</p>	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	Melanoma Unit to improve upon the detection of disease recurrence in patients with American Joint Committee on Cancer Stage I-III cutaneous melanoma.		AJCC Stage I-III	Modes of detection	<p>(range, 2.0-60.5) months</p> <p>- stage II 13.2 (range, 2.4 -71.0) months</p> <p>- stage III: 10.6 (range, 2.3-53.8) months</p> <p>51% locoregional recurrences detected by patients, 64% distant metastases detected by physicians</p> <p>physician-detected recurrences:</p> <ul style="list-style-type: none"> - 57% by history or physical examination - 18% by abnormal chest X-ray - 23% by CT scan or MRI - 2% by elevated LDH <p>median survivals:</p>	design	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>34 months for locoregional vs. 13 months for distant recurrences</p> <p>All 19 patients with MPM were identified by physician-performed physical examination.</p>		
von Schoultz et al. (1996)	To assess the potential prognostic value of serum concentrations of S-100β	Serum levels of S-100β protein were measured in a consecutive series of 643 patients with cutaneous malignant melanoma during 08/1990-10/1992	643 patients in total 553 patients: stage I (with/without satellites within 5 cm), 24 patients: stage II (in-transit metastases and/or regional lymph node metastases), 66 patients: stage III (distant metastases)	Overall survival	<p>Significant correlation of serum concentrations of S-100β to clinical stages. They were significantly higher in men than in women ($p < 0,001$).</p> <p>Association between OS rate with serum levels of S-100.</p> <p>observed/expected death ratio was markedly increased with increasing</p>	<p>No information about number of blood samples taken</p> <p>Poor information about population</p> <p>No information about study design (prospective/retrospective?)</p> <p>Disease classification different from AJCC was used</p> <p>study included in</p>	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					levels of S-100 β (P<0,001). A fivefold increase in relative hazard was indicated by a value of S-100 β >0,6 μ g/l (P<0,001) and when its cut-off level was used S100 β had additional prognostic value independent of clinical stage (P<0,001).	Mocellin et al. 2008	
Kaufmann, Crone-Münzbrock (1992)	To evaluate the value of CT and US in detecting abdominal metastases.	Diagnostic study	849 patients with malignant melanoma	Sensitivity specificity	Interval between therapy of primary melanoma and diagnosis of recurrence: 2,5 years US: sensitivity; 53%, specificity; 98% CT sensitivity 85%, specificity 94%	Selection criteria not described No information about time interval between ultrasound and CT	2b-
Kelly et al. (1985)	To develop	Prognostic study	295 patients with	disease-free	independent	Incomplete patient	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	guidelines for the follow-up of patients with primary cutaneous melanoma		metastatic malignant melanoma (clinical Stage I).	interval predictors of disease-free interval recurrence rate	significant predictor of DFI: tumor thickness ($p = 0.0015$) (not significant: sex, age, elective regional LN-dissection, tumor location) diminution of DFI from 3.97 years (< 1.0 mm) to 1.10 years (> 5.0 mm) is evident with increasing thickness. Association between increased risk of recurrence and increases in tumor thickness >1.5 mm in the first 4 years (greatest increase in risk is in the 1st year)	records (of 295 patients, only 177 were included in multivariate analysis) For details of survival and recurrence statistics, see original article	
Alvarado et al. (2011)	to assess the frequency of the	Prevalence study	146 patients with primary melanoma	incidence rate of metastases	Recurrences in 75% of patients	Limitation of study and bias not	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	pelvic metastases in patients with primary melanoma in the head and neck to identify evidence supporting the use of pelvic CT scans in this group of patients.		who had adequate follow-up evaluation for at least 5 years. (109: stage I or II disease, 33: patients stage III, 4: stage IV)	Survival Time to recurrence	median time to the first recurrence: 13 months. Median duration of the OS: 3.8 years. Median duration of the OS for the 110 patients with recurrences: 2.3 years. 48% of patients had remained alive >4 years from the time of the first diagnosis of melanoma, developement of metastases in 56% of patients, developement of pelvic metastases in 7% of patients most common sites of first recurrence: lymph nodes (n=41, 37%),	described Patients with mucosal melanoma included	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					satellite soft tissue (n=41, 37%), chest (n=33, 30%), abdomen (n=13, 15%), and the brain (n=7, 6%).		
DeRose et al. (2011)	to determine the utility and cost effectiveness of radiological restaging of patients with stage IIB–IIIC melanoma at the 3-year follow-up time point	Economic and prevalence study	210 patients with stage IIB–IIIC melanoma	Recurrence rate Time to recurrence TP FP costs per diagnosis	Recurrences in 55% of patients, in 69% with disease symptoms 88% recurrences before 3 years (median time to recurrence 12 months, 95% confidence interval: 10–16 months) 25 head CTs, 27 head MRIs, 52 torso CTs were performed. In total: 3 FP and 2 TP Total cost per diagnosis: \$312 990.	Reference standard not described	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hansel et al. (2009)	To analyse the frequency of late recurrent MM in south-eastern Germany	Prevalence study	1881 patients in stage I or II (AJCC) with a follow-up of > or = 10 years (1 uveal melanoma, excluded)	Overall survival Relapse-free survival	20 patients with late recurrence of melanoma . largest period from diagnosis of PM to recurrence: 25.1 years, median 13.9 Loco-regional metastases in 63.2%, distant metastases in 42%, deaths in 75% All but one of the survivors had in-transit metastases only (n=3). OS: between 10.9 and 35.7 years (median 14.7). Statistical variate analysis failed to identify possible factors significantly associated with late recurrence	Conclusion about infrequency of late recurrence can be drawn, but statistical conclusions inside this small cohort are not valid because of small patient sample	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Einwachter-Thompson, MacKie (2008)	To review patients with invasive melanoma thinner than 0.5 mm followed for at least 5 years to provide an evidence base for considering modification of guidelines.	cohort study	430 patients with invasive melanoma < 0.5 mm	Deaths Interval between two primaries	19% deaths from melanoma in the whole group. 11 patients developed simultaneous or subsequent primary melanoma (3 simultaneously, 5 within 36 months, 1 between 3-5 years, 2 between 69 and 73 months after the first diagnosis.)	Data on thin melanomas only Retrospective design In some cases pathological review showed melanoma > 0.5 mm at diagnosis or some patients developed thicker SPM	3b
Francken AB et al. (2008)	To assess the frequency of patient detection of both first primary melanomas (FPMs) and second primary melanomas (SPMs)	Prevalance study	112 patients with recently diagnosed SPM	FPM and SPM-detection rate	Patients detected 59% of the FPMs vs. 46% of the SPMs themselves significant predictors for a patient-detected FPM: - females gender - greater Breslow tumour thickness - younger age (OR 4,9; 3,2 and	Only patients with SPMs were interviewed (both in situ and invasive melanomas were included.) Excluded were patients who had multiple primary melanomas or who developed a	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					0,9 respectively). predicting factors for the patient detection of a SPM: - greater tumour thickness - ready visibility of the lesion to the patient (OR 1,9 and 3,6 respectively)	recurrence earlier than the SPM (amongst others)	
Francken et al. (2007)	In this prospective study the frequency of detection of first melanoma recurrence (FMR) by patient or doctor was analyzed	Prevalence study	211 patients with a first melanoma recurrence (FMR) were interviewed	Median time to detection of an FMR Sites of recurrence Modes of detection Mean survival	median time to detection of FMR: 28 months (range, 2–322) Symptoms present in 74%, in 39% FMR detected as a consequence of symptoms. in 56 patients FMRs detection was at a follow-up visit: - 63% by physical examination - 14 % by chest x-	risk of bias (in group B, only patients with unambiguous information in patients records were included)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>ray</p> <ul style="list-style-type: none"> - 11% by LN ultrasound <p>Detection of FMR:</p> <ul style="list-style-type: none"> - in 154 patients by patient, partner, or relative - in 57 patients by a doctor <p>mean survival time: 23.8 months.</p>		
Zogakis et al. (2007)	To estimate survival and time to first recurrence in patients with negative sentinel nodes.	Prevalence study	773 melanoma patients with tumor-negative SLNs	<p>Overall survival</p> <p>Disease-free survival</p> <p>Time to first recurrence</p>	<p>Recurrence in 8,9 % of patients with tumor-negative SLNs</p> <p>1-year, 3-year, and 5-year DFS rates: 98%, 91%, and 88%, respectively.</p> <p>1-year, 3-year, and 5-year OS rates: 99.7%, 96%, and 92.7%, respectively.</p> <p>Significant</p>	<p>Subgroup of sentinel-node-negative patients</p> <p>Retrospective design</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>differences in survival between patients with local/in-transit and nodal vs. distant first recurrence</p> <p>No significant difference in time to the development of local/in-transit vs. nodal vs. distant recurrence</p>		
Beyeler M et al. (2006)	To compare the efficacy of imaging techniques and serum S100 in the early detection of melanoma progression	Diagnostic study	127 patients	<p>Sensitivity</p> <p>Mode of detection</p>	<p>In 5.5% of patients, S100 was the first indicator of disease progression.</p> <p>40.2% of relapses noted by the patients themselves, 27.6% diagnosed by a doctor. Imaging procedures lead to detection of melanoma recurrence in</p>	<p>Population not described.</p> <p>Small patient number in every stage</p> <p>specificity not given</p> <p>No information about time interval between imaging procedures and blood samples.</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>26.8%. (US in 6 patients, PET scan in 12 patients, CT scan in 13 patients, PET-CT in 3 patients, chest x-ray in 0 patients)</p> <p>S100 sensitivity: 37%.</p>		
DiFronzo et al. (2001)	To investigate whether routine reassessment and careful education of postoperative patients would facilitate earlier diagnosis of a subsequent second primary melanoma, as reflected by reduced thickness of that lesion.	cohort study	3310 patients with primary melanoma AJCC stage I/II	Rate of patients who developed SPM	<p>114 patients with AJCC Stage I or II melanoma developed a SPM</p> <p>AJCC stages of SPM: - lower in 48% - same-stage in 50%</p> <p>mean tumor thickness for PM: 1.32 +- 1.02 mm, for SPM: 0.63 +- 0.52 mm</p> <p>level of invasion of SPM vs. PM - decreased in 60%</p>	Standard follow-up procedure is defined	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>- remained the same in 27%</p> <p>- increased in 13% of patients.</p> <p>significant differences in stage, tumor thickness, and level of invasion between PM and SPM (paired t test)</p>		
Dicker et al. (1999)	To address the following questions: (i) what is the overall risk of recurrence? (ii) When do recurrences occur? (iii) How are they detected? (iv) What is the risk of recurrence from melanomas which appeared to be confined to the epidermis when they were excised? (v) How are second primary	Prevalence study	1568 patients with stage I melanoma	<p>Risk of recurrence</p> <p>First site and detection of recurrences</p> <p>Changes in behaviour (see full text)</p>	<p>Overall 19% developed recurrences</p> <p>79% of recurrences occurred during the first 3 years. <8% after the 10-year interval.</p> <p>patients detected their recurrences more often than doctors at follow-up clinics</p> <p>The first site of recurrence was:</p>	<p>Large patient cohort</p> <p>No standardized follow-up protocol</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanomas detected? (vi) Do patients alter their behaviour after attending a melanoma follow-up clinic?				<ul style="list-style-type: none"> - local 17% - in transit 6% - local nodes 56% - distal 22% 		
Johnson et al. (1998)	To characterize the subgroup of patients with multiple melanomas.	cohort study	60 with with multiple primary melanomas, and	<p>Time to diagnosis of second melanoma</p> <p>Tumor thickness of second melanoma</p>	<p>In 30% MPM were diagnosed concurrently within 1 month, in 63% > 1 month apart, and in 7% concurrently and subsequently (>2 primaries).</p> <p>median time interval between subsequent diagnoses of 2nd PM: 63 months (range 2-456)</p> <p>in patients with > 2 PM: median time interval between subsequent lesions: 42 months (range 2-456).</p>	<p>Retrospective design</p> <p>Small patient cohort</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>Appearance of subsequent primary</p> <ul style="list-style-type: none"> - 42% within 3 years - 17% between 3-7 years - 42% > 7 years - 19% > 10 years - 6% > 15 years <p>After initial diagnosis</p> <p>mean tumor thickness from the 1st primary lesion to the subsequent lesion(s) decreased from 0.98 to 0.90 mm.</p>		
Sylaidis et al. (1997)	To investigate the incidence of recurrence in thick (> 4 mm) localized melanoma to draw conclusions about duration and frequency of follow-up.	cohort study	244 patients (176 patients had their first recurrence between years 1 and 10 postoperatively)	<p>Overall survival (= disease specific survival in this study)</p> <p>Survival after first recurrence</p>	<p>5-year survival: 45% (95% CI 39%, 51%)</p> <p>10-year survival: 37% (95% CI: 31%, 43%).</p> <p>- 42 patients with local recurrences:</p>	<p>Retrospective design</p> <p>Patient cohorts only includes patients with melanoma > 4 mm thickness</p> <p>No attempts to</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>5-year survival rate of 26% (95% CI: 13%, 39%).</p> <p>- 93 with regional recurrences: 5-year survival rate of 18% (95% CI: 10%, 26%).</p> <p>- 41 with distant metastases: 5-year survival rate of 5% (95% CI: 0%, 11%).</p>	<p>recover patients lost to follow up</p> <p>Patients who died of other diseases were excluded</p>	
Martini et al. (1994)	To establish a follow-up guide for cutaneous melanoma.	Prevalence study	840 stage I cutaneous melanoma patients (recurrence in 202 patients)	Time to first recurrence Pathway of first recurrence	<p>Mean time to first recurrence: 22.27 months (median 13.5 months).</p> <p>45.54% of relapses occurred during the 1st year, 79.21% during the first 3 years, 89.6% in the first 4 years and 94.55% in the first 5 years.</p> <p>Recurrences significantly earlier (mean 18.18 months, median 10.5 months) in</p>	<p>Retrospective design with incomplete patients records (only 675 of 840 patients "histologically evaluable").</p> <p>Patient cohort contains melanoma in situ (105 lesions not invasive).</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>males than in females (mean 26.78 months, median 17.5 months).</p> <p>Pathway of first recurrence: 81.19%: lymphatic 17.33%:hematic 1,48%: unknown</p>		
Baughan et al. (1993)	To assess the objective value of follow-up in diagnosing and treating tumour relapse and its subjective value as perceived by patients.	cohort study	339 melanoma patients (65 patients developed recurrences)	<p>Time to relapse</p> <p>5-year-survival</p> <p>Questionnaire results (subjective value of follow-up to patients)</p>	<p>82% of first relapses occurred within 3 years and none has yet been seen after 7 years.</p> <p>Actuarial 5-year-survival (doctor-diagnosed vs. patient-diagnosed recurrences): 18 vs. 20 % (P>0,8)</p> <p>For time to first relapses over year of follow-up, see fig. 1 in original article.</p>	<p>Retrospective design</p> <p>No standard follow-up protocol</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Kang et al. (1992)	To examine the natural history and impact of regular follow-up evaluation of multiple primary cutaneous melanoma	cohort study	41 patients with multiple cutaneous melanoma	Interval between melanoma diagnoses Tumor thickness	In 39% the MPM were diagnosed concurrently (vs. 61% subsequently). Significant decrease in Breslow's thickness from the 1st PM (1.21 ± 0.28 mm) to the second (0.51 ± 0.08 mm) (P<0.05) median time interval between sequential melanomas: 36 months (range 2-372)	Retrospective design Small patient cohort	3b
Brandt et al. (1990)	To investigate the prognostic value of several factors on cancer-specific survival and cancerspecific disease-free survival, from time of excision on, by performing life-	Prevalance study	231 patients who underwent local excision as the single treatment of melanoma with a thickness of ≤ 1.5 mm.	Cancer-specific survival (CSS) cancer-specific disease-free survival	During follow-up: - 14/206 patients died. - (6 patients as a result of the disease, 8 from other causes) Recurrence in 11 patients: - 4 local	Retrospective design No standard therapy and follow-up protocol Different excision margins have been used	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	table analysis on 206 evaluable patients.				<p>recurrences</p> <ul style="list-style-type: none"> - 4 LN metastases - 3 distant disease. <p>- Actuarial 5-year CSS: 96.1%</p> <p>- 10-year CSS: 92.3%</p> <p>- 15-year CSS: 92.3%.</p> <p>cancer-specific DFS after 5 years: 95.2%, after 10 years: 86.9%, after 15 years: 86.9%.</p>		
McCarthy et al. (1988)	To re-examine follow-up regimens and provide follow-up guidelines tailored to the risk of the individual patient.	Prevalence study	886 melanoma patients with evidence of recurrent disease	<p>Recurrence rate</p> <p>Site of first recurrence</p> <p>Time to first recurrence</p>	<p>Time to first recurrence depended upon:</p> <ul style="list-style-type: none"> - thickness of the tumor - whether ELND was performed or not <p>Times to recurrence for 50% respectively 95% of the recurrent patients in months:</p>	<p>Retrospective design</p> <p>Different follow-up schedules over time</p> <p>Large patient cohort</p>	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<ul style="list-style-type: none"> - 32 months and 134 months for 0.1 – 0.7 mm tumor thickness - 25 months and 116 months for 0.8 – 1.5 mm tumor thickness without ELND - 36 months and 145 months for 0.8 – 1.5 mm tumor thickness with ELND - 16 months and 108 months for 1.6 – 3.0 mm tumor thickness without ELND, - 20 months and 112 months for 1.6 – 3.0 mm tumor thickness with ELND - 12 months and 60 months for > 3.0 mm tumor thickness without ELND - 19 months and 60 months for > 		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					3.0 mm tumor thickness with ELND		
Buljan M et al. (2010)	To analyse the clinical, histopathological and epidemiological characteristics of 36 patients, with multiple primary melanomas (MPM)	cohort study	36 patients (3,6%) were diagnosed with MPM. 28 patients: 2 primary melanoma 6 had 3 melanoma and 2 had 4 melanomas.	Time interval between first and subsequent melanoma	Diagnosis was established synchronously in 11 patients in the the other patients time interval between PM and SPM varied from 1 month to 16 years, average time interval : 41 months.	Retrospective design Small population No data concerning examination intervals of follow-up	3b-
McMeniman et al. (2010)	To define the risk factors for multiple primary melanoma (MPM).	Prognostic factors	58 patients with more than one primary were interviewed via telephone	Rate of patients who developed MPM Age at diagnosis Tumor thickness Risk factors	50% of patients had their first melanoma between 40–59 years of age. 68% had the same or a less invasive level of melanoma on their subsequent lesion/s.	Data incomplete or inaccurate on many patients Risk of recall bias Small patient cohort	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					<p>With subsequent melanomas a greater proportion were found by the dermatologist.</p> <p>Risk factors: see full-text</p>		
Zissimopoulos et al. (2009)	To evaluate ¹¹¹ In-O Scintiscan in malignant melanoma for the detection of recurrence and metastatic disease, after clinical and histological diagnosis and initial surgery treatment and during 3 years of follow-up.	Diagnostic study	<p>35 patients with malignant melanoma</p> <p>20 female, 15 male, mean age 46±7, range 32-51 years</p> <p>Treatments in some patients: Interferon alpha, IL-2</p>	Positive- rate	<p>During 3 years of the follow-up period, 26/35 of the patients had clinical recurrence.</p> <p>(17 patients: regional lymph node metastases, 9 distal metastases)</p> <p>In ¹¹¹In-O Scintiscan 20/26 patients had positive scans with 56 lesions, 6 had negative scans. CT images showed only 31 lesions.</p>	<p>Selection criteria not given</p> <p>Small sample size</p> <p>No information about false positives and false negatives.</p> <p>Positive CT: only number of metastases is given but not number of patients</p> <p>No information about interval between CT and ¹¹¹In-O Scintiscan</p> <p>No information</p>	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						about results of other staging modalities	
Solivetti FM et al. (2006)	to assess the potential of ultrasonography (US) in the detection of in-transit or satellite metastases.	Diagnostic study	600 patients who had thick melanoma (>1 mm) and who were clinically free of in-transit or satellite melanoma metastases during follow-up.	Number of detected metastases US features of in-transit metastases	US suspicion of in-transit or satellite metastases in 63 patients. A total of 95 lesions were identified. Lesion diameter ranged from 4 mm to 17mm (mean diameter 8 mm). Four of 95 lesions had a diameter >1 cm; most (82 cases) had diameters of 6–8 mm. No false positive or false negative US US features: see full-text		4
Dancey et al. (2004)	to assess patient opinions on follow-up.	cohort study	231 melanoma patients and 50 GPs who filled out a questionnaire	Patients` opinion on follow-up GP satisfaction	98% found the clinics to be useful 22,5% felt it was		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	to ascertain whether GPs would be willing to follow melanoma patients up in a primary care setting				<p>difficult to attend the clinic</p> <p>53% expressed some degree of anxiety at attending the outpatient department</p> <p>12%: recurrence, 52% of them detected it themselves</p> <p>60% of patients would be happy to consider routine follow-up with their GP</p> <p>70% of local GPs would be unhappy to monitor their patients.</p>		
Johnson et al. (1999)	to determine the value of follow-up in two subgroups of patients with a thin melanoma less	Prevalence study	306 patients: 178 with a melanoma < 0.76 mm (group 1) and 128 with a melanoma of 0.76	Recurrence rate	Recurrences in 4 patients (2.2%) in group 1 and 16 (12.5%) in group 2	Standardized follow-up procedure	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	than 0.76 mm and 0.76- 1.5 mm thick.		- 1.5 mm (group 2)		<p>group 1: all patients presented with untreatable, widespread metastatic disease, detected by a clinician in the follow-up clinic.</p> <p>group 2: 1: local recurrence, 1 in-transit recurrence, 3 subcutaneous recurrence, 7 nodal metastases and 4 patients distant metastases. In 13/16 patients, recurrence was detected by clinician in the follow-up clinic.</p>		
Mooney et al. (1998)	To asses the impact on survival by components of a surveillance program (physical examination, blood tests, and chest	Prognostic study	1004 patients AJCC Stage I or II	<p>Method of detection</p> <p>Survival</p> <p>5-, 10- and 15-year survival</p>	Physical examination detected 72% constitutional symptoms indicated 17% and chest radiograph	<p>Retrospective design</p> <p>No information about verification/reference test</p>	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	radiograph) used to detect recurrences in patients with cutaneous melanoma				revealed 11% of recurrences. Blood tests did not predict any recurrence. 9/17 patients with recurrences detected by chest radiograph alone underwent curative surgical resection. These patients had a statistically significant prolonged survival compared to those surgical candidates who did not undergo resection. No statistically significant difference in OS between patients with asymptomatic pulmonary recurrences and those with symptomatic pulmonary metastases		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					The 5-year, 10-year, and 15-year OS rates, with their associated 95% CI, for patients who remained disease free: 92%±2%, 85%±3%, and 77%±4%, respectively. The rates for patients with recurrences are 46%±8%, 17%±6%, and 14%±6%, respectively.		
Mooney et al. (1997)	To assess costs and potential benefits of an intensive chest X-ray (CXR) screening program to detect asymptomatic pulmonary metastases in patients with intermediate-thickness, local, cutaneous melanoma.	Economical study	A hypothetical cohort of patients diagnosed in 1996 with intermediate-thickness, local, cutaneous melanoma. Intermediate thickness melanoma was defined as ≥ (AJCC) Stage I - classification pT2	Potential savings in years of life from surgical resection of lung metastases in quality-adjusted and non-quality adjusted life years (QALY AND NQALY), undiscounted and discounted Cost-effectiveness ratio (C/E) of CXR screening	For the base case, cost of screening per NQALY was \$150,000 and was \$165,000 for QALY in 1996 dollars using undiscounted health benefits. Screening accounted for approximately 80% of program costs and treatment accounted for 20%.	No level of evidence was assigned because of unique study design and hypothetical cohort of patients	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Annual cost-effectiveness ratios were lowest in Years 3-10 of screening. The total cost of a 20-year screening program for patients diagnosed in 1996 was estimated to be between \$27-\$32 million.		

8.2.5. Literatur

Literatur:	Zuteilung zur Fragestellung:		
	VII.4	VII.5	VII.6
Alvarado et al. (2011)	x	x	x
Basseres et al. (1995)	x	x	x
Baughan et al. (1993)	x	x	
Beyeler et al. (2006)			x

Literatur:	Zuteilung zur Fragestellung:		
	VII.4	VII.5	VII.6
Bower et al. (2010)	x	x	
Brandt et al. (1990)	x		
Brobeil et al. (1997)	x	x	
Brown et al. (2010)			x
Buljan et al. (2010)	x	x	
Dancey et al. (2004)	x	x	
De Giorgi et al. (2010)	x	x	
DeRose et al. (2011)	x	x	x
Dicker et al. (1999)	x	x	
DiFronzo et al. (2001)	x	x	
Egberts et al. (2009)			x
Einwachter-Thompson, MacKie (2008)	x	x	
Ferrone et al. (2005)	x	x	
Francken et al. (2008)			

Literatur:	Zuteilung zur Fragestellung:		
	VII.4	VII.5	VII.6
Francken et al. (2005)	x	x	
Francken et al. (2007)	x	x	x
Fusi et al. (1993)	x	x	
Garbe et al. (2003)	x	x	x
Goggins et Tsao (2003)	x	x	
Hansel et al. (2009)	x	x	
Hengge et al. (2007)	x	x	x
Hohnheiser et al. (2010)	x	x	
Johnson et al. (1998)	x	x	
Johnson et al. (1999)	x	x	x
Kang et al. (1992)	x	x	
Krüger et al. (2011)			x
Kaufmann, Crone-Münzbrock (1992)		x	x
Leiter et al. (2009)			

Literatur:	Zuteilung zur Fragestellung:		
	VII.4	VII.5	VII.6
Leiter et al. (2010)	x	x	
Leiter et al. (2011)	x	x	
Machet et al. (2005)			x
Manola et al (2000)	x		x
Martenson et al. (2001)			
Martini et al. (1994)	x	x	
McCarthy et al. (1988)	x	x	
McMeniman et al. (2010)	x	x	
Meyers et al. (2009)	x	x	x
Mooney et al. (1997)			
Mooney et al. (1998)	x	x	x
Moore Dalal et al. (2008)	x	x	x
Morton RL et al. (2009)		x	x
Mruck S et al. (1999)			x

Literatur:	Zuteilung zur Fragestellung:		
	VII.4	VII.5	VII.6
Murchie et al. (2010)	x	x	
Peric et al (2011)			x
Poo-Hwu et al. (1999)	x	x	
Rueth et al. (2010)		x	
Schlagenhauff et al. (2000)			x
Solivetti et al. (2006)			x
Stucky et al. (2010)	x	x	
Sylaidis et al. (1997)	x	x	
Tarhini AA et al. (2009)	x		x
Turner et al. (2011)	x	x	
Voit et al. (2001)			x
von Schoultz et al. (1996)			x
Zissimopoulos et al. (2009)			x
Zogakis et al. (2007)	x	x	

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9. AG Begleittherapie

9.1. Frage VIII.1. Misteltherapie

Frage VIII.1. Beeinflusst eine Misteltherapie das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?

9.1.1. PICO, Suchwörter

PICO - Schema			
Population	Intervention	Comparison	Outcome
Melanoma patients	Mistletoe	Observation	Overall survival, progression free survival

Suchwörter				
Stichwort	melanoma	mistletoe	primary	
Synonyme				
Ober-/Unterbegriffe	Skin cancer	Viscum album		
Mesh Term	melanoma	mistletoe		

9.1.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	("melanoma" OR "melanoma"[MeSH Terms] OR "skin cancer") AND ("mistletoe" OR "viscum album" OR "mistletoe"[MeSH Terms])	28.09.10	41
Cochrane Library	(melanoma and (mistletoe or viscum album)).ti,ab.	28.09.10	2
Embase	(melanoma and (mistletoe or viscum album)).ti,ab.	12.10.10	47
Update Suche			
Medline	s.o.	26.01.12	42
Cochrane Library	s.o.	26.01.12	2
Embase	s.o.	23.01.12	53

9.1.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	97
Einschlusskriterien	Klinische Studien zur Misteltherapie bei Melanompatienten, alle Stadien Vergleichsarm: Beobachtung oder Standardtherapie, Sprachen: e,dt

Auswahl der Literatur	
Ausschlusskriterien	Studien oder Reviews mit Einschluss anderer/gemischter Tumorentitäten Case Reports, Experimentelle Arbeiten
Anzahl nach Abstractscreening, vorgesehen für Bewertung	3
Anzahl ausgewählter Studien durch Handsuche (Durchsicht der Referenzlisten der ausgewählten Arbeiten)	3
Ausgeschlossene Studien (mangelhafte methodische Qualität)	3
Berücksichtigte Studien	3

9.1.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
<p>Kleeberg et al. 2003</p> <p>Final results of the EORTC 18871/DKG 80-1 randomised phase III trial:rIFN-a2b versus rIFN-g versus ISCADOR M1 versus observation after surgery in melanoma patients with either high-risk primary</p>	<p>To clarify whether claims of the efficacy of Iscador M were justified</p>	<p>Prospective, randomised phase III adjuvant trial</p>	<p>803 pts: 423 pts were randomized in the EORTC 18871 3-arm trial, 407 pts in the DKG-80-1 4-arm trial (102 pts in the control arm, 101 pts in the rIFN-alpha arm, 102 in the rIFN-gamma arm and 102 in Iscador-M arm). Thus 204 pts were used to assess the</p>	<p>Disease free Interval rate (DFI)</p> <p>Overall Survival (OS)</p>	<p>Iscador M1 versus control</p> <p>HR 1.32 (0.93, 1.87)</p> <p>HR 1.21 (0.84, 1.75)</p> <p>The data support, but do not provide significant proof of earlier warnings</p>	<p>The trials were stopped after reaching the planned sample size for the IFN-question and after having the results of an interim evaluation showed an approximately 10% lower 2-year DFI rate in the Iscador arm compared with the control group.</p>	<p>1b</p> <p>Individual RCT</p>

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(thickness >3 mm) or regional lymph node metastasis			<p>value of Iscador: 102 controls vs. 102 pts in the Iscador group.</p> <p>Stage IIb: 48%/49% Stage III: 52%/51%</p> <p>Baseline characteristics were well balanced</p>		about a potential negative effect of mistletoe extracts in melanoma patients, since the observations did not reach significance.	Funding: In part by grant DKG 80-1	
<p>Augustin et al. 2005</p> <p>Safety and Efficacy of the Long-term Adjuvant Treatment of Primary Intermediate- to High-Risk Malignant Melanoma (UICC/AJCC Stage II and III) with a Standardized Fermented European Mistletoe Extract (Viscum album L.)</p>	To evaluate the therapeutic safety and efficacy of Fermented European Mistletoe Extract (FME)	Multicenter, comparative, epidemiological cohort study	<p>686 Patients, 329 treated with FME vs. 357 controls from 35 centers;</p> <p>UICC/AJCC tumor stage (II/III) % 91,5/8,5 vs. 95.0/5.0</p> <p>Treatment group: 83,3% patients received FME P 16,7% received FME M, Q or others</p> <p>median duration of therapy: 30 months</p>	<p>Prim. endpoint Tumor-related survival</p> <p>Sec. endpoint Overall Survival</p> <p>Disease-free-survival</p> <p>Brain metastasis-free survival</p>	<p>Significant reduction of tumor-related mortality hazard in the FME group</p> <p>Tumor-related mortality rate 8,9% FME group vs. 10,7% control group</p> <p>Adjusted hazard ratios (FME vs. control): HR Tumor-related survival = 0,41 HR Overall survival = 0,64 HR Disease-free Survival = 0,73</p>	<p>Limits: Not randomized design</p> <p>Thus, baseline characteristics were well balanced</p> <p>Potential biases were well addressed by using a standardized parallel groups study design, independent auditing of data quality, multivariate adjusted endpoint criteria for</p>	<p>2b</p> <p>Individual Cohort Study</p>

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					HR Brain metastasis-free survival = 0,33	potential confounders and other measures. Funding: The study was supported by an educational grant of the Research Institute Hiscia, Arlesheim (Switzerland) (Iscador)	
Albarrán Weick, M. 1998 Retrospektive Fall-Kontroll-Studie zum Stellenwert der adjuvanten Therapie des malignen Melanoms mit Iscador P.c.Hg.	To evaluate the impact of adjuvant Iscador on progression free survival and Overall Survival	Matched pairs (1:3) retrospective cohort study	Of 1288 documented melanoma patients of the University Hospital Freiburg, 458 patients received Iscador. 273 of this patients were evaluated in the study Control group: 819 of more than 25 000 melanoma patients within the German Central Malignant	Progression free survival Overall Survival	No significant differences between the groups regarding overall survival (p=0,9669) and progression free survival (p=0,5746) Iscador treatment had no detrimental effect on overall survival	Study is well reported Invasionlevel was not well balanced between the groups (more Level IV and III in control group) Limits: Retrospective design, Iscador preparation was not standardized Funding: not reported Inaugural Dissertation	2b Individual Cohort Study

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			Melanoma Registry.				

Ausgeschlossene Studien

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
<p><i>Stumpf et al. 2003</i></p> <p><i>Retrospective Study of Melanoma Patients Treated with Mistletoe Extracts</i></p>	<p><i>to analyze survival time and survival rate of all patients with malignant melanoma who had been counseled at the Tumorambulanz Herdecke</i></p>	<p><i>Retrospective Study</i></p>	<p><i>284 melanoma patients of the Tumorambulanz Herdecke were included, 94 patients with sufficient data were analysed, 66 of this patients received mistle toe treatment. This 66 patients were compared with patient data from the literature</i></p>	<p><i>Survival time</i></p> <p><i>Survival rate</i></p>	<p><i>Survival time and survival rate were comparable to controls of literature</i></p>	<p><i>Poor quality → study excluded</i></p> <p><i>Limits: retrospective design, heterogeneous patient collective: patients with and without metastases, clinical stage was not indicated, Comparison with literature data based on clark level</i></p> <p><i>Different treatment regimens (Iscaador M, Iscaador P and others)</i></p> <p><i>Funding:</i></p>	<p><i>4</i></p> <p><i>poor quality cohort study</i></p>

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						The study was partially initiated and financed by Helixor GmbH&Co	
Grossarth-Maticcek et al. 2007 Efficacy and Safety of the Long-term Treatment of Melanoma with a Mistletoe Preparation (Iscador)	To investigate if the long-term application of the mistletoe preparation Iscador show any effect in prospective controlled studies on survival, tumor progression, and psychosomatic self-regulation of patients with melanoma	Study 1: Randomised matched-pair study (22 pairs) Study 2: Non-randomised matched-pair study (32 pairs)	Study population consisted of 1499 melanoma patients of different german centres Melanoma patients without metastases, receiving conventional therapies were matched to melanoma patients with same characteristics to receive additionally Iscador	Overall survival Progression free survival Self regulation	Overall survival: No difference between Iscador and control group Significant better progression free survival in Iscador group: HR, 95% CI Study 1: HR 0,49 (0,32, 0,75) Study 2: HR 0,72 (0,54, 0,97) Self regulation: Significant better self regulation after Iscador therapy p=0,0048	Poor quality → study excluded Recruitment period was between 1973 and 1988 Two studies were analysed seperately but were reported together Limits Small sample size Questionable method of randomisation (two slips of paper with the names of two patients were drawn of a hat) kaplan meier curves available of overall survival (n.s.) but not of progression free survival	4 poor quality cohort study

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						(significant) Funding: No statement included Affiliation of Corresponding author: Institut Hiscia, CH-Arlesheim (Iscador)	
Schuppli R. 1990 Adjuvant treatment of malignant melanoma with Iscador P c Hg.]	To assess the therapeutic effect of Iscador plus Hg on overall survival	Controlled study	High risk melanoma patients 114 patients treated with BCG alone 84 patients treated with BCG and Iscador P c Hg	Overall survival	Risk factor Survival Iscador group: 3,4 Contol group: 2,3	Poor quality → study excluded The study was conducted at the Department of Dermatology, Universitiy Basel, 1981-1988 Limits: Study reporting of low quality No baseline characteristics, (groups balanced?) Statistical methods were not reported Funding: No statement included	4 poor quality cohort study

9.1.5. Literatur

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10. AG Versorgungsqualität und Qualitätsindikatoren

10.1. Frage IX.1. Klinische Studien - Adaptation

Frage IX.1. Welchen Patienten sollte eine Teilnahme an klinischen Studien empfohlen werden?

Die Frage wurde letztendlich Konsens-basiert beantwortet

10.1.1. Synopse Quelleitlinien (kurz)

Thema/Fragestellung	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
1. Sollte Patienten die Teilnahme an klinischen Studien empfohlen werden?	Teilnahme an Studien sollte Patienten ab St. I nach Resektion des Primärtumors angeboten werden (B); Patienten sollten darüber informiert werden, dass sie von der Teilnahme an einer Studie wahrscheinlich keine Nachteile zu erwarten haben (A)	Teilnahme an Studien sollte allen Patienten ermöglicht werden, auch unter 19-jährigen; kein Beweis für Vor- oder Nachteile für den Studienteilnahme	Keine Erwähnung	<i>Nur relevant für medikamentöse Therapien</i>

10.1.2. Empfehlung, Hintergrundtext und Literatur australischen und französischen Quell-Leitlinien

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Schlüsselempfehlungen	<p>S. 128</p> <p>Patients can be informed that they are unlikely to be disadvantaged by participation in an RCT.</p> <p>Grade of Recommendation: A</p>		Keine Erwähnung	<p>Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma: Updated Guideline Recommendations 2009</p> <p>S. 2 Recommendations Patients with high-risk melanoma should be encouraged to participate in appropriate clinical trials exploring novel therapeutics, given that at most a small OS benefit exists with currently available therapies.</p>
Hintergrundtexte	<p>S. 127</p> <p>20. Clinical Trials The clinical trial is an instrument designed to assess the effectiveness of potentially new or altered interventions</p>	<p>Patient-centered care</p> <p>C. Evidence</p> <p>S. 41 Clinical trials</p>	Keine Erwähnung	Keine Erwähnung

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	<p>that involve a wide range of clinical activity. Trials frequently involve drug therapy, but may address new devices, surgical procedures, treatment by external instrumentation (e.g. radiotherapy), or psychosocial aspects of clinical management. [1]</p> <p>Commonly, the study question is whether a new treatment is better than the old one. It is customary to compare each new treatment group with a control group, the members of which must be offered treatment matching the best standard currently available for their consideration before joining the trial. [1]</p> <p>The randomised clinical trial (RCT), which involves random allocation of patients to their treatment or control group, is becoming the 'gold standard' for assessment of new management processes.</p>	<p>One high-quality systematic review investigated patient outcomes related to mortality and morbidity among participants and nonparticipants in clinical trials. RCTs of different specialties were included, but the largest proportion was of patients with cancer. The review found little evidence for better outcomes through participation in trials aside from those arising from the effects of the treatments compared, or differences between participants and non-participants.</p> <p>The same review found no evidence of greater risk arising from trial participation. A previous, poorer-quality systematic review than the one cited above examined evidence for better patient outcomes through RCT participation. The majority of RCTs were of patients with cancer. The review concluded that it is</p>		

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	<p>Clinical trials involve significant funding and require the informed consent from patients and frequently, the involvement of a number of centres and health professionals to obtain an appropriate number of subjects to ensure sound statistical power.</p> <p>The conduct of trials by cooperative groups of trialists is the most likely way to advance evidence-based medicine through well-designed protocols and rigorous evaluation. [2]</p> <p>However, in our community some people are concerned about RCTs, believing that patients involved in such trials may be at risk from factors that would not occur in treatment outside a trial. On the other hand, others see participation in an RCT as being of benefit to the trial subject and probably an optimal way of receiving the best contemporary care and</p>	<p>likely that clinical trials have a positive, rather than a negative, effect on survival and morbidity outcomes, with benefits arising from the use of trial protocols. One literature review found that children and adolescents with melanoma are not entered into clinical trials. Retrospective studies have found that adolescents with cancer are not as likely to be entered into clinical trials as children and adults.</p> <p>An audit of skin cancer MDT activity undertaken in the South West of England found that many trusts did not have sufficient infrastructure to ensure that patients are offered trial entry.</p> <p>An audit of implementation of recommendations made in the Calman-Hine Report (1995) undertaken by the Commission for Health Improvement (CHI) and the Audit Commission in 2001 found that only a small</p>		

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	<p>clinical oversight. A recent Cochrane Review assessed the effect of participation in RCTs ('trial effects') independent both of the effects of the clinical treatments being compared ('treatment effects') and any differences between patients who participated in RCTs and those who did not. [3] The outcome of this review led its authors to conclude that there is no greater risk from participating in RCTs than there is from being treated outside an RCT. The authors considered that the belief or assertion that results of RCTs cannot be applied to usual practice is challenged by the review. [2] This outcome would appear to provide a sound basis for clinicians to offer participation in RCTs to their patients. Any uncertainty about the effects of treatment can best be resolved through a randomised</p>	<p>proportion of patients with cancer are involved in clinical trials. Trial participation was less likely in settings outside of large cancer centres.</p>		

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	<p>trial as long as the eligibility criteria for the trial match the patient population seen in usual practice, or the trial treatment is applied only to patients who match the eligibility criteria. [4]</p> <p>Evidence summary Outcomes for patients who participate in RCTs on average do not differ from those of patients who receive similar treatments and do not participate in a trial. LoE: I Reference: [2]</p>			

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LL Australien New Zealand Guidelines Group 2008

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3. Poirier V, Wright S, Lucke T, Verne J, Sandhu J, De Berker D, et al. Auditing current Skin Cancer Multi-disciplinary Team (MDT) practices against the Manual of Cancer Services Standards in the South West Region.
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11. Abkürzungsverzeichnis

AUC	area under curve
BCG	Bacille Calmette Guerin
BM	brain metastases
BT	Breslow Thickness
CD	conventional diagnostics
CI	confidence interval
CLND	Complete lymph node dissection
CM	cutaneous melanoma
CR	Complete Response
CR	conventional radiography
CS	conditional survival
CSP	conventional screening procedures
CT	chemotherapy
CWS, P3	cell wall skeleton and purified trehalose dimycolate
CXR	Chest X-ray CXR
DFI	disease-free interval
DFS	disease- free survival
DM	distant metastases
DMFD	distant metastasis-free survival
DMFI	distant metastasis-free interval
DMFS	distant metastasis-free survival
DMM	desmoplastic malignant melanoma
DNCB	Dinitrochlorobenzene
DNM	desmoplastic neurotropic melanoma
DPCP	Diphencyprone

DSS	disease-specific survival
DTIC	dacarbazine
ELND	‘elective lymph node dissection’
FAS	full analyses set
FMR	first melanoma recurrence
FN	false negative
FP	false positives
GIT	gastrointestinal tract
GKS	Gamma Knife surgery
Gy	Gray
HACE	Hepatic artery chemoembolization
HAI	Hepatic artery infusion
HDI	high dose interferon
HR	Hazard ratio
HRQL	health related quality of life
IDI	intermediate dose interferon
IES	Impact of Event Scale
IFN	Interferon
IHP	Isolated hepatic perfusion
IL-2	Interleukin 2
IL-BCG	intralesionally - bacillus Calmette Guerin
ILP	isolated limb perfusion
incl.	including
ITT	Intent To Treat
LDI	low dose interferon
LM	lentigo maligna
LMM	lentigo maligna melanoma
LN	lymph node(s)
MCS	Mental Component Summary
MER	methanol extraction residue of bacillus Calmette-Guerin
Mets	metastases
MM	malignant melanoma
MPM	multiple primary melanomas
MPV-BCG	multiple puncture vaccination - bacillus Calmette Guerin

MUP	melanoma with unknown primary
MV	Megavolt
n.r.	not reported
n.s.	not significant
NC	no change
NED	no evidence of disease
NMM	nodular malignant melanoma
NR	not reached
OBS	observation
OR	Odds ratio
OS	Overall survival
PCS	Physical Component Summary
PD	Progressive Disease
PDS	power Doppler sonography
PE	physical examination
PM	primary melanoma
PP	Per protocol
PR	Partial Response
PV-10	10% w/v Rose Bengal in saline
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse-free survival, Recurrence free survival
rIFN-beta	recombinant interferon beta
RR	Relapse Rate
RR	relative risk
RSCL	Rotterdam Symptom Checklist
RT	radiotherapy
s.c.	subcutaneous
SD	Stable Disease
SIRT	selektive interne Radio-Therapie
SLN	sentinel lymph node
SLNB	sentinel-lymph node biopsy
SM	second melanoma
SPM	second primary melanoma

SRS	stereotactic radiosurgery
SSM	superficial spreading melanoma
ST	soft tissue
TACE	Trans-arterial chemoembolization
TD	Total dose
TLND	therapeutic lymph -node-dissection
TMZ	temozolomide
TN	true negatives
TP	true positives
UICC	Union International Contre Cancer
US	ultrasound
WBRT	whole brain radiation therapy
WHO	World Health Organisation
Vs.	versus
Wb	whole body