Leitlinienprogramm
Onkologie

Evidenztabellen

der S3 Leitlinie „Diagnostik, Therapie und Nachsorge des Melanoms“

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Ergänzung zum Leitlinienreport

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1.1.1. 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	Klinische Untersuchung, Dermatoskopie	Klinische Untersuchung, Dermatoskopie	(nur relevant für medikamentöse Therapien)

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
	digital dermoscopy imaging“ und/oder „Total body photography“ kann in Zweifelsfällen in Erwägung gezogen werden (B)			
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	

1.1.2. Empfehlung, Hintergrundstext 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	S. 31 1. Training and utilisation of dermoscopy is recommended for clinicians routinely examining	S. 84 A. Recommendations Investigation and diagnosis	Die französische LL gibt keine Empfehlungen zur klinischen Erstdiagnose eines Melanoms; die Dermatoskopie wird jedoch im Abschnitt über Untersuchung und

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	pigmented skin lesions Grade of Recommendation: A 2. Consider the use of sequential digital dermoscopy imaging to detect melanomas that lack dermoscopic features of melanoma Grade of Recommendation: B 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	GPs should receive training as recommended in the NICE *Referral guidelines for suspected cancer* [44] on the diagnosis of precancerous and cancerous lesions, and should receive feedback through audit on their diagnostic accuracy. 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. All excised skin specimens should be sent for histopathological examination as recommended in the NICE *Referral guidelines for suspected cancer*. [45] Dermatoscopy should be available in all MDTs, but its use requires training. There should be equity of access so that all tissue samples are reviewed in high-quality histopathology services.	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:

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
		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.	
Hintergrundtexte	S. 29 – 30 5.6 Evidence-based assessment of aids to the clinical diagnosis of melanoma 5.6.1 Dermoscopy	S. 90 E. Evidence Dermatoscopy One RCT found that, following a brief training intervention for GPs in the use	S. 44 EXAMEN CLINIQUE, DERMOSCOPIE Les performances diagnostiques de l'examen clinique et de la dermoscopie dans le diagnostic des tumeurs cutanées font actuellement l'objet

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	Dermoscopy (surface microscopy, oil 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] 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] 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	of dermatoscopy, there was a significant 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. 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. Teledermatology 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	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'*Agency for healthcare research and quality* (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 que la dermoscopie, une technique

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	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 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] While there are fewer studies on dermoscopy in general practice, all three that were undertaken in this context (one study with both general	further, independent face-to-face skin examination with a consultant dermatologist. For each randomised group, concordance between the two consultations for each patient was 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. 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	initialement mise au point en Europe et en Australie, soit largement diffusée aux États-Unis. Deux méta-analyses récentes ont montré que pour les dermatologues expérimentés, la dermoscopie améliorait les performances diagnostiques [160, 161]. Dans l'étude de Bafounta *et al.*, 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 *et al.* a confirmé ces données, montrant clairement que seuls les opérateurs expérimentés amélioraient leurs performances diagnostiques [161]. *KLINISCHE UNTERSUCHUNG, DERMATOSKOPIE* *Die diagnostische Leistungsfähigkeit der klinischen Untersuchung und der Dermatoskopie in der Diagnostik von Hauttumoren ist zur Zeit Gegenstand*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	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 studies). For this reason, and based on other evidence [34], some formal training in dermoscopy is required to achieve improvement in diagnostic accuracy. 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	69% of patients examined by the still image method, compared to 46% of patients examined by videoconferencing and 45% of patients examined in person. One RCT compared teledermatology with standard referral and found that patients in the teledermatology group received definitive treatment 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. One RCT compared teledermatology consultation using a videolink with outpatient consultation and found no difference between the groups in the reported clinical diagnoses. One RCT of teledermatology compared to traditional consultation found no	*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-Dermatologen überlegen ist. [17]*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	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 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	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. 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. Audit data from the UK indicates that GPs report quicker referral of dermatology patients through teledermatology. S. 99 E. Resource implications Investigation and diagnosis	*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].*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	to be assessed. 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 diagnosis of melanoma compared with specialists. In all studies sample sizes were not large enough to be able to detect potential differences in the	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. It is estimated that approximately 1.75 additional consultant histopathologists/dermatopathologists would be required per network to 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	

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	sensitivity for melanoma. Further studies are required to assess the impact of automated instruments against human performance in the clinical field. 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]	£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.)	

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	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. 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		

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	examination, but there was no evidence of an effect on specificity. LoE: I, References: 21, 22, 24–31 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 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 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,		

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	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 Eight level IV studies and one level III-3 study examined surveillance of high-risk 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. All studies were designed to assess the outcomes of surveillance in high-risk groups rather than the value of TBP. LoE: IV References: 43-51		
Bemerkungen		Diese Leitlinie bezieht sich auf MM und auf NMSC.	Das Gutachten der HAS, der Artikel der AHRQ, auf den die Leitlinie sich bezieht, sowie dessen Aktualisierung

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
		Referenzen und ausführliche Evidenztabellen dieser Leitlinie werden wegen ihres Umfangs als separates Dokument zur Verfügung gestellt: GB NICE Guideline Evidence Review, S. 174 bis 211.	aus dem Jahr 2009 werden als Zusatzmaterial zu dieser Tabelle zur Verfügung gestellt.

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1.2. 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)

1.2.1. PICO, Suchwörter

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

1.2.2. 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] "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]	26.01.2012	275 92
Cochrane Library	melanoma and (confocal or "laserscan microscopy" or clsm).ti,ab. melanoma and (oct or "optical coherence tomography" or “optical coherence tomographic” or “multiphoton").ti,ab.	26.01.2012 26.01.2012	1 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 Literaturauswahl zur konfokalen Laserscanmikroskopie wurde die Literatur, die bei der systematischen Recherche gefunden wurden, reevaluiert. Die Tabelle wurde daraufhin ergänzt entsprechend der angegeben Ein- und Ausschlußkriterien. Abschluß Konsultationsphase, Stand 09/2012: Das Statement zur konfokalen Laserscanmikroskopie wurde aus der Leitlinie herausgenommen (Details: s. „Kommentare zur Konsulationsfassung“). Eine Überarbeitung der Evidenztabelle nach erneuter sytematischer Literaturrecherche ist für das Update der Leitlinie geplant.		

1.2.3. 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

1.2.4. 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 multiphoton laser tomography with regard to statistical evaluation of	Diagnostic study	83 patients	Sensitivity and specificity in and ex vivo Accuracy	Overall sensitivity 75% in vivo, 93% ex vivo Specificity 80% in vivo, 74% ex vivo	Specificity and sensitivity for single criteria: see full-text of publication	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	sensitivity, specificity, accuracy, and reliability.			Interobserver reliability	Diagnostic accuracy 85% in vivo, 97% ex vivo Interobserver agreement: kappa values for different criteria ranging from 0.6 to 0.8		
Gambichler et al. (2007)	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.	Diagnostic study	75 patients with 92 MSL	Frequency of several characteristics of lesions	See full-text for frequency of all investigated characteristics of lesions.	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	3b
Subtopic: Confocal laser scan microscopy (CLSM)							
Gerger et al. (2007)	To validate diagnostic confocal	A total of 3709 unselected CLSM	60 patients	Sensitivity and specificity	Sensitivity 97.5%	High risk of verification bias (no	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	examination of melanocytic skin tumours using unselected tumour images.	tumour images obtained from 20 malignant melanomas and 50 benign naevi		Positive and negative predictive value (PPV, NPV) Diagnostic accuracy	Specificity 99% PPV 97.5% NPV 99% Diagnostic accuracy 92.4% for benign naevi and 97.6% for melanoma images	histology if diagnosed "on unequivocal clinical and conventional dermoscopic criteria as benign nevi") Computerized images were provided, a loss in sensitivity or specificity through acquisition of the images by an unexperienced examiner could therefore not be observed	
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% and	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.				99%, PPV 100% and 96.3%, NPV 99% Senior physician without dermatopathologic qualification: sensitivity 92.6% and specificity 99%, PPV 96.2%, NPV 98% 2 Dermatopathologists: sensitivity 96.3% and 59.3%, specificity 94% and 96%, PPV 81.3% and 80%, NPV 99% and 89.7% Overall sensitivity 88.2%, specificity 97.6%, PPV 90.7%, NPV 96.9%.		
Gerger et al. (2006)	To systematically investigate the	Diagnostic study	119 patients with 117 melanocytic	Sensitivity, specificity	Diagnostic differentiation of	High risk of verification bias (see	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	diagnostic impact and reliability of well described morphologic features in a large series of melanocytic and nonmelanocytic skin tumors.		and 45 non-melanocytic skin lesions	Positive and negative predictive value (PPV, NPV)	MM from BCC, BN, 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%.	above)	
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	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
	tumours in in vivo confocal laser-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	Classification tree analysis: correct classification in 93.60% of melanoma and 90.40% of nevi images of the learning set When applied to the independent test set 46.71 ± 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 ±	Risk of verification bias (verification by histopathology dependent on clinical examination) ROC curve: see full-text	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					14.58% (range 30.65–83.59%; t-test: $P < 0.036$) in malignant melanocytic skin lesions 78.95% of melanocytic skin tumours (62.50% of the melanoma and 84.50% of the nevi) correctly classified by independent clinical dermatologist		
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	Sensitivity, specificity Positive and negative predictive value (PPV, NPV)	Dermoscopy: sensitivity 89.2%, specificity 84.1%, PPV 70.2%, NPV 94.9% CSLM: sensitivity 97.3%, specificity 83.0%, PPV 70.6%, NPV 98.6% No melanomas misidentified when both techniques were used	No verification bias (all diagnoses were confirmed histologically) Clinical, dermatoscopic and confocal imaging were performed sequentially by a single observer;	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					together	result of clinical examination and 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.

1.2.5. Literatur

Dimitrow E, Ziemer M, Koehler MJ, et al. Sensitivity and specificity of multiphoton laser tomography for in vivo and ex vivo diagnosis of malignant melanoma. J Invest Dermatol 2009;129:1752-1758

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

Gerger A, Hofmann-Wellenhof R, Langsenlehner U, et al. In vivo confocal laser scanning microscopy of melanocytic skin tumours: diagnostic applicability using unselected tumour images. Br J Dermatol 2008;158:329-333

Gerger A, Koller S, Kern T, et al. Diagnostic applicability of in vivo confocal laser scanning microscopy in melanocytic skin tumors. J Invest Dermatol 2005;124:493-498
Gerger A, Koller S, Weger W, et al. Sensitivity and specificity of confocal laser-scanning microscopy for in vivo diagnosis of malignant skin tumors. Cancer 2006;107:193-200
Gerger A, Wiltgen M, Langsenlehner U, et al. Diagnostic image analysis of malignant melanoma in in vivo confocal laser-scanning microscopy: a preliminary study. Skin Res Technol 2008;14:359-363
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

1.3. 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 Patienten indiziert?

1.3.1. 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 Patienten mit Primärdiagnose des MM das Krankheitsstadium?
- Ändert die Durchführung des Verfahrens bei Patienten mit Primärdiagnose des MM die Therapie?
- Ändert die Durchführung des Verfahrens bei Patienten mit Primärdiagnose des MM das Überleben?
- Wie hoch sind die zusätzlichen Kosten bei Durchführung des Verfahrens bei Patienten mit Primärdiagnose des MM?

1.3.2. Datenbanken, Suchstrategie, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche		Der letzten Update-Recherche:	Insgesamt (Update-Recherche)
Medline	"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])) "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])	26.01.2012	3153 83

Datenbank	Suchstrategie	Datum	Treffer
	"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])		588
	"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])		595
	"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-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])		936
	"melanoma"[tiab] AND (“staging”[tiab] OR "diagnosis"[tiab]) AND ("scintigraphy”[tiab] OR “scinti*”[tiab]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		66
	"melanoma"[tiab] AND ("LDH"[all fields] OR “lactate dehydrogenase” OR "S100"[all fields] OR "MIA"[tiab] OR "melanoma-inhibiting activity"[tiab]) AND		594

Datenbank	Suchstrategie	Datum	Treffer
	(“staging”[all fields] OR "diagnosis"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		
Cochrane Library	(melanoma and (staging or diagnosis) and ("chest x-ray" or "chest radiography")).ti,ab. (melanoma and (staging or diagnosis) and ("ultrasonography" or "sonography" or "ultrasound" or sonogr*)).ti,ab. (melanoma and (staging or diagnosis) and ("magnetic resonance" or mri)).ti,ab. (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. (melanoma and (staging or diagnosis) and (scintigraphy or scinti*)).ti,ab. (melanoma and (staging or diagnosis) and (ldh or "lactate dehydrogenase" or s100* or mia or "melanoma inhibiting activity")).ti,ab.	19.01.2012	7 7 5 9 4 10
Embase	(melanoma and (staging or diagnosis) and ("chest x-ray" or "chest radiography")).ti,ab. (melanoma and (staging or diagnosis) and ("ultrasonography" or	23.01.2012	79 546

Datenbank	Suchstrategie	Datum	Treffer
	"sonography" or "ultrasound" or sonogr*)).ti,ab.		
	(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

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.

Bezüglich Tumor-Marker: da eine Meta-Analyse (Mocellin et al. 2008) vorliegt, wurden lediglich Studien eingeschlossen, die nicht in der Meta-Analse enthalten waren, die nach der Metaanalyse erschienen sind oder die bestimmte Teilaspekte abdecken, die in der Meta-analyse nicht berücksichtigt wurden.

Bezüglich PET und PET/CT: 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.

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.

1.3.3. Auswahlkriterien

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

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

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	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

	melanoma patients.						
Bafounta et al. (2004)	To investigate whether lymph-node ultrasonography improves detection of nodal invasion during the initial staging and follow-up of patients with melanoma.	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 ratio 41.9, negative likelihood ratio 0.024 Palpation: Positive likelihood ratio 4.55, negative likelihood ratio 0.22	Variations in the definition of false negatives and verification bias in included studies	1a
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%	Preliminary report (400 of 650 patients)	1b

					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 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	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%	Patients with mucosal melanoma included	1b

	preoperatively before sentinel-node biopsy (SNB), to define hrUS resolution, and to evaluate which US criteria should be used.				NPV 75.2% Non-stringent criteria: Sensitivity 20.6% Specificity 89.8% PPV 41.2% NPV 76.5%		
Saiag et al. (2005)	(1) to compare the respective ability of ultrasonography 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	Diagnostic study	160 consecutive patients with stage I to stage III CM	Sensitivity, Specificity	Sonography: Sensitivity 76.9% Specificity 98.4% Palpation: Sensitivity 41.5% Specificity 95.7%	Patients with mucosal melanoma included	1b

	images, to evaluate whether ultrasonography remains useful once patients have undergone radical LD						
Stoffels et al. (2011)	to clarify the reliability of preoperative ultrasonography (US) in direct 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).	Diagnostic study	221 patients with primary malignant melanoma with a Breslow index of >= 1.0 mm	Sensitivity Specificity PPV NPV	US: Sensitivity: 13.6% Specificity: 96.9% PPV: 97.2% NPV: 12,6% SLNE alone: Sensitivity: 94% Specificity: 98.6% PPV 100% NPV 98,3% Preoperative US in conjunction with dynamic lymphoscintigraphy, followed by SLNE: detecting ratio: 100% (n = 28) for micrometastases, 98.6% (n = 42⁄43)	Reference standard for SLNE not described	2b

					for macrometastases		
Hinz et a. (2011)	To evaluate whether high-resolution ultrasound combined with power Doppler sonography (PDS) is an appropriate tool for preoperative identification and characterization of sentinel lymph nodes (SLNs) in patients with cutaneous melanoma.	Diagnostic study	81 consecutive patients with CM in whom dissection of SLNs was indicated underwent ultrasound examinations before and after the preoperative lymphoscintigraphy.	sensitivity, specifity, PPV, NPV positive likelihood ratio negative likelihood ratio	A total of 170 SLNs (mean 2.1 per patient) were removed and examined by histopathology. sensitivity, specifity, PPV, NPV of ultrasound: 22.2% (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.	patient cohort with only 9 positive SLNs in total No information about follow-up	2b
Chai et al. 2011	To assess feasibility and staging	Diagnostic study	325 patients with melanoma	Sensitivity, specificity, PPV, NPV	sensitivity of ultrasound: 33.8%,	No information about time interval	2b

	results of clinically targeted ultrasound (before lymphoscintigraphy) compared to SLNB.		underwent ultrasound before SLNB without palpable lymphadenopathy in regional nodal basins		specificity: 85.7%, PPV: 36.5%, NPV: 84.2%	between US and SLNB Confidence interval not given	
Sanki et al. (2009)	To reassess traditional ultrasound descriptors of sentinel lymph node (SLN) 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	Diagnostic study	716 CM patients	Sensitivity and specificity Positive and negative predictive value Positive and negative likelihood ratios Diagnostic accuracy	Targeted high-resolution sonography for the detection of SLN: Sensitivity 24.3% Specificity 96.8% PPV 60.3% NPV 86.2% Diagnostic accuracy 86.7%	Design (retrospective vs. prospective) not described	2b

	melanoma surgery can be used as a substitute for excisional SLN biopsy.						
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 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.	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
Hocevar et al. (2004)	The aim of this	Diagnostic study	57 patients with	Sensitivity and	Sensitivity 71%	Risk of verification	2b

	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.		CM, in whom SLN biopsy was planned	specificity Positive and negative predictive value	Specificity 84% PPV 59% NPV 90%	bias Design of study not described (retrospective versus prospective)	
Hafner et al. (2004)	To evaluate the sensitivity and specificity of baseline staging in the early detection of regional lymph node metastases or distant metastases in patients with MM.	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
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	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

	sentinel lymph nodes (SLN) in patients with cutaneous melanoma.						
Schmid-Wendtner et al. (2004)	to evaluate whether signal enhanced color Doppler sonography (CDS) is superior to native CDS in detection of characteristic vascularity patterns that are important for the differentiation between benign and malignant lymphadenopathy in patients with cutaneous melanomas.	Diagnostic study	22 melanoma patients	Sensitivity Secificity	signal-enhanced sonography : sensitivity = 92.3%, specificity=100.0%. For melanoma metastases, a sensitivity of 90.0% and a specificity of 85.7% was calculated. For both P-values <0.05	Prospective two-center study lack of histopathologic correlation in all presumptive sonographic diagnoses small study group sensitivity and specifity of native CDS not given study inclinded in Xing et al. 2011	3b-
Uren (1999)	to determine if high-resolution ultrasound could identify metastases in newly palpable	Diagnostic study	52 patients (61 individual node fields)	Ultrasound features in metastatic lymph nodes Sensitivity	specifity = 87% sensitivity = 94% accuracy = 89% If presence of 2 US-	No information about the time interval between ultrasound and FNAB/excision	3b-

	lymph nodes found during clinical follow-up for melanoma, and to define the ultrasound features that were associated with this diagnosis			specifity	features (=node thicker greater than two-third of the length and low-level internal echos) were present: Sensitivity = 94%, specifity = 100%, accuray 98%	biopsy Small population Different examined fields: axilla, groin, supraclaviculaire, submental, cervical study inclinded in Xing et al. 2011	
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 inclinded in Xing et al. 2011	2b
Vermeerenet et al. (2011)	to evaluate therapeutic consequences of preoperative staging with Chest X-ray (CXR) in patients with a primary melanoma planned for sentinel node biopsy (SNB).	diagnostic study	248 medical records of patients treated for primary melanoma CXR in 227 patients CXRs were made prior to SNB	False positives	Preoperative CXR did not identify pulmonary metastasis and did not change planned treatment strategies. In 5%, the CXR was inconclusive → false positives	Reference standard: complementary radiodiagnostic imaging and/or follow-up.	3b
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		3b

					patients relapsed. Detection of relapse: .- in 33.1% by physical examination - in 38.1% by chest X-ray - in 16,9% by 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	Cohort consisting of stage I – IV patients	3b

					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%		
Hofmann et al. (2002)	Assessment of the performance, 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.	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 Detection rate Cost-efficiency of imaging procedures Survival	524 total chest x-rays 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)	Diagnostic standard procedures varied over time; no defined gold standard of diagnosis	3b
Terhune et al. (1998)	To evaluate the use of an initial staging chest x-ray film in asymptomatic	Diagnostic study	876 CM patients at initial staging	True and false positives .	130/876 (15%) patients with suspicious findings Additional workup	X-rays not obtained from all patients “Initial” chest x-ray up to 6 months	3b

	patients who present with localized primary cutaneous melanoma.				led to 1/876 true positives (0.1%) 129/876 false positives (14.7%)	after diagnosis	
Iscoe et al. (1986)	The description of predictive value of clinical, laboratory and radiologic investigations in the staging of patients with clinical stage I melanoma.	Diagnostic study	393 consecutive CM patients	True and false positives Positive and negative predictive value	Number of chest x-rays: 345 True positives: 0 False positives: 8 Positive predictive value: 0% Negative predictive value: 97.6%	Index tests not carried out on all patients	3b
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	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%	Design (prospective vs. retrospective) not clear Follow-up time not given	3b-

	and abdominal ultrasonography to detect silent metastases in asymptomatic melanoma patients				true negatives		
Meyer and Stolbach (1978)	To evaluate radiographic evaluation for the recognition of occult sites of metastatic disease beyond the regional nodes in malignant melanoma.	Diagnostic study	53 CM patients without symptoms to suggest distant metastasis	True and false positives	4/53 true positives (8%) 0 false positives	Cohort probably included patients with lymph node metastases	3b-
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	Diagnostic study	378 patients with histologically confirmed CM	True and false positives	0% positive results for chest x-ray at initial staging		3b-

	examinations are necessary for patients with malignant melanoma.		(stage not given)		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.		
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	Sensitivity and specifity not given No reference test Population not described in detail	4

					Normal PA and lateral radiograph: 60,8%. Abnormality equally visible on PA and lateral radiograph: 16,7%. Abnormality more easily visualized on PA than on lateral radiograph: 11%. Abnormality more easily visualized on lateral than on PA radiograph: 4,4%. Abnormality on PA radiograph not visualized on lateral projection 6,6%. Abnormality on lateral radiograph not visualized on PA projection: 0,44%	No information about the study design No information about selection criteria Sensitivity or specificity not given	
Webb (1977)	to describe the frequency of radiographic patterns of thoracic metastasis in	diagnostic study	65 patients with malignant melanoma metastatic to the thorax	radiographic patterns of thoracic metastasis Survival rates	Abnormalities in chest x-ray in 42/62 patients	11 patients received x-ray and tomogram Tissue specimen in	4

	patients with melanoma, and to correlate these patterns with the symptoms, clinical course, and survival of the patients.				Survival: see full-text	only 31 Small population, asymptomatic patients included	
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	Diagnostic standard procedures varied over time; no defined gold standard of diagnosis	3b

					(6421 EUR due to false positive results)		
Pandalai et al. (2010)	To evaluate the clinical utility of standardized radiographic staging.	Diagnostic stuy	58 consecutive asymptomatic patients with stage III AJCC melanoma .	True- positive (TP) rate false-positive (FP) rate	Initial staging examinations: 9% TP, 91% FP All examinations: 3% TP; 23% FP. 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). analyzed by type of radiograph, the 5	Small sample size Sensitivity and specificity not given Small number of MRI/CT of the head, PET and bone scan No routine standardized staging procedure was followed	3b-

					TP findings were found in 3 (13%) of 23 suspicious chest CT scans, 1 (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)	Poor information about selection criteria and population Poor data about patients` follow-up Small population	3b-

					In patients with only US and LS (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	diagnostic study	464 patients with cutaneaous	Detection rate of metatasis	Ultrasound appearances typical	No further information about	4

	gallbladder pathology, other than gallstones in this group o patients.		melanoma except one which arose on the nasal mucosa.		of gallbladder metastases in 4,1%	the population.	
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 > 3cm 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 discusses which of these imaging modalities yields the most information in patients with intraabdominal metastatic melanoma	Diagnostic study	163 patients with malignant melanoma in clinical stage III examined by RN liver scan, US, and CT in various combinations over a 2-years-period. 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)	False negatives (FN) False positives (FP)	Group 1: CT, US and RN demonstrated 20, 22 and 23 normal results respectively and 18, 17 and 15 abnormal results respectively 1 FN (CT) 1 FN (US) 8 FP and 1 FN (RN) Group 2: CT, RN demonstrated both 7 normal results and both 3 negative results. 2FP and 1 FN (RN) Group 3: US and RN demonstated 52 and 75 normal results respectively and 43 and 40 abnormal results	Sensitivity and specificity not given No information about follow-up	4

					respectively 2 FP (US) 10 FP (RN)		
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

Pfannenberg et al. (2007)	to compare the overall and site-based accuracy and impact on patient management of positron emission tomography/computed tomography (PET/CT) and whole-body (wb) magnetic resonance imaging (MRI) in staging of advanced melanoma.	Diagnostic study	64 patients: 25 patients stage III, 39 patients stage IV	Sensitivity Specificity positive predictive value (PPV) negative predictive value (NPV) accuracy	The overall accuracy: PET/CT: 86.7% wbMRI: 78.8% CT: 75.0% PET: 74.3% PET vs. wbMRI: P = 0.0007 PET vs. PET/CT: P < 0.0001 . Sensitivity, specifity, TN, FN, TP, FP: see full text/table 2	Cerebral lesions in wbMRI were recorded, but excluded from the 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	2b

Dellestable et al. (2011)	to assess the Se and specificity (Sp) of wb-MRI with a diffusion sequence for detecting melanoma metastasis compared to PET/CT.	Diagnostic study	40 patients were included and a total of 72 metastases were noted	Sensitivity specificity	CT: sensitivity: 80%, specificity: 95% PET/CT sensitivity: 74% specificity: 89% Wb-MRI sensitivity: 83% specificity: 96% The sensitivity of MRI was distinctly superior to PET/CT for both hepatic and pulmonary lesions.	no detailed information about patient cohort small patient cohort	2b-
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	Diagnostic study	35 patients	Sensitivity specificity	sensitivity and specificity for whole-body MRI: 82% and 97% PET-CT: 72.8% and 92.7%.	prospective blinded study small patient cohort	2b-

	advanced melanoma.				DW sequence allowed the detection of 14 supplementary malignant lesions (20%) in comparison with 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 AJJC stage III-IV malignant melanoma	Metastasis detection rate	wbCT vs. wbMRI: detection of 522 vs. 730 metastases wbCT vs. wbMRI: -pulmonary metastases: 188 vs. 143 - metastases in kidneys, adrenal glands and lymph	4 patients had choroid malignant melanoma specifity and sensitivity not given no follow-up small population	3b

					nodes: same number of detected lesions - liver: 122 vs. 199. - spleen 26 vs. 54 - subcutaneous 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.	uninterpretable results not described	
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 with cutaneous melanoma	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-
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	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-)	Pooled sensitivity: 83% Pooled specificity: 85% LR+: 4.56	In 17 studies, patients enrolled exclusively for initial staging; in 11 studies, proportion	1a

	fluorodeoxyglucose (FDG) positron emission tomographic (PET) imaging in the initial staging of cutaneous malignant melanoma (CMM)			Diagnostic odds' ratio (OR) Changes in disease management	LR-: 0.27 Overall diagnostic OR: 19.8 Early-stage subgroup (10 studies, 755 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	of initial staging patients 18 - 97% Overall, many low-quality studies resp. small 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	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	Overall, many low-quality studies resp. small patients cohorts	2a

	cutaneous melanoma.				grouped in the left margin, indicating global high specificity		
Schwimmer et al. (2000)						Data included in Jimenez-Requena 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	study included in Xing et al. 2011 and Jimenez-Requena 2008	2b

					Sensitivity to detect distant metastases CT scan 78% PET scan 86%		
Pfannenberg et al. (2007)	See above	See above	See above	See above	See above	See above	2b
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, 4patients 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	Diagnostic study	25 CM patients with lesions > 4 mm	Sensitivity, specificity	Initial tumor site: 14/19 true	Prospective design	2b-

	fluorodeoxy-D-glucose positron emission tomography scanning in the detection of regional and/or distant metastasis				negatives (74%) 5/19 false positives (26%) Sensitivity 17%, specificity 74% Microscopic lymph node disease: 12/19 true negatives (63%) 7/19 false negatives (37%) Sensitivity 0%	small number of patients Study included in Xing et al. 2011	
El-Maraghi and Kielar (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 studies 4, 2 letters/opinion articles 5 Overall, many low-quality studies resp. small patients cohorts	3a
Pleiss et al. (2007)	to assess the potential of fluor-	Prognostic and diagnostic study	95 Patients with maligant melanoma	overall 5-year survival	Sensitivity, specificity, and	No information about the final	3b

	18-FDGPET in order to evaluate the survival prognosis in melanoma		who had received a PET	sensitivity specifity	accuracy of FDG-PET were 91%, 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%	assessment of findings (e.g. 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	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	22/64 patients with T4 lesions Study included in Xing et al. 2011	3b

	sentinel lymph node dissection without clinically suspected metastases				19/64 false negatives (regarding 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	Retrospective diagnostic study CSP= chest X-ray,	100 PET scans on 84 melanoma patients with regional or distant recurrences	Sensitivity Specifity Accuracy	At the single lesion level: Sensitivity: PET: 85% CSP: 81%	Comparison of PET scan and CSP results at a lesion-based level→ see full-text	3b

	compared with 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.	blood analysis, ultrasonography, (US), computed tomography (CT), magnetic resonance imaging (MRI) and nuclear bone scans	according to CSP	Therapeutic impact	Specificity: 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	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.	3b-

			or of distant metastasis.			Results: no differentiation 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	Diagnostic study	33 patients with cutaneous	sensitivity specificity	Sensitivity and a specificity for	Small patient cohort	3b-

	implementing whole-body FDG-PET as a routine investigation in stage III melanoma patients with sub-clinical regional lymph node metastases diagnosed by SNB.		malignant melanoma and subclinical lymph node metastases diagnosed by sentinel node biopsy (SNB)	NPV	melanoma metastases: 80% and 88%, respectively. NPV: 96%.	Only cases with 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	Sensitivity and specificity not given	3b-

					location. In 1 patient the finding was a new and clinically relevant metastasis, in 3 other patients the leg manifestations were already known. In 6 other patients a validation of the positive PET findings was not possible		
Krug et al. (2000)	To assess the diagnostic value of fluor-18-Fluorodeoxy-glucose 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	Different reference tests Sensitivity and specifity not given	3b-

					of organs invaded by metastases was higher with PET in 5 patients and 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. (Results for the different organs (lungs, liver…): see full text)		
Dietlein et al. (1999)	To examine if - FDG-PET can improve staging of patients with melanoma when compared with combinations of standard	Diagnostic study	91 FDG-PET examinations perfomed on 68 patients with advanced melanoma.	True positives False positives	FDG-PET detected more lymph node and bone metastases High proportion of non-verifiable PET findings	FDG-PET images from various institutes Different staging examinations Sensitivity	3b-

	radiological examinations currently used in routine practice? – if the setting of indications for PET can be opimized?				Comparision of ultrasonographic and radiological methods with FDG-PET for examining the lungs, abdominal organs, LN and skeleton: see full-text.	/specificity not given No data 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
Pfannenberg et al. (2007)	See above	See above	See above	See above	See above	See above	2b
Dellestable et al.	See above	See above	See above	See above	See above	See above	2b-

(2011)							
Hausmann et al. (2011)	See above	See above	See above	See above	See above	See above	2b
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	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

					(47%) Pelvis True positives: 3 (38%) False positives: 5 (62%) 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	study included in Xing et al. 2011	3b

					(37%) Abdomen/ pelvis CT 10 of 11 (18%) Cranial CT 2 of 57 (4.0%) True negatives: Chest CT 50 of 57 (88%) 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	True and false	Chest CT:	Index tests not	3b

			patients	positives Positive and negative predictive value (PPV, NPV)	Number of exams: 59 True positives: 0 False positives: 9 PPV: 0% NPV: 98.0% Cranial CT: Number of exams: 52 True positives: 0 False positives: 9 PPV: / NPV: 98.1%	done on all patients	
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,	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

	to evaluate the impact of the discovery of pulmonary nodules on the clinical therapy of melanoma.						
Aloia et al. (2006)	To analyse the efficacy of routine radiologic staging in asymptomatic patients with microscopic nodal involvement before completion of lymphadenectomy.	Diagnostic retrospective cohort study	270 staged patients with positive SLNB melanoma	True positive and False negative rate	TP detection rate of occult distant metastases: 1,9% FP: 12%.	Calculation of sensitivity and specificity not possible False and true negatives not given	3b-
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:	Not in every case of indeterminate findings additional diagnostic was performed Sensitivity/specificity not given	3b-

					- 1 positive finding, - - 123 negative - 22 indeterminate. 96 underwent MRI imaging (brain), 16 underwent CT (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	Diagnostic study	127 asymptomatic patients stage III (28 patients: microscopic disease at ELND. 99 patients with palpable disease diagnosed by fine	True (TP) and false positives (FP)	20 patients: TP CT scan revealing unsuspected metastases. 15 patients: abnormal CT scans subsequently	TP and FP rates: see full text FP and FN not given	3b-

	III melanoma metastatic to the regional nodes		needle aspirate, open biopsy, or TLND)		shown to be a benign process or second malignancy. No difference in the incidence of TP CT between the groups of patients with clinically apparent vs. occult nodal disease. 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.		
Buzaid et al. (1995)	To determine the value of CT scans in the staging of asymptomatic melanoma patients	Diagnostic study	89 patients who either presented with or developed localregional disease as the first	TP-rate TN-rate	Findings on CT scan were TP for six patients (7%), FP for 20 (22%), and TN for	No detailed data about the follow-up regime/time of follow up	3b-

	who presented with or developed localregional disease as the first site of recurrence and had both a normal chest radiograph and serum lactate dehydrogenase (LDH) level.		site of recurrence		63 (71%).	Sensitivity and specificity not given Study included in Xing et al. 2011	
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	Extent of staging examinations and extent/ length of	3b-

					(15%) Cranial CT: 0/51 true positives 0/51 false positives	follow-up depended on center and tumor site	
Patten et al. (1990)	To determine 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.	Cross-sectional study	125 CM patients	Prevalence of bone metastasis	Examinations: CT 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	Not enough data given to differentiate between prevalence of bone metastasis in early stage and advanced stage melanoma	4
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	4

						different staging examinations unclear	
Silverman et al. (1984)	To assess the value of computed tomography in the detection of abdominal spread of malignant melanoma.	Cross-sectional study	70 CM patients	Prevalence of abdominal metastases	52 scans of abdomen and 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%	Most patients symptomatic at time of CT scan (abdominal pain, abnormal liver function tests or liver imaging)	4
Ginaldi et al. (1981)	To investigate the value of CT as a staging procedure in neurologically asymptomatic	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	No clear distinction between patients of different stages	4

	melanoma patients, and to describe the neurological features of metastases and their incidence in melanoma patients.				in the liver and lung, 2/9 others recurrent local disease, 5/9 other systemic metastases		
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	diagnostic and prognostic study	125 consecutive patients	specificities sensitivities NPV	Overall specificity for FDG PET/CT: 96.8% (95% CI,		2b

	compared to the tumor markers S100B and melanoma inhibitory activity (MIA) in patients with high risk melanoma.		Patients who had a Breslow tumor thickness .2.0 mm, elevated S100B or MIA level	PPV	89.1% to 99.1%) corresponding sensitivity: 96.8% (89.0% to 99.1%) 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]	Diagnostic study	78 patients	Impact on patient management	In 27% of the patients the	AJCC 2001 staging System was used	2b

	FDG-PET/CT on the restaging and changing management of patients with malignant melanoma.		(Initial restaging/before PET/CT): local recurrence in 11 patients, locoregional recurrence in 23 patients and distant recurrence in 44 of 78 patients.	Sensitivity Specificity	management was changed after the [F-18] FDG-PET/CT studies. Upstaging in 5 of 23 (22%) 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	Diagnostic study	56 CM patients after surgical resection who underwent combined PET/CT imaging and had sufficient follow-	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	Insufficient data for 24% of patients Study included in Xing et al. 2011	2b

	patients with newly diagnosed and resected cutaneous malignant melanoma.		up; 18 of them in stage III or IV		84.3% Sensitivity and specificity regarding M-stage: PET-CT 38.5% and 100% 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% NPV75% Diagnostic accuracy 73%	Study included in Xing et al. 2011	2b
Lagaru et al. (2007)	To analyse sensitivity and	Diagnostic study	106 CM patients who had whole-	Sensitivity and specificity	Per patient: Sensitivity 89.3%	Studies were done for disease re-	2b

	specificity of PET/CT for the detection of metastases of malignant melanoma.		body FDG-PET/CT, 30 of them with stages IIIC and IV		Specificity 88.0% True positives 50 False positives 6 False negatives 6 True negatives 44 Per lesion: Sensitivity 89.6% Specificity 84.6% True positives 78 False positives 8 False negatives 9 True negatives 44	staging in all patients; time interval from initial diagnosis not given Studie included in Xing et al. 2011	
Pfannenberg 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	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%	Cohort includes patients with already known metastasis Study included in Xing et al. 2011	2b

	negative findings for metastases at PET, by using histologic findings or additional imaging and/or follow-up findings as reference standard.				With dedicated CT readout: 52/124 true positives (34%) 4/124 false positives (3%) 67/124 true 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	Images were interpreted by a specialist, aware of all clinical findings/not blinded Small patient cohort, not described in detail	2b-

					indeterminate PET in 13% of patients		
Mansour et al. (2010)	(1) to determine the anatomic scatter plot of false-positive and 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.	Diagnostic study	342 CM patients with PET/CT	True and false positives	True positives: Breslow 0 – 2 mm: 46.9% Breslow 2.01 – 4 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%	Limited purpose of the study (musculo-skeletal findings in PET/CT) No fixed indications for PET/CT	3b
Revel et al. (2010)	To assess the utility of PET-CT 18FDG in a group of N patients with cutaneous head and neck melanoma,	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

	combined with SLNB.						
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 PET/CT studies: 42 Positives: 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	study included in Xing et al. 2011	3b
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.	No reference standard	4

					In 14 patients with macroscopic stage 3 disease at, or subsequent to, their initial 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	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 lympho-scintigraphy or unusual drainage pattern included	2b

	inconclusive, and whether this influences the surgical approach.						
Subtopic BONE 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 positinves	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	Diagnostic standard procedures varied over time; no defined gold standard of diagnosis	3b

					false positive results)		
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	0/141 true positives 3/141 false positives (2%)	Criteria for selecting staging examinations unclear	3b-
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							
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

	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 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	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). disease recurrence in 70% of patients with an increased preoperative serum LDH level compared with 53% patients with a normal serum LDH level (P	Results for RT-PCR: see full-text	1b

					= 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.	LDH was omitted from the analysis because only 8 patients showed elevated LDH serum levels	1b-

					median survival was 4.1 months. 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]. 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).		

Essler et al. (2011)	To assess the prognostic value of FDG PET/CT compared to the tumor markers S100B and melanoma inhibitory activity (MIA) in patients with high risk melanoma.	Retrospective diagnostic and prognostic study	125 consecutive patients Patients who had a Breslow tumor thickness .2.0 mm, elevated S100B or MIA level	specificities sensitivities NPV PPV	S100B: Overall specificity 85.7% (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%) 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%). Patients with elevated S100B- or MIA values or PET/CT positive findings showed a significantly		2b

					(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.		
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	No relation was found between S-100B and SUV. DFS for patients with an elevated vs. normal S-100B: 31% vs. 44,6% (HR = 3.1; p = 0.02) DFS for patients with normal vs. elevated SUV: 42% vs. 29% (HR = 1.1; p = 0.8). DSS for patients with normal vs.		2b

					elevated S100B: 60.7% va. 44.7% (HR = 2.2; p = 0.07). DSS for patients with normal vs. elevated SUV: 59.1% vs. 43.5% (HR = 1.1; p = 0.8). S-100B is associated with tumor load and a strong predictor for DFS in stage III melanoma		
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	The serum level of CRP correlated with increasing number of LN node metastases. Significant elevated serum levels of S100 in patients with more than one positive SLN		2b
Bouwhuis et al.	To determine the	Prognostic study	918 serum samples	distant metastasis-	Multivariate		2b

(2011)	prognostic value of S100B based on updated information using serial determinations in stage IIb/III melanoma patients.		of 211 Patients who participated in the EORTC 18952 trial, evaluating efficacy of adjuvant intermediate doses of interferon a2b (IFN) versus observation Serum S100B levels were measured during treatment and follow-up	free interval (DMFI) distant metastasis-free survival (DMFS) OS HR	analyses: DMFS: HR of S100B >= 0.2 versus S100B < 0.2 was 5.57 (95% CI 3.81-8.16), P < 0.0001, after adjustment for stage, number of lymph nodes and sex. In stage IIb patients: HR adjusted for sex=2.14 (95% CI 0.71, 6.42) In stage III patients: the HR adjusted for stage, number of LN and sex=6.76 (95% CI 4.50-10.16). OS: HR: 4.73 (95% CI 3.14-7.12), P < 0.0001. In stage IIb		

					patients: HR 2.73 (95% CI 0.79–9.44; P = 0.11). In stage III patients: 5.46 (95% CI 3.52–8.45; P < 0.0001). 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		2b

					serum concentrations of S100 than patients with clinically non-apparent tumor		
Andrés et al. (2008)	To compare the value of tyrosinase 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.	Prospective diagnostic and prognostic study	90 CM patients in stages I – IV	Sensitivity Progression-free survival Overall survival	Sensitivity of S100: 22.2% for stage I 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	Very small control group for S100 (2 healthy subjects, 3 patients with breast cancer, Hodgkin lymphoma and Ewing's sarcoma, respectively) Also contains data on tyrosinase Patients in stage I – IV	2b
Kruijff et al. (2009)	To investigate whether the	Prognostic study	56 patients with clinically and	Disease-free survival	2-year DFS in patients with	Follow-up diagnostic	2b

	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 selected for therapeutic lymph node dissection		cytologically proven regional nodal metastases of melanoma	Prognostic factors	- elevated vs. non-elevated preoperative S-100B concentrations: 34% vs. 61% (HR:2.6, P=0.03) - elevated vs. non-elevated postoperative S-100B concentrations: 30% vs. 51% (HR:2.0, P =0.1). 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.	procedures and follow-up intervals not stated in article Design not descirbed (prospective/retrospective)	
Wang et al. (2004)	See above	Diagnostic study	210 CM patients without clinical	True and false positives and	LDH results available in 96		2b

			evidence of metastasis	negatives	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 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, specifity, 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 specifity both 92% PPV value (cut-off 0,114 µg/L) for newly occurring	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

					metastases: 65%, NPV (no metastases): 99%. FN results included patients with unknown primary melanoma and those with amelanotic melanoma metastases.		
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	Different reference standard for patients with abnormal laboratory values	2b-

					Breslow thickness		
Garbe et al. (2003)	To evaluate the diagnostic accuracy of protein S-100B, melanoma-inhibitory activity (MIA), LDH, AP, and tyrosinase/MART-1 reverse transcription-polymerase chain reaction (RT-PCR).	Diagnostic and prognostic study	296 consecutive AJCC Stage II or III clinically disease-free melanoma patients 120 healthy controls without melanoma or other known malignancies.	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: 93%, PCR : 80% MIA: 97%, AP: 89% LDH: 90% Diagnostic accuracy: MIA: 86%, S100: 84%, AP: 79%, LDH: 77% RT-PCR: 72% ROC analysis: diagnostic accuracy: S-100: 66%, MIA: 62%, LDH: 53%, AP: 51% Significant P values	Different reference standard (CT) for patients with abnormal laboratory values (may lead to a higher sensitivity of the tumor markers than in reality) Detailed description of follow up; no drop-outs	2b-

					for S-100 (0.001) and MIA (0.011), but not for LDH (0.571), AP (0.807), and PCR (0.519). Somer's Dxy : S-100 had the highest predictive value Kaplan-Meier 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.		
Agarwala et al. (2009)	To assess each of the three stratification factors in this study	Prognostic study	760 patients (in study 301) and 760 (in study 18951)	Overall survival	LDH was within the upper range of normal for a large number of patients.	Post-hoc analysis of two randomised trials (Oblimersen GM301 and EORTC	2b

	(performance status, metastatic site and LDH) for an interaction with treatment on survival.				highly ordered and monotonic relationship between LDH and survival: survival worsened as LDH became more elevated, even when LDH remained within normal range. LDH and tumour size poorly correlated; elevated LDH was not associated with any one disease site. LDH was highly predictive of oblimersen effect. Kaplan-Meier survival curves: see full-text	18951)	
Deichmann et al.	LDH was compared	Diagnostic study	91 patients with	Sensitivity	LDH not	Sensitivity and	2b-

(2004)	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.		histologically proven melanoma progressing into stage IV, 125 patients stage I, II or III in follow-up examinations	specificity	significantly elevated in patients entering stage IV melanoma (P=0.785), whereas CRP was (P<0.001). LDH did not discriminate between the defined groups of patients (AUC=0.491; 95% CI, 0.410, 0.581), whereas CRP did (AUC=0.933; 95% CI, 0.900, 0.966; P<0.001). CRP in diagnosing AJCC stage IV entry: cutoff =2,1 or 2,2mg/dl: specificity=80%, sensitivitie=83,5%. cutoff 2,4 or 2,5mg/dl:	specificity for LDH not given Small population No information on blinding	

					specificity = 83,2% and 85,66, respectively. sensitivity of 81,3%. Cutoff=2.9mg/dl: Specificity=89,6% sensitivity=79,1 cutoff point=3.0mg/dl: specificity=90,4 sensitivity=76,9		
Deichmann (2001)						Same data as in: Deichmann et al. (1999): S100-Beta, melanoma inhibiting activity, and lactate dehydrogenase discriminate progressive from non-progressive amercan joint committee on cancer stage IV melanoma	
Stoitchkov et al.	To define the	Diagnostic study	60 melanoma	Overall survival	In stage III	Small patient	2b-

(2003)	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)		patients (24: stage I-II, 18 stage III, 18 stage IV)	Change in serum concentrations by therapeutic interventions	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 38% (P 0.04) and the S100B level by 45% (P 0.02) in stage IV responders. increase in one or both markers during follow-up in patients with progressive disease:	numbers divided into many subgroups Study included here in addition to S100 meta-analysis because of results about L-dopa/L-tyrosine ratio	

					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. No correlation between L-dopa/L-tyrosine ratio and S100B.		
Stoitchkov et al. (2002)	Prospective 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	Diagnostic study	89 melanoma patients with histologically proven primary and/or metastatic melanoma or measurable metastatic disease (by imaging). (9 stage I, 33 stage II, 19 stage III, 28	Sensitivity and specificity	overall sensitivity 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) no statistical difference between stages I, II and III patients for both	Precursor study to Stoitchkov et al., 2003 Patients lost to follow-up are not included in analysis (risk of bias)	

	in metastatic patients and survival).		stage IV).		markers. Significant higher median ratio in stage IV. In stage III-IV patients, both markers were significantly higher in evolutive patients than in stable ones. The ability (sensitivity/specificity) of markers to predict disease progression in 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	Diagnostic study	373 melanoma patients (284 with melanoma in situ or stage I/II and 89	Sensitivity Specificity	Presence of lymph node, visceral and brain metastases: Sensitivity (for	No follow-up as reference standard (cross-sectional design)	2b-

	melanoma patients		with melanoma stage III/IV; 54 of these tumor free and 29 with newly occurred metastases) 10 control subjects		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		
Deichmann et al. (1999)	serum levels of S100-beta (S100b) and melanoma-inhibiting activity (MIA) were assessed for the ability to discriminate progressive from nonprogressive disease.	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 elevated in patients with progressive disease. Sensitivity: S100b=91% MIA=88% LDH=79% Specificity: S100b=76% MIA=73	Patients received different therapies Small population No information about follow-up	2b-

					LDH=92% 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.		
Hofmann et al. (2011)	to assess the utility of melanoma inhibitory activity (MIA) serum marker in the follow up and primary diagnosis of stage III melanoma patients	Diagnostic study	138 melanoma patients in stage III at time of primary diagnosis and during periodical routine follow up	Sensitivity Specificity 5-year survival rate	MIA cut-off value of 12 ng⁄mL: 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).	No information about time interval between blood sample and staging/restaging examinations "relapse" not described in detail, staging results not given.	3b

Garnier et al. (2007)	L-DOPA/tyrosine ratio (an index of tyrosinase activity), melanoma antigens S100B and MIA, lactate deshydrogenase (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 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		3b

					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 level was lost	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 reported	3b
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	Data from 179 patients Stage III-IV melanoma patients at diagnosis: (37 in Stage III,142 in Stage IV). The age of patients	Specificity Sensitivity PPV Overall Survival	Stage III: 5-S-CD was 60 % sensitivity, 91.6 % specificity, 93.8 % PPV Stage IV: LDH:	In stage III data for sensitivity and specificity for S100B and LDH not given No further information about	3b

			ranged from 22 to 88 years (mean 59.8). Median follow up time was 15 months. 63 patients (with other skin diseases) were enrolled as control group.		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 calculated median survival: 4.6 months. Kaplan-Meyer analysis of the survival of patients with elevated vs. normal marker levels indicated significant differences in case of all the 3 markers, with the shortest survival of patients with elevated S 100B or LDH levels ($p<0.05$).	staging (reference standard)	

Meral et al. (2001)	To investigate the hypothesis that the decline in serum melanoma-inhibiting acitivity (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 level: 8.7 ng/ml (mean + 2SD). 1-year OS rates: no change according to the site of the primary tumour, the type of surgical or radiation treatment	See original article for overall survival curves (Kaplan-Meier) Survival analysis were not perfomed with serum S100 levels Analysis of LDH kinetics revealed no useful information.`	3b

					or the chemotherapy regimen. Advanced stage MM patients in whom serum MIA levels did not decrease during systemic treatment had a less favourable prognosis.		
Brouard et al. (2000)	To determine if serial PS100B is a marker for metastatic evolution by observation of its level/variation/evaluation in patients in complete remission and patients receiving chemotherapy	Diagnostic study .	239 blood samples were taken in 122 patients with cutaneous melanoma (56 patients in complete remission, 56 patients with melanoma in progression	Sensitivity and specifictiy	The threshold to separate patients with metastases from those in complete remission was 0,09µg/L (Specificity 92%, sensitivity 70%). PPV (Stage III/IV): 77%, NPV 89%	Only results of 90 patients are presented. Drop outs are not commented.	3b
Schmitz et al. (2000)	To analyse the serum levels of S100B and MIA in non-melanoma	Diagnostic study	87 CM patients	Specificity Positive results	Specificity for S100 regarding the diagnosis of melanoma:	No follow-up (cross-sectional design)	3b

	control patients and melanoma patients to report on the sensitivity and specificity of both tumor markers				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 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) 8 of them had detection of metastases at the same time, 5 of them 2 – 6 months later		3b

					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 with brain tumors, 243 patients with advanced epithelial and mesenchymal tumors	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 full-text S100-positivity, cut-off: 0.15 ng/ml - 30/49 (61%) sera from stage III and IV	Sample of stage II and III patients small 5 patients during chemotherapy of stage IV melanoma Sensitivity/specificity not given	3b

					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 patients with different stages of malignant melanoma and to determine the value of serum S100 in the follow-up of melanoma patients	Diagnostic study	Blood samples from 73 patients with malignant melanoma (25 patients: stage I/II, 14: stage III, 34: stage IV) Control group: 130 healthy patients.	sensitivity	1/25 stage I/II patients, 3/14 stage III patients (sensitivity 21,4%) and 27/34 stage IV patients (sensitivity 79,4%) showed detectable S100 levels. For metastatic melanoma (stage	Small population Choroid melanoma included (n=1) No information about staging given	3b

	during treatment				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)		
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 elevated only in stage IV patients (p = 0.02) MIA significantly elevated both stage II, III and IV MIA levels	Low patient numbers for each stage Selection critera for patients and healthy volunteers not given	3b-

					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 lymph nodes	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% sensitivity and 82% specificity of MIA	No follow-up as reference standard (cross-sectional design)	3b-
Arenberger (2007)	quantification of the following five melanoma markers by establishing a	Prospective study	65 patients with resected cutaneous melanoma stage IIB-III	Detection rate	Tumour marker mean levels in patients with progression: MIA,	Small population Elevation of tumour markers varies	3b-

	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 The final aim is the routine usage of this method for rapid screening of early metastasis and		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		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. In patients with progression, in 39% three markers were concomitantly	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.	

	treatment response in high-risk melanoma patients.				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)	
Smit et al. (2008)	to evaluate S-100B for monitoring response to chemoimmunotherapy followed by surgery and its predictive value for relapse and overall	Prognostic study.	44 patients with locoregional-lymph node or intransit metastases (cytologically proven, clinically detectable regional metastases of	Overall survival Renissionrate	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	Small population	3b-

	survival in patients with clinically detectable localized disease. 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.		melanoma without evidence of distant metastases.		statistical significance		
Lugovic et al. (2007)	To determine and compare levels of S100, MIA, LDH and tyrosinase in the serum of patients with MM in different disease stages, and to conclude whether these might be useful	Diagnostic study	50 melanoma patients (30% in stage I, 52% in stage II, 16% in stage III and 8% in stage IV)	Positive results	Increased MIA in 26% of stage I patients, 26% of 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	No follow-up as reference standard	3b-

	prognostic tools for MM progression				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 growth patterns and site of metastases.	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 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	No data given for specificity Reference test not described in detail	3b-

					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 posttreatment levels of MIA and survival in 70 patients with advanced	Diagnostic and prognostic study	70 patients with histologically confirmed metastastic melanoma. (50 stage III, 17 stage IV)	Overall-survival Specificity	Mia positivity concentrations: >8,8ng/l.: - stage III: 46% - stage IV: 65% Median OS in MIA positive patients	No data for sensitivity given Small population	3b-

	melanoma.				(stage III/IV): 13 vs. 28 months in patients with negative pre-treatment MIA levels. 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. Specifitiy (cut-off>8,8ng/l) = 95%		
Klimek et al. (2002)	To evaluate the sensitivity of serum MIA levels in predicting the risk of relapse in patients with AJCC stage II, III and IV	Diagnostic study	39 patients with stage II, III and IV melanoma 14 patients with clinically advanced melanoma (IV or unresectable III) as	Sensitivity False positives	MIA: 17% sensitivity for recurrence 6% false positives No significant difference in the proportion of	MIA values taken at different intervals after diagnosis and treatment of melanoma	3b-

	melanoma		positive controls Serum from 20 patients with prostate or small cell lung cancer to establish a background reference range		patients with elevated MIA levels between the group of patients who relapsed (17%) and those who did not relapse (6%)		
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 patients at high risk for recurrence treated with various immunotherapy	Diagnostic study	84 CM patients (16 in stage II, 29 in stage III and 39 in stage IV) under treatment Most of stage II and III patients (36/45) were treated with polyvalent	Sensitivity and specificity	At a threshold of 4.5 ng/ml values for discrimination between progression and no progression were: Sensitivity of 82% and specificity of 71% before	Low patient numbers for each treatment modality Method of assigning patients to treatment regimens not described	3b-

	regimens		melanoma vaccine after surgical resection; all patients treated with IL-2 were stage IV		treatment Sensitivity of 67% and specificity of 79% after treatment		
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 11), 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. Inceased 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. Inceased levels in 34% of patients stage III and IV.	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-

					For the whole group: sensitivity of S100 and NSE: 30 and 26%, respectively For patients I and II: Poor sensitivity for NSE, S-100 values were normal in all patients. For patients stage III and IV: sensitivity for S-100 and NSE: 55% and 34% respectively ($p < 0.5$).		

1.3.5. 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
Bosserhoff et al. (1997)	x	x	x	x
Bouwhuis et al. (2011)	x	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	
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
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
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
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
Pfannenberg et al. (2007)		x	x	x

Pleiss et al.(2007)	x	x	x	x
Revel et al. (2010)	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			
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
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		
Zartman et al. (1987)	x			

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1.4. 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.

1.4.1. 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
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

1.4.2. Empfehlung, Hintergrundstext und Literatur Australische Quell-Leitlinie

(mit Seitenangaben der Quellleitlinie)

	LL Australien **New Zealand Guidelines Group 2008**
Schlüsselempfehlungen	Recommendation 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. Recommendation grade: D
Evidenzgrundlage	Evidence summary 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 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
Hintergrundtext	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

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	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.
Referenzen	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
3. Tefany FJ, Barnetson RS, Halliday GM, et al. Immunocytochemical analysis of the cellular infiltrate in primary regressing and non-regressing malignant melanoma. J Invest Dermatol 1991;97:197-202
4. Vijuk G, Coates AS. Survival of patients with visceral metastatic melanoma from an occult primary lesion: a retrospective matched cohort study. Ann Oncol 1998;9:419-422

1.4.3. Ergänzende Recherche, Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	("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]))	26.01.2012	9
	("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]))		9
	("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])		0
	("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])		0
	("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])		3

Datenbank	Suchstrategie	Datum	Treffer
	NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh]) ("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])		8
	("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])		0
	("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])		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.		

1.4.4. 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 Primary	this article questions whether extensive physical examinations (opthalmoscopy, otoscopy, rhino-pharygoscopy, laryngoscopy, sigmoideoscopy, and in women, gynecological examination) are necessary.	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 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		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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.		

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

2. AG Sentinel Node Biopsie

2.1. Frage II.1. Sentinel-Node-Biopsie - De-novo-Recherche

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

2.1.1. PICO, Suchwörter

PICO-Unterfragen:

- Senkt die Durchführung einer Sentinel-Biopsie die Rezidzivrate
- 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

2.1.2. 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 "sensitivity"[tiab] OR "specificity"[tiab] OR "accuracy" OR "outcome"[tiab] OR "prognos*"[tiab] OR "predict*"[tiab] OR "assoc*"[tiab])	26.01.2012	1039
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)

2.1.3. 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

2.1.4. 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 recurrence and for distant/all	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 12.5%	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 excluded, or in other subgroup	1a

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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					involvement in CLND for patients 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	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	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					publication bias 4 melanoma-related deaths were reported	positive SLN	
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 ≤ 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	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
					melanoma, 13.4% in superficial spreading melanoma, 8.8% Spitzoid melanoma and 38.3% of ulcerated melanomas In multivariate analysis, tumor thickness and histological tumor type significantly associated with SLN status Melanoma with tumor > 4 mm revealed 11.68-fold risk for a positive SLN in comparison with tumors < 1 mm 9.8% (63/641) of SLN negative		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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) 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	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)	Post-hoc analysis of the multi-center, randomized Sunbelt Melanoma Trial See full text (p. 1539) for complete partition tree	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	require SLN biopsy.				On multivariate analysis, Breslow thickness, age and lymphovascular invasion were predictive of positive SLN		
Testori et al. (2009)	To investigate the relationship between primary tumor characteristics, SLN findings, and the clinical outcome	Observational study	1313 consecutive patients	Overall survival Predictors of SLN positivity and survival	Overall SLN identification rate 99.3% 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	Large patient cohort Long median follow-up	1b

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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				mortality and survival	Disease-free survival rate at 5 years: in the biopsy group 78.3%; in the observation group 73.1% Melanoma-specific death: 13.8% in the observation group and 12.5% in the biopsy group Melanoma-specific survival rate: 90.1% and 93.2%, respectively, at 3 years, and 86.6% and 87.1%, respectively, at 5 years Melanoma-specific mortality rate in the biopsy group: 9.7% when sentinel		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					tumor-free and 26.2% if sentinel positive 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		
McMasters et al. (2001)	To identify prognostic factors that are predictive of sentinel lymph node (SLN) metastasis in melanoma.	Prognostic study	Total of 1058 patients evaluated; 961 patients had complete data and were included in the statistical analysis	Positive sentinel node	SLN identification rate 99.7% SLN positivity 22% Independent predictors of SLN metastasis, in order of importance: Breslow thickness, Clark level, ulceration, and	Prospective design Subgroup analysis of Melanoma Sunbelt Trial (multi-center, randomized trial); therefore patients partially identical with patients in Mays et al. (2010)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patient age		
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
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,		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					respectively).		
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 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; $P = 0.93$).	Post hoc analysis of a multicenter prospective randomized trial	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 ulceration and 2.0 for SLN positivity ($p=0.001$ and $p=0.002$ respectively).	CLND was performed in 119 patients and these patients were analyzed for recurrence and survival.	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 ($p < 0.001$).		
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 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.		
Göppner et al. (2011)	To investigate the prognostic relevance of SLNB and other risk factors in the subgroup of	Prognostic study	87 patients with thick melanomas 1 4.0 mm (T4).	Recurrence-Free Survival Overall survival	Multivariate analysis: SLN and ulceration, analyzed as separate risk factors as well as their combination,		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanomas > 4.0 mm and to compared it to previously published results.				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 >= 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 and 39% in SN-positive patients cancer-specific		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					survival rates: 88·6% and 46% respectively (P < 0·001). 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.		
Tejera-Vaquerizo et al. (2012)	To determine whether growth rate (GR) of cutaneous melanoma predicts the histological sentinel lymph node (SLN) positivity	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 independently	surrogate measure for GR in primary invasive melanoma was calculated as the ratio of Breslow thickness to time to melanoma development.	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					associated with SLN positivity. 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). 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).		
White et al. 2011	Prognostic study	undergoing sentinel lymph node (SLN) biopsy for primary	3463 patients (561 (16.3%) had a positive SLN biopsy)	Predictive factors	multivariate analysis: increasing Breslow thickness,	retrospective and prospective data	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		melanoma			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 <	Retrospective design Large patient sample	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					40 years was significantly 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)	Prognostic study	1251 consecutive patients with CM	Overall survival Disease-free	TIL status of lesion correlated with the Breslow thickness,	Retrospective analysis (though of prospective	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	are able to predict the sentinel lymph node (SLN) positivity, the disease-free survival (DFS) and overall survival (OS) in clinical stages I-II AJCC primary cutaneous melanoma (PCM).			survival Correlation between TIL status and SLN status	Clark level and regression No difference in other variables evaluated, including SLN status or the presence of ulceration, among patients with brisk, non-brisk and absent TILs SLN identified in 394 patients (97.5%) 18.8% positive SLNs In multivariate analysis, increasing Breslow thickness, anatomical site and absence of TILs independently associated with positive SLN	database)	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					5-year DFS 75.9% in negative SLNs, 35.2% in positive SLNs 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	Probability of recurrence-free 5-year-survival: 42.5 ± 5% overall, 26.3 ± 6.6 % for SLN+ and 58.7 ± 7.1 % for SLN- In multivariate	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				SLN positivity Relative risk (RR) for SLN positivity	analysis the pathological status of the SLN had a highly significant prognostic value (p = 0.000009); relative risk (RR) 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	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
					cases and 3.22 mm for SN-positive cases Breslow thickness only statistically significant predictor for metastases 46% of positive and 11% of negative SN patients recurred False-negative rate 8.6%, sensitivity 91.4%. 5-year DFS 43% for patients with positive SN and 83.5% for patients with negative SN 5-year DSS 49.1% for SN-positive patients and 87.4% for SN-negative		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients		
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 melanomas.	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
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	Statistically significant greater proportion of individuals without regression showed sentinel lymph node (SLN) positivity (p=0.028) compared with patients without regression Correlation of age, sex, site and presence of tumour	Retrospective design, but 1 – 6 years prospective follow-up in 79% of the patients (recording survival and metastasis)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					infiltrating lymphocytes (TIL) with regression and sentinel node status not statistically significant		
Morris et al. (2008)	To assess whether the presence of RG was associated with a higher probability of a positive SLN or an increased risk of local or distant recurrence.	Prognostic study	1349 patients with cutaneous melanoma	Correlation between regression and SLN positivity Overall survival Disease-free survival	10% of patients with RG and 18% of patients with NRG who underwent SLN 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	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 model for the better selection of which patients with melanoma should undergo SLN biopsy.	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 presence of angiolymphatic invasion, the number of mitoses, and body site location of the melanoma	Retrospective design	2b
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	SLN identification rate 98.6% SLN positivity rate 17.6% By multivariate logistic regression		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				survival	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 significant predictors of a negative SLN compared with absent TILs, by univariate and multivariate analysis Histologic status of SLN was the most significant predictor of DFS and OS Negative SLN: 5-year DFS 80.0%		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Positive SLN: 5-year DFS 32.8% When stratified by SLN status, no survival advantage present with TILs		
Morton et al. (2005)	The objective of this study was to evaluate, in an international multicenter phase 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.	Randomized controlled clinical multi-center trial .	2001 patients with invasive primary cutaneous melanoma	Accuracy of sentinel node identification Dissected-basin recurrence in patients with negative sentinel node Surgical morbidity	Overall rate of SN identification: 95.3% 6.3% of patients 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:	Method of randomization described in Morton et al. (2006) No intention to treat analysis (ITT); instead an as-treated analysis was performed	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					37.2% for LM/SNB with immediate CLND vs 10.1% for LM/SNB without CLND		
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% Among patients with one or more metastatic SLN, 21% had further metastases in non-SLNs in the dissected basin Micrometastasis in SLN in 68%, macrometastasis in 32%	Prospective design Relatively short mean follow-up time	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					3-year DFSI for negative and positive SLN patients: 82 and 55%, respectively 3-year overall survival for negative and positive SLN: patients 93% and 83%, respectively By multivariate analysis, Breslow thickness the only statistically 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	SLN positivity rate 20.2% No positive SLN in MM ≤ 1.0 mm and in patients with regression > 50%	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Small cell and ulceration were significant prognostic factors in multivariate analysis SLN positivity rate for small cell: 56.9% SLN positivity rate for ulceration: 35.5% SLN positivity rate for small cell and ulceration: 86.3%		
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	Prognostic study	274 melanoma patients with melanoma ≥ 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	Prospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	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.				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 prognostic factors in the SLN-positive group Low-risk group:		

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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of SN metastases in patients with thin melanoma and which clinical or histopathologic factors may serve as predictors of SN tumor involvement.				tumor involvement in patients with thin melanoma None of the patients had non-SN tumor involvement		
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	SLN positivity rate 21.4% Only tumor thickness significantly correlated with SLN positivity 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 more HRFs	Retrospective design 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	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 positivity	Breslow thickness > 2 mm, upper extremity primaries, and ulceration were	Retrospective design Difficult definition	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	sentinel node biopsy.			Sensitivity and specificity, NPV and PPV	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	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					19.5% in inguinal dissection, 9.2% in axillary dissection	CLND (possible source of bias)	
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.	We directly	Prognostic study	94 patients with	Overall survival	SLN positivity rate	Small sample size	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(2009)	compared the relative contribution of lymphatic and hematogenous pathways in a cohort of patients with primary cutaneous melanoma with 3 years of clinical follow up.		primary cutaneous melanoma, 57 of which had a known SLN status	Disease-free survival Correlation between lymphatic invasion (LI) resp. vascular invasion (VI) and SLN positivity	75% in LI-positive patients, 39% in LI-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	(57 with known SLN status) Retrospective design	
Leiter et al. (2010)	To investigate the potential survival	Prognostic study	879 patients with primary cutaneous	Incidence of metastasis	Rate of regional lymph node	Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	benefit of sentinel lymph node dissection (SLND).		melanoma	Overall survival Recurrence-free survival	metastasis: 16.5% in non-SLND collective, 7.3% in SLND collective; no difference in satellite/in-transit metastases and distant metastases Disease-free survival improved in the SLND collective	Historical control group without consistent reporting of 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	Retrospective design Small patient sample	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					between metastatic and non-metastatic melanomas In multivariate 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	Mean tumor thickness in SLN-positive patients 3.01 ± 0.52mm, in SLN-negative patients 1.70 ± 0.31mm Additional prognostic parameters such as tumor ulceration, mitotic activity, regression and number of tumor infiltrating	Small patient sample Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					lymphocytes did not differ between groups Frequency of intratumoral lymphatics in SLN-positive patients 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	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						investigated further	
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. A total of 103 of the 168 patients were referred after their WLE.	Number of positive SLNB False-negatives Disease-free survival Overall survival	SLN positivity rate 32.3% both for cases and controls No significant difference in relapse-free survival: 72.3% for cases, 81.7% for controls at 2 years; No significant difference in overall survival: 94.7% incases, 96.8% in controls at 2 years	Follow-up time span too short for reliable assessment of survival	3b
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	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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	centres previous wide excision has been a contraindication for sentinel lymph node biopsy.						
Nguyen et al. (2001)	To determine whether primary melanoma histopathologic features could be applied to predict sentinel node status.	Prognostic study	112 consecutive melanoma patients	Correlation between histological features and SLN positivity	SLN positivity rate 20% False-negative rate 2.4% In multivariate analysis, the most significant cutoff for prediction of node positivity was a thickness of 1.5 mm Additional histologic features significantly predictive of occult micrometastases: ulceration and lymphovascular	Retrospective design No explicit information about inclusion criteria for SLNE	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					invasion		
Pasquali et al. (2011)	To test the discrimination, the calibration and the NPV of MSKCC nomogram in 543 patients	Diagnostic study	543 patients		positive SN in 147 patients (27%). 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). 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. incidence of SN metastasis was		3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					higher than that observed in the MSKCC series (27% vs 16%).		

2.1.5. Literatur

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2.2. 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?

2.2.1. Datenbanken, Suchstrategien, Trefferzahlen

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 Literaturbasis 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.			

2.2.2. Auswahlkriterien

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*

2.2.3. Evidenztabelle

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 cutaneous melanoma	Recurrence rate Overall survival Sensitivity, specificity, positive and negative predictive value (PPV, NPV)	Pooled positivity rate: 20.3% pathology-based In patients with pathology-negative SLN: PCR positive in 42.3% In patients with pathology-positive SLN: PCR negative (false negative) in	Funnel plot did not show publication bias	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					49% PCR positivity in patients with pathology-positive SLN: 95.1% In patients with pathology-negative SLN: 46.6% Disease recurrence rate: 16.8% among PCR-positive patients; 8.7% in PCR negative patients PCR sensitivity 57.4%, specificity 61.1%, accuracy 60.6%, PPV 16.8%, NPV 91.3%		
Elsaesser et al. (2012)	investigated survival probabilities and prognostic factors in sentinel lymph node biopsy (SLNB)	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%).		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	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.				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.		
Quaglino et al. (2011)	to evaluate which prognostic variables could predict NSLN invasion in SLN-positive patients and their impact on the overall survival (OS).	Cohort study	603 patients who had undergone SLNB for melanoma	OS prognostic variables on CLND results and disease course.	Breslow thickness, ulceration and micro/macrometastatic pattern of SLN invasion carried a significantly independent higher likelihood of NSLN involvement; Starz	Retrospective chart review	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 ≥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 II, III, and IV, Dewar criteria, Dewar criteria II, and RDC criteria	Retrospective design Large patient cohort For detailed survival rates see original article	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 limbs vs. trunk), SN	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
					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 contemporary international cohort	Cohort study	2313 patients with stage III disease	Overall survival	5-year survival for patients with micrometastases: 67% When stratified by tumor thickness,	Patient cohort partially identical with Balch et al. 2004 and 2009 For survival curves see original article	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of patients with stage III melanoma.				ulceration, and number of involved nodes, 5-year-suvival 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 For patients with nodal micrometastases independent predictors of survival were patient age, sex,		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					tumor thickness, ulceration, primary anatomic site, and number of tumor-bearing lymph nodes For patients with nodal macrometastases, age, ulceration, anatomic site, and number of tumor-bearing lymph nodes independently predicted survival		
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)	Recurrence-free survival Overall survival	CLND positivity rate 15.4% 21% recurrence rate 14% mortality rate (causes related to melanoma) In multivariate	Suggestion of new classification system Hannover II	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					analysis, independent predictors for RFS were greatest 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	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
					ulceration, and thickness of the primary melanoma 5-year survival rates: 70% for 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)	SN tumor burden increased significantly with tumor thickness. estimated 5-year overall survival: - 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%	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- for </=0.2 mm: 89%. Independent prongostic factors in OS (multivariate analysisi): - SN tumor burden - 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	NSLN involvement in the CLND specimen in 16.0% of patients Primary melanomas significantly thicker, more often ulcerated, and regressive in patients with NSLN involvement compared with patients without NSLN involvement Upon multivariate	Patient population subgroup of Meier et al. (2010)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					analysis, the three significant parameters were positivity by H&E (versus immunohistochemistry alone), relative tumor area > 10%, and presence of perinodal 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	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	10 patients lost to follow-up	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	lymph node dissection (CLND).				Prognostic factors of disease-specific survival: ulceration, maximum diameter of largest metastasis		
Satzger et al. (2007a)	To determine the prognostic relevance of histopathological characteristics of micrometastases in the SLN.	Cohort study	169 patients with primary cutaneous melanoma (Breslow's tumour thickness ≥ 1 mm) and positive SLN diagnosed from April 2000 to December 2004.	Overall survival (OS) Relapse-free survival (RFS)	Relapse rate 30% Mortality rate 20% (15% melanoma-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)	Patient population subgroup of Meier et al. (2010)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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: 1/16 = 6.3% Distant metastasis-free survival in <0,1 mm SN positive patients: 91% (identical to the 5-yr OS of SN negative patients) no additional non-SN positivity for SN-micro-metastases <0.1 mm.	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					multivariate analysis: SN tumor burden was the most important prognostic factor for DFS (P = 0.005) and OS (P = 0.03).		
Shivers et al. (2007)	To determine the relevance of low-volume disease of the sentinel lymph node detected only by RT-PCR-based assays.	Cohort study	311 Patients with melanoma	Overall survival Relapse-free survival Sensitivity and specificity of histology and PCR regarding the prediction of recurrence/death	SLN positivity rate: 19% in histology, 67% by PCR Recurrence rate: 42% of histologically and PCR positive patients 22% of histologically negative, but PCR positive patients 6.6% for histologically and PCR negative patients Prediction of death: Sensitivity of histology 47%,	Very long follow-up time (up to 15 years) Change in technique during the course of time	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					specificity 87% Sensitivity of PCR 88%, specificity 38%		
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 thickness (PMT) with respect to progression-free survival (PFS) and overall survival (OS).	Cohort study	63 patients with one or more positive SLNs were available	Progression-free survival (PFS) OS	Cox proportional-hazard regression model: After adjusting for age and gender, both MMS maximum metastasis size (MMS)and PMT primary melanoma thickness were highly significant and provided independent prognostic information.		2b-
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	Retrospective study	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 SN and non-SN status (P<0.001) 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)		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					no statistically significant difference between the three classifications (P=0.6).		
Murali et al. (2010)	To investigate clinicopathologic factors that predict NSN positivity in an attempt to identify patients who may be safely spared completion lymph node dissection (CLND).	Cohort study	409 patients	NSN positivity	Predictive of NSN status in muultivariate analysis: clinical characteristics (sex), primary tumor characteristics (ulceration and regression), and %PosSN	Retrospective design For details of the score, see original article	2b-
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	Description of study drop-outs described in another publication	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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)		
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 survival: 100% in S-I, S-II 80% in S-III 3-year disease-free survival rates: were 83% in S-I, S-II 60% in S-III	Small patient cohort	2b-
Frankel et al. (2008)	To examine whether	Cohort study	144 melanoma	Presence of	Independent	Design not	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	the size and location of the metastases within the SLN may help further stratify the risk of additional positive NSLN.		patients	metastatic non-sentinel nodes	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	consequently prospective	
Satzger et al. (2007b)	To determine the prognostic significance of isolated HMB45 and/or Melan A positive cells (immunhistochemically positive cells, IPC) in melanoma SLN.	Cohort study	477 patients with primary cutaneous melanoma	Overall survival (OS) Relapse-free survival (RFS)	3 groups were differentiated according to the findings in the SLN: Group 1 included 308 patients with histologically and immunohistochemically negative SLN, group 2 included 47	Patient population subgroup of Meier et al. (2010)	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients with IPC, and group 3 included 122 patients with micrometastases. Relapse rate: 11.7% of SLN negative patients, 12.8% of IPC+ patients, 37.7% of histology+ patients Mortality rate: 5.5% of SLN negative patients, 6.4% of IPC+ patients, 23.8% of histology+ patients		
Namikawa et al. (2012)	to re-evaluate microscopic classifications of metastatic sentinel lymph nodes (SLN) in the Japanese population	Cohort study	450 patients, including the 149 cases with SLN metastasis,	LN positivity-rate	additional LN positivity rate of 0% only in patients with a maximum diameter category of less than 0.1 mm.	retrospective study	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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.		
Starz et al. (2004)	to identify the relevant predictors for the presence versus absence of nonsentinel lymph node metastases in CLND specimens	Cohort study	SLNE cohort: 324 patients pre-SLNE cohort:274 consecutive melanoma patients	Overall survival survival without distant metastases	S-classification was the most significant independent predictor of the presence/absence of NSN-metastases in binary logistic regression: (P =	Patients who underwent SLNE → same population as in Starz et al. 2001 (see above)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					.010; adjusted relative risk = 3.31). 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). Overall survival: Kaplan-Meier curves diverge after about 4 years of follow-up (P-= .03). Cox regressions: S-classification is a significant independent predictor for distant metastasis (P = .014) and overall survival (P = .009)		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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	18/70 patients had non-SN metastases. No non-SN-metastases in patients with: - 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 lm - a Breslow thickness <2.0 mm and a diameter of the largest SN deposit <500 lm logistic regression: the SN metastatic area was the only independent factor predicting the presence of non-SN	Differences in survival between different microanatomic locations of sentinel node metastases not investigated No follow-up	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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	evidence of melanoma metastases in NSN in 24 of CLND specimens (16.4%) 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%) strong correlation between depth of metastatic deposit from the capsule of	Retrospective study differences in survival between different microanatomic locations of sentinel node metastases not investigated No follow-up	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					the SN and NSN involvement (3/24 patients (12.5%) with positive NSNs had deposits less than 1mmin 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 and 9 of 15 in S3	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
					SLNs (P = 0.001; chi-square test). The risk of developing distant metastases was dependent on the T classification (P < 0.0001; log rank test) and S-classification (P < 0.0001) T classification of the primary melanoma and S-classification= highly significant predictor for distant metastasis (P < 0.001). It turned out to be an independent factor of influence on distant metastasis and		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					survival in multivariate Cox analyses, which included tumor thickness, primary tumor site, patient gender, and patient age as covariates.		

2.2.4. Literatur

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3. AG Chirurgische Therapie

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

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

3.1.1. 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	

3.1.2. 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

	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.			

3.1.3. 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

3.1.4. 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 (HR: 1.05,	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
					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	Primary outcomes: 1. Time to death (any cause) 2. Time to combined endpoint of death (any cause) or recurrence (local, in transit, regional, distant) Secondary outcomes: 1. Quality of Life 2. Adverse events/outcomes	No significant difference in overall survival when comparing narrow with wide excision Overall survival wide excision: Hazard Ratio 1.04 compared with narrow excision; not significant Recurrence-free survival wide excision: Hazard Ratio 1.13 compared with narrow excision; not significant	Limited RCT data assessing treatment of thin melanomas < 1 mm and thick melanomas ≥ 4 mm. Melanomas in specific body sites not sufficiently investigated	1a
Gillgren et al. (2011)	to test whether survival was diff erent for a wide local excision	randomised, multicentre trial	936 patients with cutaneous melanoma thicker than 2 mm, at	Overall survival	5-year overall survival was 65% (95% CI 60–69) in the 2-cm group and		1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	margin of 2 cm compared with a 4-cm excision margin		clinical stage IIA-C (465 were randomly allocated to treatment with a 2-cm resection margin, 471 to receive treatment with a 4-cm resection margin)		65% (60-70) in 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	Recurrence-free survival rate 83% over 3 years and 79% over 5 years Tumour thickness and Clark invasion level were the only significant risk factors for disease-specific survival in Kaplan-Meier univariate analysis.	Prospective study design Patients not randomized between groups with different excision margins; recommendations for excision margins were reduced during the observation period (1976 - 2004); confounding	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						by other historical factors possible. 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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Mohrle et al. (2003)	To evaluate clinical parameters and surgical strategies influencing the prognosis of patients with facial melanoma.	Prognostic study 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. Surgical margins were successively reduced during the observation period, starting from 5 cm in 1980. For functional and aesthetic reasons, recommendations for surgical margins could not always be	368 patients with facial melanoma	Overall survival (5 years) Recurrence-free survival (5 years)	Significant predictors for survival: tumour thickness, Clark level and ulceration, surgery with 3D histology and histological tumour subtype	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.	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		followed in the head and neck regions.					
Pockaj et al. (2003)	To evaluate the prognostic variables and clinical ramifications of melanoma of the ear.	Prognostic study, retrospective design	84 patients with invasive melanoma of the external ear	Lymph node involvement Local, regional and systemic recurrence	Local recurrence in 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)	Retrospective design Patient numbers not sufficient for an evaluation of the influence of different surgical procedures on recurrences	3b
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	No control groups Data on elective lymph node dissection biased (decision about ELND was left to the surgeon) and not sufficient (small numbers of	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					mm acral-lentiginous melanoma Of 79 patients with melanoma ≥ 1.5 mm, 15 (19%) presented with regional node disease All 13 patients with subungual melanomas had lesions ≥1.5 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 In patients with	patients)	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					ALM, 71% presented with lesions ≥1.5-mm thick and were treated with wide excision or amputation; local recurrence in two (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	Very small patient numbers No control group	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					developed systemic metastases (all of whom died) One patient presented with stage II disease and developed local recurrence 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	Very low LoE (case series, retrospective design)	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 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 oor absence of muscle fasciae in patients with stages 0 and I	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	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	malignant melanoma correlates with prognosis.					fact that the control group is historical (other potential changes in melanoma management in the meantime)	

3.1.5. Literatur

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3.2. Frage III.2. Prophylaktische Lymphadenektomie - Adaptation

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

3.2.1. 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)

3.2.2. Empfehlung, Hintergrundstext 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 Standard Le curage prophylactique systématique est contre-indiqué. *Standard* *Die prophylaktische LAD ist*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
			kontraindiziert.
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 LoE: I References: 7, 12	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) Summary of the supporting evidence for the recommendations Observational study evidence suggests	S. 30 – 31 Curage ganglionnaire prophylactique systématique DESCRIPTION DES ÉTUDES La méta-analyse de Lens *et al.* 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 disponibles dans la publication, et après vérification auprès des auteurs, étaient insuffisantes [87]. SURVIE GLOBALE Aucun des quatre essais randomisées n'a montré de bénéfice

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		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. 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	en faveur du curage [85-89] *(Tableau IX)*. 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] *(Tableau X)*. 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 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]. COMMENTAIRES MÉTHODOLOGIQUES ET CLINIQUES

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		amongst patients who have undergone complete level I-III axillary lymph node dissection for melanoma is 10%, and 53% after additional axillary radiotherapy. • 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	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. 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. CONCLUSION DE LA LITTÉRATURE 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).

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		(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 increased survival in patients with node metastases only. • 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	*S. 30 – 31* *Systematische prophylaktische Lymphadenektomie (LAD)* *BESCHREIBUNG DER STUDIEN* *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].* *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].* *GESAMTÜBERLEBEN* *Keine der vier randomisierten Studien konnte einen Vorteil der LAD zeigen [85–89] (Tabelle IX).*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		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.	*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).* *KOMPLIKATIONEN* *In der Metaanalyse sind keine Informationen über Komplikationen verfügbar.* *Diese Art der LAD geht immer mit einer gewissen Morbidität 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].* *METHODOLOGISCHE UND KLINISCHE*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
			KOMMENTARE *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 gezogen werden, an denen nur ein lymphatischer Abflussweg existiert, d.h. im Wesentlichen bei Läsionen an den Extremitäten.* *SCHLUSSFOLGERUNG AUS DER LITERATUR* *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).*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
Bemerkungen		Diese Leitlinie bezieht sich auf MM und auf NMSC. 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.	Im Volltext der Leitlinie tabellarische Darstellung der einbezogenen Studien (S. 30).

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

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

3.3.1. 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

3.3.2. 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

	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			
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.			

3.3.3. 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.		

3.3.4. 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 lymph node	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.	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	3b

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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months (0.8–69.7 months). Regional recurrence in 6 (8.3%) of 72 patients (at a median of 4.9 months (0.9–32.0 months). Extranodal spread adversely associated with disease-free survival. 5-year DFS: 38% (95% CI 26–50), OS 47% (95% CI 33–60). Lymphoedema was reported in 32 (44.4%) of 72 patients.		
Lee et al. (2008)	Clinical outcomes of patients with MUP and known primary melanoma (MKP) with regional nodal	Prognostic study Cohort study	1,571 patients who underwent therapeutic regional lymphadenectomy	Overall survival Disease-free survival	significant factors on multivariate analysis: age, sex, nodal tumor burden, decade of	Retrospective design No control group (comparison of	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastases were compared to investigate the prognostic significance of MUP.		(262: MUP, 1,309: MKP)		diagnosis, status of primary. Greater risk was associated with age ≥ 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). 5-year and 10-year rates of OS for patients with MUP versus patients with MKP were 58% ± 7% versus 40% ± 7%, respectively, and 52% ± 7% versus 36% ± 7%, respectively. Median OS was also	lymph node dissection vs. no lymph node dissection not possible)	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					significantly longer in the MUP group than the MKP group (165 months vs. 34 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%	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
					(central tumors) estimated 5-year DFS for different categories of nodal status (N1, N2, N3): 31%, 15% and 10%, respectively. significant different estimated 5-year OS rate for different intervals of diagnosis until TLND.		
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	maximum follow-up: 386 months (32 years) rates of 15-, 20- and 25-year melanoma-specific survival: 36% ± 1%, 35% ± 1%, and 35% ± 1%, respectively. Median melanoma-	Retrospective design Long follow-up No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					specific OS: 28.1 months in the palpable and 90 months in the non-palpable group. When stratified by 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 surfvival	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)	Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- male sex (p=0.011) - CM site in head/neck region (p = 0.05) negative factors for DFS: - nodal 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%	Retrospective design Small patient cohort No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 postoperative radiotherapy. 34/64 patients died, median time to death=12 months (range 2-35 months).	For data on complications, see original article	
Fisher (2002)	To evaluate the effects on survival, disease-free interval, and recurrence patterns for patients undergoing elective, therapeutic, and	Cohort study	1444 melanoma patients: - 219 patients with ELND, histologically proven negative lymph nodes - 27 patients with ELND, histologically	Disease-free survival Overall survival	overall rate of nodal recurrence for all patients: 129/1045 patients 12%. significant improvement in survival for DLND	Retrospective design Study included here for data on delayed lymph node dissection (DLND); for further data on	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	delayed lymph node dissection for malignant melanoma of the head and neck.		proven positive lymph nodes - 106 patients with DLND for regional lymph node recurrence - 112 patients with TLND for clinically positive lymph nodes		when compared with patients undergoing ELNDQ or TLND (P=0.01). Five-year survival after DLND and TLND was 56% and 36%, respectively.	ELND and TLND see original article No control group for DLND (comparison of lymph node dissection vs. no lymph node dissection not possible)	
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	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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients undergoing neck dissection: 61 months.		
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 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. Estimated recurrence-free survival rates at 5, 10, 15, and 20 years: 33% (31-	Retrospective design Missing data led to exclusion of patients No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					35%), 28% (26-30%), 25% (23-27%), and 22% (18-26%) respectively, Both curves appeared to plateau at approximately 20%, no first recurrences after 21 years.		
Hughes et al. (2000)	to identify disease- and treatment-related factors that influence the outcome of patients undergoing therapeutic groin dissection for clinically detectable melanoma lymph node metastases	132 patients With clinically detectable LN-metastases 60 patients: superficial inguinal lymph node dissection (SLND) 72 patients: combined superficial inguinal and pelvic lymph node dissection (CLND)		Morbidity Overall survival Recurrence rate	no difference in postoperative morbidity or major lymphoedema between SLND and CLND overall 5-year-survival-rate: - 34% 5-year-survival-rate: -pelvic lymph node metastases (CLND): 19%	Retrospective study	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- 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) Systemic recurrence rate: 62% Median time to systemic recurrence: 9 months .		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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	Of 240 patients 122: wide excision and immediate node dissection 118: wide excision and dissection delayed until the time of appearance of clinically detectable node metastases.	Time to first recurrence Overall survival	36/118 patients (30.5%) developed regional node metastases 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 “Delayed” patients had a survival rate at 5 years of 51.3% (95% CI 41.7–60.1).	Study included here for the data on delayed node dissection (not immediate node dissection) 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 question of indication for therapeutic node dissection	3b
Jonk et al. (1998)	To identify prognostic factors determining overall survival in patients	Cohort study	70 surgically treated with curative intent for cervical lymph node metastasis	Overall survival	overall survivals after 5 and 10 years: 23% and 20%, respectively. Median	Retrospective design Small patient cohort	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	with surgically treated neck node metastases of cutaneous melanoma		- radical neck dissection: 64 patient - - modified radical neck dissection: 4 patients - postero-lateral neck dissection:2 patients.		survival: 22 months. Following a therapeutic neck dissection, 5-year survival rate: 22% following elective dissection, 5-year survival rate: 29% (difference not significant).	Patients predominantly male No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	
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 nodes: 73% and 67% respectively, rates for those with positive nodes: 39% and 29%, respectively. 10-year survival rate for patients with	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
					negative nodes was 63% and for those with positive nodes 33%. 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%. For patients with positive nodes only in the inguinal region: 5-year overall and disease-free survival rates were 43% and 35% respectively; for		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 melanoma following axillary or inguinal lymphadenectomy	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. Median survival of patients with: - single-site	Retrospective design Missing tumor characteristics for circa half of the patient population; also missing treatment information in some	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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-year survival rate of	patients No separate analysis for elective and therapeutic dissections Comparison between surgical and nonsurgical therapy, but groups not randomized	

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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			information was available		analysis:the 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	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- clinically negative nodes: 60%. 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. Considering all patients with elective and therapeutic node dissections: recurrence in 53 patients (40%), 74% of them within 2 years.	possible)	
Karakousis et al. (1986)						Patient cohort is a subset of Karakousis and	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Driscoll (1994); see above	
Finck et al. (1982)	To review the results of ilioinguinal dissection and to compare results for patients with inguinal and iliac node involvement with those with only inguinal involvement.	Cohort study	82 melanoma patients with inguinal lymph node metastases.	Disease-free interval Overall survival	Significant difference in disease-free interval for patients with inguinal and iliac node metastases and patients who had only inguinal involvement. ($p < 0.01$). Disease recurrence: - 20/24 (83.3%) patients with positive iliac nodes - 32/58 (55.2%) patients with negative iliac nodes. Median disease-free interval: - 5.8 months for patients with iliac metastases - 25.6 months for	Retrospective design Small patient cohort Missing information on primary tumour characteristics in many patient files No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients without iliac nodal involvement. 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	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	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					survival rates for delayed dissection: 48.7% for males 62.0% for females	of evidence concerning the question of indication for therapeutic node dissection 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	5-year OS survival for patients who originally presented in stage I, depending on treatment method: Surgery 27% Irradiation 23% Combined 67% 5-year overall survival for patients who originally presented in stage II, depending on treatment method: Surgery 27%	Retrospective design Insufficient control group of patients who did not receive treatment	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Irradiation 33% Combined 0/4 Stage III: 5-year survival for irradiation 33% Insufficient data 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	27 of 50 patients had clinically positive nodes on presentation. Of these 2 refused treatment (0% survivors) and 27/25 patients with clinical positive nodes received regional lymph node dissection: 20% survivors	Retrospective design Small patient cohort Very old patient cohort (1931 - 1956), questionable transferability to current situation Very small, probably biased control group (2 patients with clinically	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					14/23 patients with had clinically negative nodes; received regional lymph node dissection: 43% survivors	involved nodes who refused treatment)	
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-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 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% Complication-rate - during operation: 3% - postoperative: Approximately 60%	Very old patient cohort (1931 - 1956), questionable transferability to current situation No control group (comparison of lymph node dissection vs. no lymph node dissection not possible) For further prognostic data see original article	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Mortality rate within 30 days after operation: <0,5% Morbidity rate (relative to other than wound problems: 19,4%) Recurrence rate total for first year: 55,8%		

3.3.5. Literatur

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

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

3.4.1. 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.			

3.4.2. Auswahlkriterien

Auswahl der Literatur		
Gesamttreffer inkl. Dupletten		10252
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt, ab Erscheinungsjahr 1978 population ≥ 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

3.4.3. 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 melanoma.	Cohort study	1720 patients with metastatic pulmonary melanoma 318 patients underwent resection (with curative intent)	Survival 1-, 2- and 5-year-survival	OS (n=1720) - 1 year: 34% - 2-year: 14% - 5 years: 6%. median survival: 7.3 months. complete vs	Retrospective design complete follow-up on all patients large sample data collection	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					incomeplete pathologic resection: - median survival: 19 vs. 11 months - 5-year survival: 21 vs. 3% (P<0.0001). single vs. repeated metastasectomy: - median survival: 17 vs.15 months (P<0.9). Significant predictors of survival (multivariate model): - nodular histologic type (P=0.033) - disease-free interval (P<0.001) - number of pulmonary metastases	during a span of 35 years.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(P=0.012) - presence of extrathoracic metastasis (P<0.001) - performance of pulmonary metastasectomy (P<0.001). disease-free interval after surgery > 5 years: Survival: 19 months (vs 7 months, P<0.01) Patients without extrathoracic metastasis: 18 (vs 8 months, P<0.01).		
Leo et al (2000)	To evaluate the long-term results of lung metastasectomy for melanoma and to	Cohort study .	328 patients who underwent lung metastasectomy Surgical patients	Overall survival Mortality Prognostic factors	5-year-survival: 18% 10-year-survival: 14% median survival 17 months.	Retrospective design Old patient cohort	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	define a subset of patients with better prognosis.		underwent resection with curative intent only	of survival	R0-resection: 5- and 10-year survival: 22% and 16%(median survival 19 months) R1/R2-resection: 5-year-survival: 0% (median survival 11 months). Long- term survival according to the radicality of metastasectomy (16% vs 0% at 10 years, $P < 0.01$) independent unfavourable prognostic factors: - time to pulmonary metastases (TPM) <36 months - presence of multiple metastases	(1945-1995) /questionable transferability to current situation Bias: chemo-/radiotherapy	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Patients without these risk factors: 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					further surgery: 19%		
Harpole et al. (1992)	To analyse patients from a melanoma data base - overall risk of pulmonary metastastic disease? - pulmonary resection as a primary therapy for metastases? - multivariate risk factors for survival?	Cohort study	945 patients withpulmonary metases.	1-, 3- and 5-year survival-rates survival	1-, 3- and 5-year survival-rates: 30%, 9% and 4% Multivariate predictors of improved survival (p<0,001): -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) curative resection	Retrospective analysis No information about follow up	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					for a solitary nodule (n=84) vs. no operation (n=142): 2-year and 5-year survival: 42% versus 20% (p<0,001)		
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 pedicitive 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).	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	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					median survival of patients with metastasectomy vs. no surgical treatment: - 40 vs. 13 months Median time to recurrence: 5 months estimated 5-year survival of patients undergoing metastasectomy: 29%. Patient who were followed up 3 and/or 5 years: 3-year- survival: 50% 5-year- survival: 23%	Bias: systemic therapy	
Andrew et al.(2006)	To describe the experience with pulmonary	cohort study	86 patients 1-4 pulmonary metastases.	relapse-free survival	overall median time to relapse: 8.4 months	Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastasectomy		(10 patients with unknown primary site)	overall-survival 5-year-survival	median survival: 35 months. 5-year survival rate: 33% 48/86 patients died (median survival time = 24 months), 16% of patients were relapse-free at a median follow-up of 35 months. median survival of patients with a solitary vs. multiple lesions: 41 vs. 25 months (P = .05)	Short follow-up Patients received different postsurgical therapies	
Schuhan et al. (2011)	to determine the clinical course, outcome and prognostic factors in a subset of patients	Cohort study	30 patients with pulmonary metastases from malignant melanoma who	5-year survival rate Median survival prognostic	Cumulative 5-year survival rate after pulmonary resection: 35.1%, median survival:	Small patient cohort	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	recently treated by metastasectomy.		underwent pulmonary resection Complete pulmonary resection in 27 patients	parameter for OS	18.3 months. patients with complete pulmonary vs. patients with incomplete resection: median survival: 20.5 months vs. 13.0 months completeness of resection=no statistically prognostic factor for survival. Multivariate analysis: only significant prognostic parameter for overall survival: gender (9.4 months vs. 25.0 months for the female and male		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					group, respectively (P = 0.022).		
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	Overall-survival Disease-free survival 5-year survival rate	median survival: 15 months (range 2-144 months). 5-year-survival: 20% median disease-free-survival: 10,5 months. Statistical significance in survival (incomplete vs. radical surgery: p<0,0001)	Retrospective multicenter study No information about follow-up/recruitment period 10 patients received neo-adjuvant treatment	3b-
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), metastastic disease (n=32), lung cancer (n=1) Survival (benign vs. malignant disease):	retrospective study screening methods out of use, questionable transferability to current situation	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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%		
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,	Retrospective study Small population Population not described Old patient cohort (1957-1978) questionable transferability to	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					median survival: 12 months (3-35). 5-year survival: 0%	current data 10 patients received postoperative chemotherapy	
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 detected radiologically	Mortality Postoperative complications survival	Mortality rate after GI resection: 1.4% post-operative complications-rate: 2,5% 1-, 2- and 5-year survival rates: - for all patients: 57%, 39% and 27% - for patients having palliative resections: 34%, 19% and 0%. The median		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					survival: - after surgical resection: 16.4 mo. - after resection with curative intent: 22.6 mo. - following palliative resection: 7.7 mo. significant prognostic indicators of survival (on multivariate analysis): - presence of residual intraabdominal disease - presence of non-GI metastases at the time of surgery or after surgery were the		
Ollila et al. (1996)	To evaluate the role of surgery in the	Retrospective prognostic cohort	124 patients with metastatic	Operative morbidity and mortality	median DFI: 23.2 (range, 1-154)		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	survival of patients with melanoma metastatic to the gastrointestinal (GI) tract	study	melanoma in the stomach, small intestine, colon, or rectum	relief of symptoms median and 5-year survival	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 survival (multivariate analysis): - complete		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 metastastic melanoma of the abdomen	Cohort study	25 patients (5 patients had occult tumours)	Survival morbidity mortality	median survival after abdominal resection: 8.3 (range 0.4-41.1) months. 1-year survival: 36% 1-year-survival after surgery with curative vs. palliative intend: 89 vs 10%, P < 0.0001) Superior survival in patients with ≤2 metastases compared with ≥2 (P = 0.0001) Intent of surgery	Retrospective study Small population No information about follow-up	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(curative vs palliative) was the only factor significant on multivariate analysis (P = 0.001). Relief of preoperative symptoms: 87% Operative morbidity: 12% 30-day mortality: 4%.		
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	154 patients with adrenal metastasis 22 patients underwent surgical resection	surgical treatment survival	median OS:6.4 months (range 0,2-97 months). median OS for patients with: - synchronous metastatic disease: 6.6 months - isolated adrenal	Retrospective design Small population	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastasis: 18.7 months (p<0,0001) median OS for patients with a disease-free interval of: - <1 year: 7 months - >1 year: 11 months (*P=0,35*). After a median follow-up of 12.6 months, 9/22 (41%) Patients who underwent surgical resection were alive, incl. 7 without recurrence. Survival of patients who underwent surgery vs. those managed nonoperatively (p<0,0001).		
Pawlik et al. (2006)	To evaluated the	Cohort study	40 patients with	Survival	median time to	Retrospective	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	efficacy of hepatic resection in patients with metastatic ocular and cutaneous melanoma and to assesse factors that could affect survival after resection		metastatic melanoma involving the liver who were treated with hepatic resection with curative intent	5-year-survival Time to recurrence	recurrence: 8.3 months median survival: 28.2 months (range,4.6-93 .7 months) 5-year survival rate: 10.9%. 5-year survival rate for patients with a primary ocular melanoma: 20.5%. 5-year survival rate for patients with cutaneous melanoma (P=0.03). No clinicopathologic factors predictive of survival after hepatic resection	design Patients with ocular melanoma included Some patients had other metastatic sites (not only liver) which were not operated Bias: 17 patients (70.8%) received some form of systemic therapy	
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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					procedure: 1,9 months 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 asses 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. Intend of surgery: curative in 14	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	Small patient cohort No information about R1-Status	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			patients, palliative in 20 patients		significantly increased in patients without extra-abdominal metastases, with no evidence of non-large bowel metastases, if the DFI >24 months and when curative resection was performed. most important prognostic factors on multivariate analysis: apparently complete or palliative resection and the absence or presence of extraabdominal metastases		
de Wilt et al. (2003)	To analyse indications for surgery, complications, and	Cohort study	15 patients who underwent surgical treatment of metastases	Postoperative morbidity Overall survival	patients with splenectomy: median OS: 11 months	retrospective design Small patient number	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	overall survival with the aim of clarifying the indications for surgical treatment in such patients		98 patients were treated conservatively .	1-year-survival rate 2-year-survival rate	1-year survival rate: 35%, 2-year-survival-rate 21% patients with single splenic lesion and splenectomy: median OS: 23 months. 1-year survival rate: 70%, 2-year-survival-rate: 50% conservatively treated patients: median OS: 4 months. 1-year survival rate: 13%, 2-year-survival-rate 3% survival of patients with splenic metastases treated surgically vs. conservatively: P=0.02	Medical/conservative treatment not described in detail, 4 patients who underwent splenectomy were included in clinical trials. No information about follow-up	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Survival after splenectomy with palliative vs. curative intent: P=0,07		
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 times for the unexplored and unresected groups: 4.1 months significantly increased survival: - 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-		3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					group (P<0.0001).		
Khadra et al. (1990)	To examine if a surgical approach of metatases in the GIT is justified.	Cohort study	56 patients with symptomatic melanoma of the gastrointestinal tract (GIT) treated surgically (13 occult primary)	complication rate postoperative survival overall survival time to recurrence	relief of symptoms in 44 patients post postoperatively. postoperative complications: 8/56 patients (2 died) mean postoperative OS after 1st vs. 2nd metastases: 11.7 (range 1-60) vs. 3,6 months (range 0-12 months) median time of recurrence: 12 months (range 3-47 months) mean OS for ulcerated vs. non-ulcerated tumor: 46,6 vs. 84,9 months.	Retrospective design Methods of follow-up not described No information about metastases other than in GIT-tract Bias: Adjuvant therapy (chemotherapy in 26 patients, radiotherapy in 1 patients, immunotherapy in 4 patients)	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					mean OS when primary tumor <1,5 mm vs. >1,5 mm: 11,7 vs. 9,5 months.		
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% and 30%, respectively. Survival was influenced by - the number of metastases (P = 0.05) and the treatment received (P = 0.03). After metastasectomy: DFI and OS: 14 and 21 months, respectively. 1- and	Small patient cohort	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					3-year survival: 60% and 40%, respectively. Significant longer survival for patients with single site vs. >1 site of metastasis (P = 0.005)		
Branum et al. (1991)	To evaluate the role of resection in the management of melanoma metastatic to the adrenal gland	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: 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		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 metastases).	Median survival 5-year-survival	median survival of the study population: 7 months. Patients who underwent metastasectomy (33.6%) vs. patients without metastasectomy: median OS: 12 months vs 5 months 5-yeas OS: 16% vs. 7% (P < 0.001). In patients with M1a disease (n = 1,994): median survival of 14 months vs. 6	Those who had metastasectomy performed were compared with patients that did not.	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months, 5-year OS: 20% vs. 9% (P < 0.001). 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).		
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:	retrospective study No information about adjuvant therapies	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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) predictive factors on multivariate analyses: - earlier primary tumor stage (I vs II) (P<0.001) - absence of intervening stage III metastases		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(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	3258 melanoma patients 442 melanoma patients with distant metastases	Overall survival Prognostic factors	median survival time: 7 months 2-year, 5-year, and 10-year survival rates: 11.9%, 6.7%, and 4.7%, respectively. Of the modalities of therapy given, only surgery was associated with prolonged survival (P< 0.0001) Factors significantly related to short term survival:		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- 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	survival 1-, 3- and 5-year-survival rate Mortality morbidity	postoperative mortality: 0 overall morbidity: 15%. minimal and maximal survival: 1.5 and 142.5 months, respectively. mean OS: 56.7 months (1 year:	retrospective design bias: 90.5% underwent adjuvant therapies	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					72.1%, 3 years: 46.5%, 5 years: 23.16%). survival of reiterative surgery vs. single surgery:62.7 vs 42.4 months, median 50.9 vs 16.0, p=0.03. Reiterative surgery was shown as an independent prognostic factor (p<0.05).		
Ollila et al. (1999)	To examine whether a 2nd metastasectomy could prolong the survival of patients with recurrent stage IV melanoma.	Retrospective cohort study	131 patients who developed recurrent stage IV diseas	DFI to recurrence Survival 5-year-survival	Median DFI: 8 (range 0.6-91.8) months. Median survival: 18.2 months after complete metastasectomy vs. 12.5 months or 5.9 months after	Possibly overlapping population/ Ollila et al. 1996 2 gynecologic tumor sites included	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					palliative surgical procedure or nonsurgical management, respectively. 5-year survival: 20.0% after complete surgical metastasectomy vs. 7.0% and 2.1% after palliative surgical and nonsurgical intervention, respectively. prognostic factors for survival: - prolonged DFI (P=0,0001) - complete surgical metastasectomy (P=0,0001)		
Gohl et al. (1996)	To examine the value of surgical treatment of distant metastases of	Cohort study	In 174 cases surgery was perfomed, in 70 patients with	Survival	Median survival - after R0 (curative surgery): 13 months - R1/R2: 6 months.	Retrospective design No information	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	malignant melanoma		curative intent. 15 patients with occult melanoma.		- Patients without treatment: 3 months statistically significant difference in 1-year-survival for patients who underwent curative surgery vs.palliative surgery. 5-year-survival and 10-year-survival after curative surgery: 24% and 7% respectively	about adjuvant therapy Staging of patients not described	
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	Survival Estimated 5-year-survival 5-year-survival rate	Median survival after metastasectomy: 19 months estimated 5-year survival rate: 22%. 5-year survival rate	Retrospective design bilateral nodal metastasis or spread from one groin to the contralateral groin was considered	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					for those with: -distant subcutaneous metastases: 33% - distant LN metastases: 22% - pulmonary metastases: 74% (P=0.72). 5-year survival rate for : - combined group of s.c. and nodal metastases: 28% - pulmonary and visceral sites: 17% Significant prognostic parameters: - thickness of the primary melanoma (p=0.05) - number of metastatic lesions (p=0.03)	likely to be regional spread and these patients were excluded 93% underwent chemotherapy, 27% radiotherapy, 5% no further therapy	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- prior disease-free interval (p=0.05) .		
Overett et al. (1985)	To review clinicopathologic factors that determine the successful resection of tumor, survival, and quality of life	Cohort study	176 patients who underwent surgical intervention for distant metastases of	Survival 2- and 5-year-survival-rate Mortality Relapse rate	estimated 2- and 5-year survival rate: 2 1 % 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	Retrospective design Old patient cohort (1965-1979), questionable transferability to current situation	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					relapse in case of incomplete vs. complete resection: 3 vs. 9 months (P = 0.07). 5-years survival after repeated resection: 20% median survival in case of repeated resection vs. incomplete resection of new disease: 26 vs. 8 months (P<0.0005)		
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	263 patients having stage IV melanoma 111 patients: surgery and/or radiation therapy. (17 surgery alone) 89 patients: systemic treatment	Survival	22 patients treated with multimodality survived > 24 months (median Survival: 33 months) 16: both systemic treatment and surgery and/or	Confounder adjuvant therapy	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			48 patients: both systemic and local therapy. 111 patients: no treatment.		radiation, 3: systemic drug therapy, 3:only local treatment. 12/22 patients became tumour free after initial surgery or radiation. 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	significant survival difference between Stage IV survivors (36 months) and those who manifested disease progression (12 months) ($P < 0.02$). Characteristic of those patients who remain disease free: - initial presence	Retrospective design Small population No information about staging Poor information about follow-up	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					</=3 metastatic lesions - long prior disease-free interval		
Wornom et al. (1983)	To examine the efficacy of surgery as palliative treatment in 65 patients with distant metastatic melanoma amenable to surgical excision	Cohort study	65 patients with distant metastatic melanoma amenable to surgical	Survival mortality	overall operative mortality: 11% Relief of symptoms after excision of: - 77% of brain metastases, - 100% of lung metastases - 88% of distant LN and s.c. metastases - 100% of abdominal metastases Median survival after excision of: - brain metastases: 8 months - lung metastases: 9 months - abdominal	Retrospective design Most patients received chemotherapy No information about staging No detailed information about population	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastases 8 months - distant s.c., LN metastases: 15 months. median survival of patients with - combined visceral and resected superficial metastases: 14 months, 5-year survival: 0% - resection of superficial metastases and no detectable evidence of visceral metastasis: 17 months. 5-year survival: 14% 2-year survival: 29% for both groups.		
Feun et al. (1982)	To discuss the natural history of	Cohort study	102 patients with malignant	survival	median survival: 18 months.	Retrospective design	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	Stage IVA melanoma and the role of adjuvant therapy		melanoma who had distant metastases surgically resected and were judged to be clinically free of disease	disease-free-survival	survival depending on site of resected metastases: - brain: 15 months - lung: 16 months - intraabdominal 18 months - skin and/or LN 23 months Disease-free interval not influenced by site Similar survival of patients who had metastases resected from several organs at the same time and patients with one resected site group treated with surgery only vs. adjuvant group: median disease-	35 patients who had surgery vs. 67 patients who received adjuvant therapy	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					free interval and survival: 6 and 16 months vs. 6 and 21 months, respectively		

3.4.4. Literatur

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4. AG Adjuvante Therapie

4.1. Frage IV.1. Adjuvante Chemotherapie - Adaptation

4.1.1. 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 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 adjuvanten 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 dacarbacine[tiab] AND adjuvant[tiab])

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

Literatur:

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4.1.2. Empfehlung und Hintergrundstext französische Quell Leitlinie

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

Originaltext (Evidenztabellen und Text siehe Quell LL ab S.39)	Übersetzung
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]. 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 (odd 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]. 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 'efficacité du méthyl-CCNU sur une population de 136 patients, ce qui limite la portée des conclusions qui pourront être établies concernant cette molécule.	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 1997mit Metaanalyse überarbeitet [12]. 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]. Methodologische und Klinische Kommentare Dacarbazin ist die am meisten untersuchte Substanz, allein oder zusammen mit BCG. Nur eine randomisierte Sudie überprüfte die Wirksamkeit von Methyl-CCNU an einer Population von 136 Patienten, dies beschränkt die Aussagekraft dieser Substanz.

Originaltext (Evidenztabellen und Text siehe Quell LL ab S.39)	Übersetzung
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 dispo-nibles sont insuffisantes pour conclure sur le bénéfice/risque du methyl- CCNU en situation adjuvante chez les patients porteurs d'un mélanome cutané. Standards, Options et Recommandations Les traitements adjuvants systémiques à base de levamisole, BCG ou dacarbazine ne sont pas recommandés en dehors d'essais thérapeutiques.	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. Standard, Optionen und Empfehlungen Eine adjuvante systemische Therapie mit Levamisole, BCG oder Dacarbazin wird ausserhalb von Therapiestudien nicht empfohlen.

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_practiceGuidelinesandEvidencesum maries.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

4.1.3. Empfehlung und Hintergrundstext 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 (dacarbazine 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

4.2. Frage IV.2. Adjuvante Vakzinierung – Adaptation

4.2.1. 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 sans récidive 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	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
			Unterschied zwischen rezidivfreiem Überleben oder Gesamtüberleben zeigen können (Td >1,5 N0 und N+) Niveau BI Entspricht in etwa Level of Evidence nach Oxford 1b	
Schlüsselempfehlung	Zur Vakzinierung keine Schlüsselempfehlung	Zur Vakzinierung keine Schlüsselempfehlung	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 Vakzinierungstherapien sind als adjuvante Behandlung bei Patienten nach Operation eines kutanen Melanoms ausserhalb von	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
			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

4.2.2. Empfehlung und Hintergrundstext französische Quell Leitlinie

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

Originaltext (Evidenztabellen und Text siehe Quell LL ab S.36)	Übersetzung
VACCINATION *BCG thérapie* • Description des études Deux essais randomisés ont été retenus et ont compare l'administration de BCG *versus* observation d'une part, et BCG *versus* l'association BCG et dacarbazine *(Tableau XV)* [114, 115]. L'étude de L'OMS a concerné 761 patients randomisés en 4 bras (observation *versus* BCG seul *versus* dacarbazine seule *versus* association BCG et dacarbazine) [114] L'étude de Agarwala *et al.* 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 *versus* observation et la seconde BCG et dacarbazine *versus* BCG seul. • Survie globale	Vakzinierung *BCG Therapie* •Beschreibung der Studien Zwei randomisierte Studien wurden ausgewählt und haben die Gabe von BCG versus Beobachtung einerseits und BCG versus gemeinsame Gabe von BCG und Dacarbazin verglichen (Tab. XV) [114, 115]. Die Studie der WHO betraf 761 randomisierte Patienten in 4 Armen (Beobachtung versus BCG allein versus DTIC allein versus BCG plus DTIC) [114]. Die Studie von Agarwala et al. 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 versus Beobachtung, die zweite BCG plus DTIC versus BCG allein.

Originaltext (Evidenztabellen und Text siehe Quell LL ab S.36)	Übersetzung
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 observe une différence 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 récidive 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 difference 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 :	•Gesamtüberleben Keine der zwei Studien hat einen signifikanten Unterschied in Bezug auf das Gesamtüberleben in den Vergleichsarmen gezeigt[114, 115]. In einer 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. präsentiere detaillierte Ergebnisse. Keine letale Toxizität wurde berichtet. Regionale Adenopathien und Systemreaktionen wurden korellierten 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

Originaltext (Evidenztabellen und Text siehe Quell LL ab S.36)	Übersetzung
– 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 : – 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]	•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 den vier randomisierten Studien waren: Zelllysat 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]
• 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 difference 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].	•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

Originaltext (Evidenztabellen und Text siehe Quell LL ab S.36)	Übersetzung
• Survie sans récidive 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 difference 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 récidive [119]. La survie sans récidive 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 % 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 toxicities 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	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 zwischem 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 Beobachtungsarm; p = 0,0002). Mit den Antigenen HLA A2 und C3 war das rezidivfreie Überleben 77% in der Impfstoff Gruppe veruss 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

Originaltext (Evidenztabellen und Text siehe Quell LL ab S.36)	Übersetzung
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 condidéré [120–121]. *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	Ulzerationen am Injektionsortbei 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 Vergleicht 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]. *IFN*α versus *GMK* •Beschreibung der Studien Eine einzige randomisierte Studie ist verfügbar [123]. Diese Studie hat Hochdosis IFNα2b versus GMK Vakzin (Ganglioside GM2 konjugiert mit KLH kombiniert mit einem adjuvanten Molekül QS-21) verglichen. Diese

Originaltext (Evidenztabellen und Text siehe Quell LL ab S.36)	Übersetzung
molécule adjuvante QS-21). Cette étude a porté sur des patients atteints d'un mélanome de stades IIB ou III réséqués. • 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 IFNα2b *versus* 73 % dans le bras GMK (p = 0,035) [123]. • Survie sans récidive La survie sans récidive a été évaluée après un suivi median 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 récidive 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 symptoms neurologiques. Quarante-cinq pour cent des patients traits 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	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 IFNα2b 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

Originaltext (Evidenztabellen und Text siehe Quell LL ab S.36)	Übersetzung
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.	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% 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) • Description des études Une étude est disponible [124, 125] *(Tableau XIX)*. Il s'agitd'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 récidive Aucune différence significative en termes de survie globale et de survie sans récidive 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	*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 rezifivfreies Überleben gesehen. •Toxizität

Originaltext (Evidenztabellen und Text siehe Quell LL ab S.36)	Übersetzung
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 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 *a posteriori* (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. *Conclusions de la littérature* Aucun des procédés de vaccination utilisés jusqu'à ce jour n'a mis en évidence une différence significative sur la survie sans récidive ou sur la survie globale des patients attaints d'un mélanome cutané réséqué avec ou sans envahissement ganglionnaire et dont l'épaisseur est supérieure à 1,5 mm (niveau de preuve B1).	Insgesamt wurde die Behandlung mit TIL sehr gut toleriert. Keine Grad 3 oder 4 Toxizitäten wurden beobachtet. Die hauptsächlichen 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 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. 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). *Entspricht in etwa Level of Evidence nach Oxford 1b*

4.2.3. Empfehlung und Hintergrundstext kanadische Quell Leitlinie

Quellleitlinie: 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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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, Suciu 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.

4.3. Frage IV.3. Adjuvante Extremitätenperfusion – Adaptation

4.3.1. 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 *Eine adjuvante Extremitätenperfusion mit Melphalan scheint das Gesamtüberleben von Melanompatienten nicht zu verbessern.* *Niveau C*	–
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	–

	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
			Eine Extremitätenperfusion wird ausserhalb klinischer Studien nicht empfohlen und soll durch erfahrene Teams durchgeführt werden.	
Zugrunde liegende Evidenz	1 Studie Koops, H.S. et al. 1998	–	2 Studien Koops, H.S. et al. 1998 Ghussen, F. et al. 1989	–

4.3.2. Empfehlung und Hintergrundstext 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
Perfusion de melphalan sur membre isolé 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	Isolierte Extermitätenperfusion mit Melphalan •Beschreibung der Studien Zwei randomisierte Studien haben den Effekt einer isolierten Extremitätenperfusion mit Melphalan nach Exizision 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.

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.40)	Übersetzung
hyperthermie. 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 récidive 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 sousgroupes. 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. 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 récidive en faveur des patients qui ont reçu une	•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 Lymphknotendissektion (RR = 0,75 [IC95 : 0,55-0,98]) *[Kommentar: in der Originalarbeit bezieht sich das verlängerte rezidivfreie Überleben auf Patienten OHNE Lymphknotendissektion: "…The difference was significant for patients who did not undergo elective lymph node dissection (ELND)."]* und besonders bei Patienten mit einem Tumordicke unter 3mm (RR = 0,56 [IC95 : 0,36-0,88]). Die Subruppenanalysen 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 Schmerzen und Infektionen in der Extremität, häufig am Ort der Infusion. Die meisten Komplikationen waren jedoch reversibel. •Klinische und Methodische Kommentare Die Studie von Ghussen et al. wurde vorzeitig beendet, da eine Zwischenanalyse einen Benefit in Bezug auf das rezidivfreie Überleben

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.40)	Übersetzung
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.). CONCLUSIONS DE LA LITTÉRATURE La perfusion de melphalan sur membre isolé ne semble pas améliorer la survie globale des patients atteints d'un melanoma cutané (niveau de preuve C).	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, Suciu 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

4.4. Frage IV.4. Adjuvante Immunstimulation – Adaptation

4.4.1. 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?	–	–	Le levamisole en situation adjuvante n'améliore pas la survie des patients porteurs d'un mélanome cutané opéré (niveau de preuve A). *Eine adjuvante Therapie mit Levamisole verbessert nicht das Überleben von Melanompatienten. (Niveau de preuve A)*	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 (BCG wurde nicht in die Literatursuche eingschlossen)
Schlüsselempfehlung	–	–	Les traitements adjuvants systémiques à base de levamisole, BCG ou dacarbazine ne sont pas recommandés en dehors d'essais thérapeutiques.	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
			Adjuvante systemische Therapien mit Levamisol, BCG oder Dacarbazine werden ausserhalb von klinischen Studien nicht empfohlen.	
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

4.4.2. Empfehlung und Hintergrundstext französische Quell Leitlinie

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

Originaltext (Evidenztabelle siehe Quell LL ab S.38)	Übersetzung
LEVAMISOLE •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]. •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]. •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	LEVAMISOLE •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]. •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]. •Klinische und Methodische Kommentare Die in den vier Studien verabreichten Dosierungen von Levamisole waren

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 récidive). •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).	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) •Schlussfolgerung aus der Literatur Eine adjuvante Therapie mit Levamisole verbessert nicht das Überleben von Melanompatienten. (Niveau de preuve A)

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.
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.
126. Loutfi A, Shakr 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
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

4.4.3. Empfehlung und Hintergrundstext kanadische Quell Leitlinie

Quellleitlinie: 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, Shakr 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

34. 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

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

4.5. 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?

4.5.1. 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		

4.5.2. 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)

4.5.3. 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 Tumorentitiäten	
Anzahl ausgewählter Studien (8 Reviews, 16 RCTs, *davon 2 nur als Abstract vorliegend*)		**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

4.5.4. 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§	0.813	HR = 1.19§	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§	0.995	HR = 1.28§	0.054	1b
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

4.5.5. 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=(events/group A)/(events 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§ **benefit, HR n.r.**	0.18 **0.0237**	**Upd.: HR = 1.38§ 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§	0.995	HR = 1.28§	0.054
Kirkwood, E1690, 2000	74%	HR = 1.04§	0.813	HR = 1.19§	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**						
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**						

§ HR relates to proportion alive and proportion relapsfree

4.5.6. Evidenztabellen – Langfassung

4.5.6.1. 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 evidence published between July 2005 and June 2010 that informed the development of revised recommendations for adjuvant interferon therapy by the Melanoma DSG.	Systematic review (Update) adjuvant treatment for stage AJCC stage IIB, IIC and III.	7 new RCTs: EORTC 18991 Sunbelt Trial Pectasides et al. 2009 EORTC 18952 Stadler et al. 2006 DeCOG 2008 DeCOG 2010 Metaanalyses: Mocellin et al. Wheatley et al.	OS DFS	HDI vs. Obs: no sign. benefit Hazard Ratio: 0.93 [0.78,1.12] HDI vs. Obs: sign. Benefit Hazard Ratio: 0.77 [0.65, 0.92] P = 0.004; 9% absolute risk reduction at 5 years	most LDI studies not included Conflict of Interest: The first author received consulting fees or honoraria greater than $5000 from Schering-Plough in the past 2 years.	1a-
Eggermont et al. 2011	To present a meta-analysis of the two largest adjuvant IFN/PEG-IFN randomised trials in a combined total of	Metaanalysis of 2 studies	EORTC 18991 EORTC 18952 2644 patients with high-risk melanoma stage IIb/III	OS RFS	IDI+peg IFN vs. Obs: no sign. benefit Hazard Ratio: 0.94 [0.80, 1.11]	Conflict of Interest: Alexander M.M. Eggermont: Consultant in advisory boards for melanoma for	1a-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	2644 patients with high-risk melanoma (stage IIb/III)			DMFS	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	Merck, BMS, Roche, GSK. Poulam Patel: Ad hoc advisory boards for Schering-Plough Research Institute - honoraria paid.	
Garbe et al. 2011	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	Systematic review adjuvant and palliative treatments	Interferon alpha: 11 RCTs NCCTG ECOG 1684 ECOG 1690 EORTC 18952 SMG WHO DeCOG FCGM UKCCCR AMCG EORTC 18991	Metaanalysis Overall survival (OS) Disease free survival (DFS)	12 RCTs Significant 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	Number needed to treat not reported 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	1a- (SR with heterogeneity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						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 Schering, Bristol-Myers Squibb, Essex Pharma/Schering-Plough; Honoraria: GlaxoSmithKline, Merck, Onyx Pharmaceuticals, Pfizer, Roche Pharma, Synta Pharmaceuticals Corp.; John M. Kirkwood:	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						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 ECOG 1690 SMG WHO ECOG 1694 E2696 UKCCCR EORTC 18871 EORTC 18952 DeCOG EORTC 18991	OS DFS	Significant improvement HR for death = 0.89, 95% CI = 0.83-0.96; P=.002 Number needed to treat 29 patients Significant improvement HR for disease recurrence = 0.82, 95% CI = 0.77-0.87; p<.001	absolute risk reduction not reported Reported hazard ratio were used for meta-analysis updated data of E1684 (Kirkwood 2004) not included Data of E1694 and E2696 (control vaccination arm with potentially worse outcome) were included	1a- (SR with heterogeneity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						OS benefit was observed only when trials that used low or intermediate IFN-a 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, E1694	OS	Metaanalysis E1684, E1690, E1694: significant Improvement RR (2 years) 0.85, 95% CI = 0.73-0.99; P=.03 not significant after exclusion of E1694: HR 0.87, 95% CI = 0.71-1.07; P=.18	Number needed to treat not reported No quality assessment of studies only 3 RCTs were included into metaanalysis other RCTs and published metaanalyses were reported narratively	1a- (SR with heterogeneity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						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 regard to the schedules, the classification used and the median time of follow-up Funding/Conflict of	1a- (SR with heterogeneity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						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 alpha therapy in malignant melanoma	Systematic review	9 RCTs, 8 RCTs included, 3 178 patients AMCG FCGM ECOG 1684	OS	analysis on available data for 2 771 patients from 6 trials no study with benefit	High quality SR Number needed to treat reported for each individual trial no metaanalysis due	1a- (SR with heterogeneity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			ECOG 1690 NCCTG SMG UKCCCR WHO	RFS	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	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	

4.5.6.2. 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) a2a 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 alfa-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:	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: The study was supported by a grant from Roche Products	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					0.75-1.10; p=0.3; events: 211/338 vs 215/336	Ltd	
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	LDI vs. OBS no benefit HR n.r., p=0.72 events: 146/225 vs 138/219	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: not	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				RFS	no benefit HR n.r., p=0.5; events: 162/225 vs 158/219	mentioned	
Cameron et al. 2001 SMG	To test the possible disease-free and overall survival advantage of a short, 6-month course of low-dose IFN for patients with high-risk, surgically resected, malignant melanoma.	RCT Treatment groups OBS LDI	95 patients with at least 3mm Breslow thickness or lymph node involvement n=49 n=46	OS RFS	LDI vs. OBS no benefit 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	Jadad Score 2 of 5 not placebo controlled, not blinded, randomization scheme not described Funding: not mentioned, IFN supplied by Schering-Plough	1b
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	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:	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: not reported assistance of Schering-Plough Research Institute	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					0.93-1.53; p=0.171; events: 122/215 vs 127/212	and Schering-Plough Oncology Biotech with posttrial data collection	
Grob et al. 1998 FCGM	To assess the efficacy of adjuvant low dose interferon alpha	RCT Treatment groups OBS LDI	489 patients, tumor thickness > 1.5mm without clinically detectable node metastases n=245 n=244	OS RFS	LDI vs. OBS no benefit HR n.r., p=0.059 events: 59/244 vs 76/245 significant benefit HR n.r., p=0.035 events: 100/244 vs 119/245	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: grant from Hoffman-La Roche Ltd, also provided the interferon □-2a (Roferon-A).	1b
Pehamberger et al. 1998 AMCG	To investigate whether adjuvant IFNalpha2a 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	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Roche, Vienna, Austria.	
Rusciani et al. 1997	*to study the use of recombinant interferon-alpha (IFN-alpha) as adjuvant therapy for patients with Stage I and Stage II melanoma*	*RCT* *Treatment groups* *Obs* *LDI*	*84+ 70 patients, stages I+II,* *n=70* *n=84*	*DFS*	*Significant benefit events LDI vs. OBS 11/84 vs 21/70*	*Jadad Score 0 of 5 matched controlls, no randomisation, not placebo controlled, not blinded, no description of dropouts* *Study excluded*	*2b* *low quality RCT* *study excluded*
Kokoschka et al. 1990	*To evaluate the efficacy of rIFN alpha 2b therapy in high-risk melanoma patients stage I and stage II*	*Cohort Study* *Treatment groups* *OBS* *LDI*	*135 patients, stages I+II* *n=82* *n=53*	*OS* *DFS*	*no significant benefit*	*Cohort Study* *Only included in SR by Pirad et al.*	*2b* *study excluded*

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

4.5.6.3. 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) 24 months alone	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 no benefit	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: Schering-Plough; the Radiumhemmet Research Funds, Stockholm; and the Stockholm County Council	1b
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	1388 patients n=553 n=556	OS 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	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: not mentioned	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		OBS	n=279		vs 146/279 no benefit DFS 13 months HR 0.97; 95% CI: 0.78-1.20; p=0.72; 25 months HR 0.83; 95% CI: 0.67-1.03; p=0.05; events: 679/1109 vs 183/279	The authors declared that they have no conflict of interest.	

4.5.6.4. Evidenztabelle - Hochdosis IFN alpha

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Kirkwood et al. 2004/1996 Update E 1684 Initial Data E1684	To update the analyses To evaluate Interferon alfa-2b as an adjuvant therapy	RCT Treatment groups OBS HDI	287patients, stages IIb and III n=137 n=143	OS RFS	HDI vs. OBS Update: no benefit HR 1.22; 95% CI: n.r.; p=0.18; 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.,	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: grants from the National Institutes of Health, Bethesda, MD. Update: Grant CA-23318, awarded by the National Cancer	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					p=0.0023 events HDI vs. OBS 90/143 vs 103/137	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
					122/215 vs 127/212
						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-Plough Oncology Biotech with posttrial data collection
							1b

Creagan et al. 1995	To report a prospective	RCT	262 patients, stages I and II		HDI vs OBS no benefit	Jadad Score 2 of 5 not placebo	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
NCCTG	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	Treatment groups OBS HDI	 n=131 n=131	OS RFS	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	controlled, not blinded, randomization scheme not described Funding: supported in part by Public Health	
Agarwala et al. 2011 *E1697*	*To assess the benefit of 4 weeks of HDI compared with Observation in relation to the RFS and OS of patients with resectable intermediate and high-risk melanoma*	*RCT* *Treatment groups* *OBS* *HDI 4 weeks*	*1150 patients* *T2N0, T3N0, T4N0, T1-4N1a-2a* *n=596* *n=581*	 *5-year survival rate* *RFS*	*no benefit* *IFN vs OBS* *0.82 vs 0.85* *6.8 vs 7.3 years*	*only ASCO abstract available*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
McMasters et al. 2008 *Sunbelt Trial*	*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*	*RCT* *Treatment groups* *Observation* *HDI*	*218 patients, after SLN biopsy, 1 positive node* *n=106* *n=112*	*OS* *RFS*	*no benefit* *HR 1.07; CI: 0.65-1.78; p=0.79* *no benefit* *HR 0.82; 95% CI: 0.47-1.40; p=0.46*	*only ASCO abstract available*	
Kirkwood et al. 2001 *E 1694*	*To evaluate the efficacy of HDI for 1 year versus vaccination with GM2*	*RCT* *Treatment groups* *HDI* *vacination*	*874 patients, stages IIB/III* *n=385* *n=389*	*OS* *RFS*	*significant benefit* *events IFN vs. Vacc.* *52/385 vs 81/389* *significant benefit* *events IFN vs. Vacc.* *98/385 vs 151/389*	*Included in SR although no OBS Arm* *Funding: Eastern Cooperative Oncology Group grant no. NIH CA 39229-16 and R03 grant no. CA75950-02.*	
Kirkwood et al. 2001 *E2696*	*To evaluate the toxicity and other effects of the established adjuvant high-dose*	*RCT* *Treatment groups* *Vacc+HDI day 1* *Vacc+HDI day 28*	*107 patients, stages IIB, III, and IV* *n=36* *n=36*	*RFS* *no OS analysis due*	*significant benefit* *events IFN+Vacc vs. Vacc.* *28/72 vs 19/35*	*Included in SR although no OBS Arm* *Funding:*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	IFNalpha2b regimen in relation to immune responses to GMK	*Vacc*	*n=35*	*to short follow up*		*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.*	

4.5.6.5. Evidenztabelle - Pegyliertes IFN alpha

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

4.5.7. 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

Study	Subgroup / No. of patients	OS, HR	p	PFS, HR	p	LoE
	Ulzeration, n=238	1.05, Favour Obs, n.s.	0.809	1.04, Favour Obs, n.s.	0.829	3b
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
(High Dose)	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)						

Study	Subgroup / No. of patients	OS, HR	p	PFS, HR	p	LoE
Kirkwood et al. 2000	T4 N0 M0			1.46	0.20	3b
(Benefit of High Dose)	T1-4 N1 M0			1.16	0.74	3b
	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>=4			1.15	0.58	3b
Creagan et al. 1995	Stage I			n.s.	0.93	3b
(High Dose)	Stage II			Favour IFN, n.s.	0.09	3b

4.5.8. 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 **Nordic IFN trial**	OBS (n=284) IDI 12 months (n=285) IDI 24 months (n=286)	n=0	 n=72 (25%) n=72 (25%)	n.r.	n=106 (37%) / n=5 (2%) n=267 (94%) / n=28 (10%) n=266 (93%) / n=32 (11%)	n=108 (38%) / n=1 (<1%) n=210 (74%) / n=17 (6%) n=214 (75%)	n.r.	n=41 (14%) / n=2 (1%)* 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) Peylated IFN alfa-2b (n=627, Tox. assessed n=608)	n.r.	 n=191 (31%)	n=74 (12%) n=278 (46%)	n=252 (41%) / n=7 (1%) n=574 (94%) / n=97 (16%)	n=153 (25%) / n=3 (<1%) n=360 (59%) / n=39 (6%)	n.r.	n=221 (36%) / n=10 (2%)* 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) Intermediate IFN, 25 months (n=556, tox. assessed n=	n=0	n=87 (16%) (N=539) n=108 (20%) (N=539)	n.r.	n.r. / 78 (15%) n.r. / n=67 (13%)	n.r. / n=62 (12%) n.r. / n=56 (11%)	n.r.	n.r. / n=16 (3%) 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. (%)
	532) 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	OBS (n=219)	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. (%)
WHO	LDI (n=225)							
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.	OBS (n=137)	n=2 (lethal	26%	67%	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. (%)
1996 **E 1684**	HDI (n=143)	hepatic toxicity)			n=140 (100%) / n=69 (48%)* *constitutional symptoms including fatigue	n=118 (83%) / n=40 (28%)* *neurologic		n=89 (62%) / n=20 (14%)
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.

4.5.9. 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

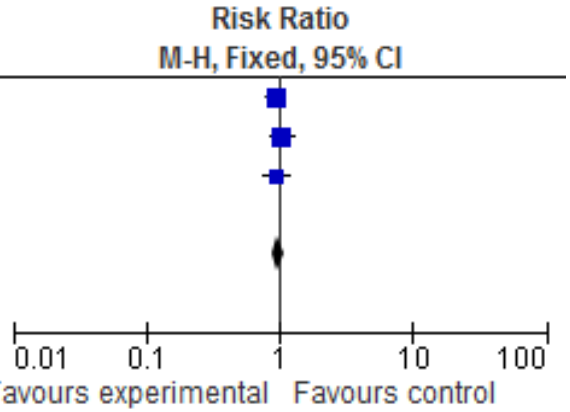
Limitation: unterschiedliche Follow up Perioden innerhalb der Studien
Auswertung durch Review Manager 5.1, The Cochrane Collaboration

Abbildung 1: Hochdosis Interferon alpha versus Beobachtung

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

Study or Subgroup	IFN Events	IFN Total	OBS Events	OBS Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
E1684 Upd, Kirkwood	93	146	95	140	36.9%	0.94 [0.79, 1.11]	2004
E1690 HDI, Kirkwood	98	215	93	212	35.7%	1.04 [0.84, 1.28]	2000
NCCTG, Creagan	68	131	72	131	27.4%	0.94 [0.75, 1.18]	1995
Total (95% CI)		**492**		**483**	**100.0%**	**0.98 [0.87, 1.10]**	
Total events	259		260				

Heterogeneity: Chi² = 0.63, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)



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

Study or Subgroup	IFN Events	IFN Total	OBS Events	OBS Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
E1684 Upd, Kirkwood	95	146	106	140	33.7%	0.86 [0.74, 1.00]	2004
E1690 HDI, Kirkwood	114	215	127	212	39.8%	0.89 [0.75, 1.05]	2000
NCCTG, Creagan	77	131	85	131	26.5%	0.91 [0.75, 1.10]	1995
Total (95% CI)		**492**		**483**	**100.0%**	**0.88 [0.80, 0.97]**	
Total events	286		318				

Heterogeneity: Chi² = 0.19, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 2.51 (P = 0.01)

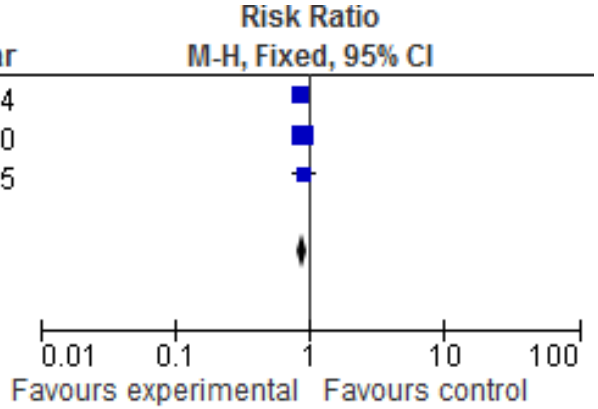
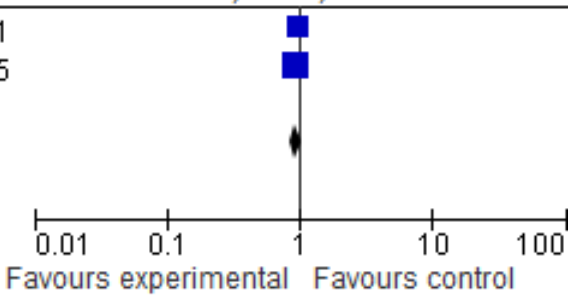


Abbildung 2: Mittlere Dosis Interferon alpha versus Beobachtung

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

	IFN		OBS			Risk Ratio		Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**	**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: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.18)



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

	IFN		OBS			Risk Ratio		Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**	**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: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)

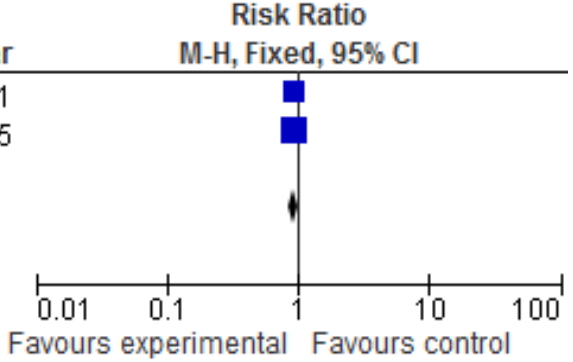


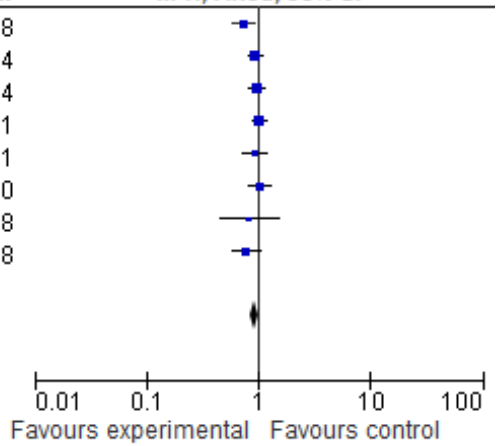
Abbildung 3: Niedrigdosis Interferon alpha versus Beobachtung

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

	IFN		OBS			Risk Ratio		Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**	**M-H, Fixed, 95% CI**
DeCOG, Garbe	65	148	88	148	11.6%	0.74 [0.59, 0.93]	2008	
EORTC 11887, Kleeberg	137	240	148	244	19.4%	0.94 [0.81, 1.09]	2004	
UKCCCR, Hancock	151	338	156	336	20.7%	0.96 [0.82, 1.13]	2004	
WHO, Cascinellil	146	225	138	219	18.5%	1.03 [0.90, 1.18]	2001	
SMG, Cameron	31	46	36	49	4.6%	0.92 [0.71, 1.19]	2001	
E1690 LDI, Kirkwood	96	215	93	212	12.4%	1.02 [0.82, 1.26]	2000	
AMCG, Pehamberger	17	154	21	157	2.8%	0.83 [0.45, 1.50]	1998	
FCGM, Grob	59	244	76	245	10.0%	0.78 [0.58, 1.04]	1998	
Total (95% CI)		**1610**		**1610**	**100.0%**	**0.93 [0.86, 1.00]**		
Total events	702		756					

Heterogeneity: Chi² = 8.56, df = 7 (P = 0.29); I² = 18%

Test for overall effect: Z = 2.05 (P = 0.04)

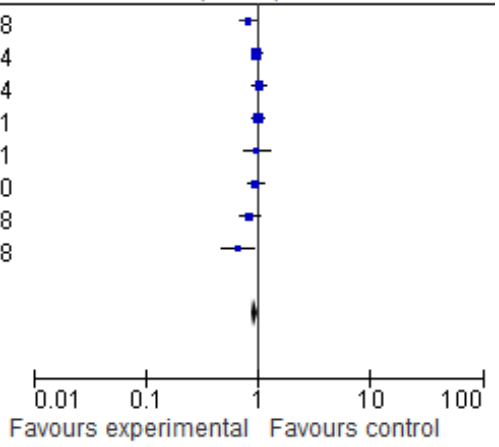


Outcome:. Progression Risk Ratio: 0.93 CI [0.88, 0.99] **sign.**

	IFN		OBS			Risk Ratio		Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**	**M-H, Fixed, 95% CI**
DeCOG, Garbe	84	148	102	148	10.5%	0.82 [0.69, 0.98]	2008	
UKCCCR, Hancock	211	338	215	336	22.2%	0.98 [0.87, 1.09]	2004	
EORTC 11887, Kleeberg	159	240	158	244	16.1%	1.02 [0.90, 1.16]	2004	
WHO, Cascinellil	162	225	158	219	16.5%	1.00 [0.89, 1.12]	2001	
SMG, Cameron	32	46	35	49	3.5%	0.97 [0.75, 1.26]	2001	
E1690 LDI, Kirkwood	122	215	127	212	13.2%	0.95 [0.81, 1.11]	2000	
FCGM, Grob	100	244	119	245	12.2%	0.84 [0.69, 1.03]	1998	
AMCG, Pehamberger	37	154	57	157	5.8%	0.66 [0.47, 0.94]	1998	
Total (95% CI)		**1610**		**1610**	**100.0%**	**0.93 [0.88, 0.99]**		
Total events	907		971					

Heterogeneity: Chi² = 10.58, df = 7 (P = 0.16); I² = 34%

Test for overall effect: Z = 2.40 (P = 0.02)



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5. AG Medikamentöse Therapie bei Metastasierung

5.1. 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?

5.1.1. 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, diphencyprone interferon beta, interferon-ß electrochemotherapy
Synonyme		Local recurrence Locoregional spread	treatment	
Ober-/Unterbegriffe				
Mesh Term	melanoma	Neoplasm Recurrence, Local	therapeutics	

5.1.2. Datenbanken, Suchstrategien, Trefferzahlen

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-ß“[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-ß“[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)

5.1.3. Auswahlkriterien

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
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)	

5.1.4. Evidenztabelle

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	Case Series Treatment: twice weekly, starting with 3 MIU Il-2	7 melanoma patients with satellitosis an cutaneous metastases	Response	Lesions: Complete remission 95.9% of treated lesions Partial remission:	Limitations: Case Series, small sample size	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastases of malignant melanoma in 7 patients.		244 lesions no other organs involved	Toxicity	3.7% of treated lesions Toxicitiy: few mild 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 addtion 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	Phase I single-center dose-escalation study	11 patients with histologically confirmed locally recurrent or	Safety Toxicity	No treatment related death, no grade 4 or dose-limiting toxicities	Limitations: Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	injection with adeno-IFN-g, and to determine the maximum tolerated dose	Treatment: 4 successive dose levels: 107 infectious units (iu) (n=3), 108 iu (n=3), 109 iu (n=3), and 1010 iu (n=2) per injection per week for 3 weeks.	metastatic malignant melanoma	Response	Most frequently observed toxicitiesgrade 1 pain and/or 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	Case Series Treatment: simultaneous external beam radiotherapy and intralesional injection of beta-interferon. 3-	20 patients with inoperable melanoma metastases	Response	17 patients evaluable CR: 12 patients (70%) PR: 5 patients (30%)	Limitations: Lack of control group Combined treatment with radiotherapy	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma	5 Mio IE / 3x/week					
Radny et al. 2003	To investigate the feasibility, efficacy, and safety of intralesionally injected IL-2 in 24 melanoma patients with skin and soft-tissue metastases	Phase II prospective open label study Treatment: 2-3 times weekly, 1-57 weeks, max. daily dose 12 MIU IL-2	24 melanoma patients with skin and soft-tissue metastases 16 patients Stage III 8 patients Stage IV 245 lesions	Response Safety	Lesions: 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	Response was evaluated for patients and for treated lesions separately. Response for patients applied to local response. Limitations: single centre study, lack of control group	4
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	Phase I study	13 melanoma	Response	Local response:	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	intralesional injections of GM-CSF induce regression of subcutanuous metastases in patients with melanoma and influence lymphoid infiltrates in and around the metastases	Treatment: weekly injections of 15-50mg GM-CSF into two subcutaneous metastases up to 6 months	patients with at least 3 subcutaneous metastases Stage III or IV (6 patients)		PR 1 patient SD 8 patients PD 4 patients		
Tan et al. 1993	To determine the role of BCG immunotherapy in malignant melanoma	Systematic review *Stage I and II: RCTs of BCG (adjuvant therapy)* 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	Selected intralesional BCG trials were not described in detail: number of treated lesions and lesions response not indicated, control groups not indicated	4*

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					and/or visceral metastases		
Fierlbeck et al. 1992	To compare the effect of intralesional beta-interferon at different dosages	Case Series Treatment: 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	10 patients with cutaneous or subcutaneous melanoma metastases 19 lesions	Lesion Response	Group 1 (n=8) CR:2, PR:1, SD:3, PD:2 Group 2 (n=8) CR:3, PR:2, SD:2, PD:1 Group 3 (n=3) CR:0, PR:0, SD:1, PD:2	Limitations: Small sample size	4
Von Wussow et al. 1988	To study the effects of higher IFN concentrations on malignant melanoma metastases, patients were treated with intalesional 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	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	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(MER-BCG)				regression: 4		
Vosika et al. 1979	To investigate the clinical pharmacology and efficacy of intralesional immonotherapy utilizing a vaccine composed of Mycobacterium smegmatis cell wall skeleton and the mycobacterial glypolipid fraction	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 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.	Limitations: Small series, lack of control group	4
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)	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	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	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
	technique	a week for 6 weeks			IL-BCG group, but no deaths were seen due to toxicity in either group	Limitations: Imbalance of groups: more male patients in the IL-BCG group, randomization 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	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	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	number of treated lesions not indicated	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	compare it with BCG in terms of tumor regression and side effects.	local reaction and systemic effects			(45%), Nausea and vomiting (18%), Hypotension (14%), Lethargy (14%), Cyanosis (9%), Confusion (5%)		

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/m2) 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 metastastes	Response	Local complete response in all 3 patients	-	4
Thompson et al. 2008	To investigate the therapeutic potential of PV-10	Open label phase II study	11 patients with locoregionally recurrent	lesion response overall response bystander effect	25 lesions evaluable: CR 36% (n=9)	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(Rose Bengal) in patients with stage III metastatic melanoma.	Treatment: One single IL injection of PV-10 in 1-3 target lesions	melanoma, Stage III 26 lesions treated 28 lesions untreated (to assess potential bystander effect)	toxicity	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 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	Prospective Phase II	14 patients, Stage III	Response (8 weeks	Patients(n=14):	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	evaluate clinical activity and tolerability of ECT with i.v. bleomycin	study Treatment: ECT with i.v. bleomycin		after ECT) Local tumor control rate	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%		
Gaudy et al. 2006	To assess whether EP therapy improves the local control of skin metastases of melanoma by intralesional bleomycin	A prospective internally controlled study with randomization of melanoma skin metastases in each individual to intralesional injections of bleomycin alone or to intralesional injections of bleomycin with EP	12 patients Stage III (4 patients) and Stage IV (8 patients under chemotherapy) 54 lesions	Local response (lesions) Tolerance	Lesions treated with bleomycin + EP (n=30) versus 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	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: No comparison to standard treatments (e.g. surgery, radiotherapy)	4*

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					clinical or biologic systemic toxicity.		
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 bleomycin followed by electrical pulses, possible retreatment at wek 4, 8 or 12	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) CR 72% (n=13) PR 5% (n=1) SD 18% (n=3) PD 5% (n=1) p=0.002	Response was evaluated for treated lesions. No data available for duration of response Limitations: No comparison to standard treatments (e.g. surgery, radiotherapy)	4*
Oratz et al. 2003	To evaluate the use of a novel intralesional chemotherapy – cisplatin / adrenaline injectable gel – for the treatment of	open-label, multicentre study Treatment: up to six weekly intratumoral injections of cisplatin/adrenaline gel within an 8 week	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).		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	refractory or recurrent cutaneous and soft tissue melanoma metastases	period or until complete response			Median duration of an individual tumour response (n = 124) was 347 days (range 30–783 days).		
Rols et al. 2000	To apply the electrochemotherapy method	Case Series Treatment: 10 mg/m2 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
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:	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	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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			22 lesions		50% (n=1) Control group (n=22): SD 36% (n=8), PD 64% (n=14)		
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 electic pulses alone 9 lesions bleomycin alone	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

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	retrospective study Treatment: epifocal DNCB and intravenous DTIC	72 evaluable patients with recurrent melanoma Stage III n=39 Stage IV n=33	Response	Stage III, patients n=39 Response CR n=15 (39%) PR n=9 (23%) SD n=9 (23%)	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	DTIC, data were collected in this retrospective study			Progression free survival Overall survival	PD n=6 (15%) Median PFS: 10 months (range 3 – 120 months) median OS 14 months (range 3 – 120 months)		
Damian et al. 2009	To report DPCP treatment of 7 patients with cutaneous metastastic melanoma	Case Series Treatment: 2 weeks after sensitization weekly applicatio of DPCP cream to all cutaneous metastases	7 patients with cutaneous metastastes	Response	CR 4 patients PR 3 patients	-	4
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	Case Series Treatment: Local DNCB 2% solution in acetone	59 patients with the presence of locoregional metastases, Stage III 63% (n=37) or Stage	Response	Overall Response (patients) CR 25% (n=15) PR+SD 12% (n=7) PD 63% (n=37)	No detailed data regarding local response available Limitations: Combination	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	with regional cutaneous metastases	alone for 4 weeks, start of DTIC i.v. after 4 weeks	IV 37% (n=22).		Local Response (patients) CR+PR 68% (n=40)	therapy	
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 injecitons every 4-6 weeks DNCB group: topical application until hypersensitivity occured (within 2 weeks) thereafter intralesional injections every 4-6 weeks	18 patients with intradermal or subcutaneous melanoma metastases, Stage III Randomisation in two treatment groups: 9 patients reveived BCG with 177 dermal and 22 subcutaneous lesions, 9 patients reveived DNCB with 504 dermal and 63 subcutaneous lesions	Response Survival Toxicity	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) 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	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
					(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

5.1.5. Literatur

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5.2. 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?

5.2.1. 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	

5.2.2. Datenbanken, Suchstrategien, Trefferzahlen

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 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)

5.2.3. Auswahlkriterien

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)

5.2.4. Evidenztabelle

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/m² i.v. or paclitaxel 175mg/m² 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 anoma patients	RCT, open label Treatment: Group A dabrafenib (150 mg orally twice daily)	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
	whose tumours harboured a BRAFV600E mutation.	Group B dacarbazine, 1000 mg/m² 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/m² 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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
O´day et al. 2011	To evaluate the safety and efficacy of Intetumumab (CNTO 95), a fully human anti-alpha(v)-integrin monoclonal antibody	RCT, double-blind (Group A+B) Treatment q3w: Group A 1000 mg/m² dacarbazine + placebo, (n=32) Group B 1000 mg/m² dacarbazine + 10 mg/kg intetumumab (n=32) Group C 10 mg/kg intetumumab (n=33) Group C 5 mg/kg intetumumab (n=32)	129 chemotherapy-naive patients	Median Overall Survival Overall Response Rate Duration of Response	DTIC vs. DTIC+ intetumumab vs. intetumumab 10mg vs. intetumumab 5mg 8 vs. 11 vs. 15 vs. 9.8 months, n.s. 10% (n=3) vs. 3% (n=1) vs. 6% (n=2) vs. 0%, n.s. 3.9, 7.3, and 10.3+ months vs. 7.0 months vs. 6.3 and 8.2+ months	Jadad Score 5 Funding: Centocor Ortho Biotech, Inc., Malvern, PA, USA.	1b
Kefford et al. 2010	To evaluate the	RCT, double-blind	80 patients with		DTIC+Bosentan vs.	Jadad Score 4	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	effects of bosentan - a dual endothelin receptor antagonist - in patients receiving first-line dacarbazine therapy for stage IV metastatic cutaneous melanoma	Treatment: Group A DTIC 1000 mg/m2 every 3 weeks starting on Day 1 +Bosentan 500 mg twice a day (n=40) Group B DTIC 1000 mg/m2 every 3 weeks starting on Day 1+Placebo (n=40)	previously untreated metastatic melanoma	Median Overall Survival Overall Response Rate Duration of Response	DTIC+Placebo 13.0 months (95% CI, 7.8-16.6) vs. 10.6 months (95% CI, 6.9-14.7), n.s., (HR, 1.044; 95% CI, 0.584-1.865; p = 0.8841) not reported not reported	tumor assessment not described as blinded Funding: 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/m2 plus carboplatin (AUC 6) + sorafenib 400mg (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	Median Overall Survival Overall 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%	Jadad Score 5 Funding: Bayer AG and Onyx Pharmaceuticals, Inc.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Group B paclitaxel 225 mg/m2 plus carboplatin (AUC 6) + placebo (n=135)	the advanced setting	Rate Duration of Response	(n=15), n.s., p=1.0 not reported		
O´Day et al. 2009	To evaluate whether the addition of elesclomol to weekly paclitaxel could improve efficacy in patients with stage IV metastatic melanoma	RCT, double-blind Treatment: Group A elesclomol 213 mg/m² plus paclitaxel 80 mg/m(2) (E + P) (n= 53) Group B paclitaxel 80 mg/m² alone (n= 28)	81 metastatic melanoma patients with one or fewer prior standard chemotherapy regimens	Median Overall Survival **Progression Free Survival** Overall Response Rate Duration of Response	Elesclomol +Paclitaxel vs. Paclitaxel 11.9 vs. 7.8 months **3.7 months vs. 1.8 months, sign., p=0.035** 15.1% (n=8) vs. 3.6% (n=1) (p=0.153) ,n.s., p=0.153 range 58+ to 188+ days (censored patients), 107, 136 days vs. 115 days	Jadad Score 4 Tumor assessment by investigators, Randomization without stratification, M1c patients unbalanced (25.8% vs. 75%) Funding: Synta Pharmaceuticals, Lexington, MA.	1b
McDermott et al.	To evaluate the	RCT, double-blind	101 chemotherapy-		Sorafenib + DTIC	Jadad Score 5	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
2008	efficacy and safety of sorafenib plus dacarbazine in patients with advanced melanoma	Treatment: Group A sorafenib plus dacarbazine (n = 51) Group B placebo plus dacarbazine (n = 50)	naive patients with stage III (unresectable) or IV melanoma	 Median Overall Survival Overall Response Rate Duration of Response	vs. Placebo + DTIC 45.6 weeks vs. 51.3 weeks, n.s., p=0.927 24% (n=12) vs. 12% (n=6), n.s., p=0.193 26.9 vs. 23.0 months, n.s., p=0.194	 Funding: Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals Inc.	
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/m² and dacarbazine 1g/m² plus tamoxifen 20 mg/day (D+C+T) Group B	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	Jadad Score 2 unblinded tumor assessment, no description of dropouts and withdrawals, small sample size Funding: Not declared	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		(D+C)			months + lost to follow up at 31 months		

Immuntherapien, Immunmodulation

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hersh et al. 2011	To evaluate the safety and efficacy of **ipilimumab** alone and in combination with dacarbazine (DTIC) in patients with unresectable, metastatic melanoma	RCT, open label Treatment: 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/m²/day (n=35)	72 chemotherapy-naive patients	Median Overall Survival Overall Response Rate Durable Complete Response	**Ipi** alone (n=32) vs. Ipi+DTIC (n=32) 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)	Jadad Score 2 small sample size randomization scheme not described, tumor assessment not blinded Funding: Bristol-Myers Squibb Co.	1b
Robert et al. 2011	To evaluate	RCT, double-blind	502 patients with		**Ipi**+DTIC vs.	Jadad Score 5	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	ipilimumab (10 mg per kilogram) plus dacarbazine in patients with previously untreated metastatic melanoma	Treatment: Group A Ipilimumab (10 mg per kilogram) plus dacarbazine (850 mg/m²) Group B dacarbazine (850 mg/m²) plus placebo	previously untreated metastatic melanoma	**Median Overall Survival** Overall Survival 1 year 2 years 3 years Overall Response Rate **Duration of Response**	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 DITC+Ipi, 0.72; p<0.001)** 47.3% vs. 36.3% 28.5% vs. 17.9% 20.8% vs. 12.2% 15.2% vs. 10.3%, n.s. (p = 0.09) **19.3 months (95% CI, 12.1 to 26.1) vs. 8.1 months (95% CI, 5.19 to 19.8) (p=0.03)**	Funding: Bristol-Myers Squibb.	
Schwartzentruber et al. 2011	To investigate if the combination of a **melanoma vaccine** with interleukin-2,	RCT, open label Treatment:	185 patients with stage IV or locally advanced stage III cutaneous	Median Overall Survival	IL-2 vs. IL-2+**Vaccine** 11.1 months (95%	Jadad Score 4 tumor assessment blinded	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	an immune activating agent, could improve outcomes	Group A interleukin-2 alone (720,000 IU per kilogram of body weight per dose) Group B gp100: 209-217(210M) plus incomplete Freund's adjuvant (Montanide ISA-51) once per cycle, followed by interleukin-2	melanoma, expression of HLA*A0201, an absence of brain metastases, and suitability for high-dose interleukin-2 therapy	**Overall Response Rate** Duration of Response	CI, 8.7 to 16.3); vs. 17.8 months (95% CI, 11.9 to 25.8) n.s. (p=0.06) **6% vs. 16%, p=0.03** not reported	Funding: National Cancer Institute, Indiana University Health Goshen, Goshen Hospital and Health Care Foundation, Chiron, and Novartis	
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	RCT, double-blind Treatment: Group A ipilimumab plus gp100 (n=403) Group B ipilimumab alone	676 HLA-A*0201-positive patients with previously treated unresectable stage III or IV melanoma	**Median Overall Survival**	**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).**	Jadad Score 5 tumor assessment by investigators Funding: Medarex and Bristol-Myers Squibb	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma	(n=137) Group C gp100 alone (n=136)		**Overall Response Rate** Median Duration of Response Treatment related deaths	**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		
Eisen et al. 2010	To compare the treatment with **lenalidomide** to placebo in 306 patients with metastatic malignant melanoma	RCT, double-blind Treatment: Group A lenalidomide (25 mg/d on Days 1-21 of a 28-day cycle (n=154) Group B placebo (n=152)	306 patients with previously treated metastatic malignant melanoma	Median Overall Survival Overall Response Rate Duration of Response	**lenalidomide** vs. placebo median 5.9 months (range 5.1-7.7) vs. 7.4 months range 5.5-8.2); n.s., p=0.32 5.3% vs 5.8%; n.s., p=0.82 not reported	Jadad Score 5 Funding: Celgene Corporation, Summit, New Jersey.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 (CR+PR+SD)**	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: 49.5% vs. 32.0% P=0.009**	Jadad Score 4 tumor assessment blinded Funding: Sigma-Tau SpA, Pomezia, Italy	1b
Weber et al. 2011	To assess the	RCT, open label	184 patients with		**PF-3512676** 10mg	Jadad Score 3	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	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	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/m²) (n=45) Group D DTIC (850 mg/m²) alone (n=39)	previously untreated metastatic melanoma	Median Overall Survival Overall Response Rate Duration of Response	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 to small)	Funding: not declared	
Schadendorf et al. 2006	To demonstrate the superiority of autologous peptide-loaded **dendritic cell (DC) vaccination** over	RCT, open label Treatment: Group A DC vaccines loaded	108 metastatic melanoma patients with no prior systemic chemotherapy	Median Overall Survival	**DC vaccination** vs. DTIC 9.3 months vs. 11.6 months n.s.	Jadad Score 3 Funding: German Cancer Aid	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	standard dacarbazine (DTIC) chemotherapy in stage IV melanoma patients	with MHC class I and II-restricted peptides (n=53) Group B DTIC 850 mg/m² (n=55)		Overall Response Rate	ITT: 3.8% (n=2) vs. 5.5% (n=3), n.s. (PP:4.9 vs. 4.8%)		
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 response rates,	RCT, open label	181 patients		TMZ vs. TMZ+IFN vs.	Jadad Score 2 dropouts and	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	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	TMZ+Thalidomide 5.3 vs. 7.7 vs. 7.3 months 9% vs. 18% vs. 15% range 2.4 - 21.2 months	withdrawals not described	
Agarwala et al. 2002	To determine whether the addition of **histamine** to a subcutaneousregimen 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	RCT, open label Treatment:	61 advanced melanoma patients without previous		DTIC +**IFN-alpha** Vs. DTIC	Jadad Score 3 unblinded tumor assessment, small	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastatic melanoma	Group A DTIC +IFN-alpha (n=30) Group B DTIC (n=31)	DTIC or IFN	Median Overall Survival Survival 6 months Overall Response Rate Duration of Response	4.8 months (95% CI 2.0-8.0) vs. 7.2 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)	sample size 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	RCT, open label Treatment: Group A DTIC alone (n=69) Group B (n=68) DTIC + IFN Group C (n=66) DTIC + TMX	271 metastatic melanoma patients with no pnor chemotherapy except for adjuvant IFN	Median Overall Survival Overall Response	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%	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,	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	plus tamoxifen (TMX), or dacarbazine plus IFN plus TMX	Group D DTIC + IFN + TMX (n=68)		Rate	vs. 19% (of 250 patients)	and CA 21115 from the National Cancer Institute, National Institutes 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, N01-CM73704, NO1-CM73705, NO1-CM73706, and NO1-CM73707; National Institutes of Health Clinical Research Center	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						grant no. MOI-RR00054 to Tufts University School ofMedicine; and by Hoffman La-Roche, 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)	64 metastatic melanoma patients	 **Median Overall Survival** **Overall Response**	DTIC + **IFN alfa-2b** vs. DTIC **17.6 months vs. 9.6 months, sign., p < 0.01** **53% (n=16) vs. 20%**	Jadad Score 2 Randomization scheme not described, unblinded tumor assessment, small sample size, imbalance of groups	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Group B DTIC alone (n=31)		**Rate** Duration of Response	**(n=6), sign., p=0.007** Not reported	(more male patients in Group B) Funding: IFN alfa-2b was supplied by Scherag South Africa, 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/m² i.v. on day 1 every 3 weeks (n=194) Group B Dacarbazine, 1000 mg/m² i.v. on day 1 every 3 weeks (n=199)	393 chemonaive 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 (7.4months) (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)	Jadad Score 3 tumor assessment not described as blinded Funding: Luitpold Pharmaceuticals, Inc.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					vs. not estimated due to censoring pattern		
Patel et al. 2011	To compare the efficacy of an extended schedule escalated dose of temozolomide versus standard dose dacarbazine	RCT, open label Treatment: Group A oral temozolomide 150mg/m²/day for seven consecutive days every 2weeks (n=429) Group B Dacarbazine, i.v. 1000mg/m²/day on day 1 every 3 weeks (n=430)	859 chemotherapy-naive patients	Median Overall Survival Overall Response Rate Duration of Response	TMZ vs. DTIC 9.1 months vs. 9.4months, n.s. (p=1.0) 14.5% (n=58) vs.9.8% (n=38), p=0.05 4.6 vs. 11.2 months, p=0.015, sign.	Jadad Score 3 tumor assessment was not blinded Funding: Schering Plough, UK National Cancer Research Network	1b
Ranson et al. 2007	To evaluate tumor response, pharmacodynamic effects, and safety of a combination of lomeguatrib (LM), an O6-	RCT, open label Treatment: Group A lomeguatrib 40mg/d, 2h later	104 patients with unresectable stage III or IV cutaneous melanoma who had no prior systemic chemotherapy	Median Overall Survival	LM/TMZ vs. TMZ 7.6 months (95% CI, 6.9 - 10.3 months) vs. 7.7 months (95%	Jadad Score 2 Randomization scheme not described, tumor assessment not blinded	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	methylguanine DNA-methyltransferase (MGMT) inactivator, and temozolomide (TMZ), TMZ alone, and LM/TMZ after disease progression on TMZ alone in patients with advanced melanoma	TMZ 125mg/m2/d, orally, 5 days every 4 weeks (n=52) Group B TMZ 125mg/m2/d, orally, 5 days every 4 weeks (n=52)		Overall Response Rate	CI, 6.3 - 10.7 months), n.s. 13.5% (n=7) vs. 17.3% (n=9), n.s.	Funding: Kudos Pharmaceuticals, owned by AstraZeneca.	
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.	To evaluate and	RCT, open label	132 metastatic		TMZ vs. TMZ +	Jadad Score 2	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
2005	compare the activity and safety profile of the combination Cisplatin + TMZ versus single-agent TMZ in patients with advanced melanoma	Treatment: Group A TMZ 200 mg/m²/day orally d1-5q28 (n=66) Group B TMZ + Cisplatin 200 mg/m² daily on days 1-5 and 75 mg/m² of cisplatin on day 1 (n=66)	melanoma patients with no previous chemotherapy	Median Overall Survival Overall Response Rate Duration of Response	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., p=0.35	Randomization scheme not described, tumor assessment not blinded Funding: Kudos Pharmaceuticals, owned by AstraZeneca.	
Avril et al. 2004	To compare fotemustine and dacarbazine (DTIC) in patients with disseminated cutaneous melanoma.	RCT, open label Treatment: Group A Fotemustine 100mg/m²; weekly, 3 weeks, (n = 112) Group B DTIC 250 mg/m²/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

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	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 Overall Response Rate Duration of Response	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 13.5% (21 of 156) vs. 12.1% (18 of 149), n.s. longer in the TMZ group; 18 of the 21 TMZ responders survived longer than 12 months vs. 11 of the 18 DTIC responders	Jadad Score 3 unblinded tumor assessment, different time points for assessment between groups Funding: Not declared	1b
Keilholz et al. 1997	To determine whether the addition of Cisplatin to a cytokine	RCT, open label Treatment:	138 metastatic melanoma patients, no prior therapy with Cisplatin		IFN alpha + IL-2 vs. IFN alpha + IL-2 + Cisplatin	Jadad Score 3 tumor assessment not blinded	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	treatment regimen with IFN alpha and high-dose IL-2 influences survival of patients with metastatic melanoma	Group A IFN alpha 10 x 106 U/m2 sc. on days 1 through 5 + IL-2 on days 3 through 8 (18 mIU/m2/6 h, 18 mIU/m2/12 h, 18 mIU/m2/24 h, and 4.5 mIU/m2/24 h x 3) Group B IFN alpha + IL-2 + Cisplatin 100 mg/m2 on day 1		Median Overall Survival Overall Response Rate Duration of Response	all patients: 9 months, n.s. between groups 18% vs. 33%, sign., p=0.04 17 vs. 6 months, n.s., p=0.057	Funding: Chiron BV, Amsterdam, the Netherlands and Hoffmann-La Roche AG, Grenzach, Germany	
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 +	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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		vindesine (DV) (n=165)					
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
Chauvergne et al. 1982	To evaluate the efficacy of detorubicin in combination with DTIC versus DTIC alone	RCT, open label Treatment: Group A DTIC (250 mg/m2, i.v., over 4 days every three weeks) + detorubicin (120 mg/m2, i.v. every three weeks)	51 patient	Median Overall Survival Overall Response Rate Duration of	DTIC + detorubicin vs. DTIC alone 8 months vs. 5 months, n.s. 36% (n=8 of 22 patients) vs. 15% (n=4 of 26), n.s. 6 months vs. 5	Jadad Score 2 Randomization scheme not described, unblinded tumor assessment, small sample size Funding: Not declared	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Group B DTIC alone		Response	months,n.s.		

5.2.5. Literatur

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5.3. 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 ?

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
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.	*Leitlinie enthält keine Empfehlungen zu Therapien im fernmetastasierten Stadium*	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	Nein	Nein	-	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
Biochemotherapien im metastasierten Stadium zu einer Verbesserung des Gesamtüberlebens?	Interferon-alpha und IL-2 verbessern Ansprechen von Monotherapien aber nicht das Gesamtüberleben allein oder in Kombination mit Chemotherapien.	Durch Verwendung einer 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

5.3.2. Empfehlung, Hintergrundstext und Literatur Kanadische Quell Leitlinie

Quellleitlinie: 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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5.4. 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?

5.4.1. 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	

5.4.2. 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)

5.4.3. 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

5.4.4. 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*	
Garbe et al. 2011	*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*	*Systematic Review* *Treatment: Adjuvant and palliative treatment*	*RCTs Adjuvant and palliative treatment* *No RCTs for Polychemotherapy vs. DTIC included*			*No RCTs for Polychemotherapy vs. DTIC included → study excluded*	
Sasse et al. 2009	*To compare the effects of chemotherapy alone versus combined therapy with chemotherapy and immunotherapy (chemoimmunotherapy) in people with metastatic*	*Systematic Review* *Treatment: Chemotherapy versus Chemoimmunotherapy*	*18 RCTs, 2625 patients with metastatic melanoma*	*1 year Survival* *Response Rates*	*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*	*No RCTs for Polychemotherapy vs. DTIC included → study excluded*	

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	
	malignant melanoma.				*1.20 -1.63), p < 0.0001*		
Crosby et al. 2009	*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*	*Systematic Review* *Treatment: Systemic therapies versus best supportive care/placebo*	*0 RCTs*	*Overall survival* *Median survival* *Progression free survival*	*No RCTs were retrieved, so no analysis of the effects of the interventions was carried out.*	*No RCTs for Polychemotherapy vs. DTIC included → study excluded*	

5.4.5. Literatur

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

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

5.5.1. 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			

5.5.2. 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)

5.5.3. 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 uvealer 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:

- Resektion
- Isolierte hepatische Perfusion (IHP)
- Hepatische arterielle Infusion (HAI)
- Hepatische arterielle Chemoembolisation (HACE) / Trans-arterielle Chemoembolisation (TACE)
- Radioembolisation (selektive interne Radio-Therapie – SIRT)

5.5.4. 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 Treamtent: 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 Treamtent: - 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 qualitiy cohort study
Mariani et al. 2009	To review the surgical management of liver metastases from uveal	Retrospective evaluation Treamtent: - Surgery	798 uveal melanoma patients with liver metastase surgical resection	Survival	median overall postoperative survival All patients n=255: 14 months	No cutaneous melanoma patients Multivariate analysis included Lack of control	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma in a single institution with regard to survival and the determination of predictive factors for the optimal surgical candidate		n= 255	Predictive factors	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 ffect s disease	group	
Woon et al. 2008	To assess the survival of melanoma patients with hepatic	Retrospective evaluation Treatment:	15 patients with hepatic melanoma metastases, 9 patients suitable for	Survival	Median survival for all patients: 7 months. Curative surgical	Small series	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastases who underwent surgery	Lobectomy Cryotherapy	surgical ffect s tion		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 melanoma n=24	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 rate:	17 of 24 patients with cutaneous melanoma received systemic therapy	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	liver.				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	Prospective study Treatment: surgical approach	75 uveal melanoma patients with liver metastases	Survival	Median overall survival all patients: 9 months.	No cutaneous melanoma patients Combined treatment	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	laparotomy with hepatic resection (whenever possible), implantation of an intraarterial catheter and intraarterial chemotherapy (IACH).	removing as much liver disease as possible and intraarterial chemotherapy for 6 months			Surgery plus chemotherapy (n=61): 10 months curative resection (n=19): 22 months	Lack of control group	

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 isolated	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
	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	Retrospective evaluation	36 patients with hepatic metastases from ocular or cutaneous melanoma, 30 patients were treated	Response Survival	cutaneous melanoma patients (N=12) PR n=4 (33%) SD n=4 (33%) PD n=4 (33%) Median survival: 12		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cutaneous melanoma.		Ocular melanoma n=18 Cutaneous melanoma n=12	Toxicity	months. Toxicity (all patients N=30) grade III-IV throm-bocytopenia: 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 melanomapatients 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	Phase I/II trial escalating doses ofintrahepatic	19 patients with ocular melanoma and liver metastases	Toxicity	Toxicity: Grade 3 n=7 Grade 4 n=9	No cutaneous melanoma patients	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	to determine the role of escalation of intrahepaticarterial cisplatin dose, either alone or as part of chemoembolization.	chemotherapywithcisplatin with orwithout polyvinylsponge (PVS)		Response	PR n=3 (16%) SD n=13 (68%) PD n=1 (5%) Not evaluable n=2 (11%)		
Becker et al. 2002	To evaluate the activity of sequential fotemustine, interferon alpha, and interleukin 2 for metastatic uvea melanoma patientsin a prospectivephase II trial.	Phase I/II study Treatment: Fotemustine 100mg/m² via hepatic artery or i.v. followed by s.c. IL-2 on day 31 and s.c. interferonalpha 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	Phase II study Treatment: intraarterial fotemustine 100 mg/m² (4 hour infusion)	31 patients with liver metastases from ocular melanoma	Response	Response liver metastases (30 patients assessable) CR n=4 (13%) PR n=8 (27%) Minor Response n=2 SD n=13	No cutaneous melanoma patients No overall response data	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	treatment of liver metastases from ocular melanoma			Suvival	PD n=3 Median overall survival 14 months		
Khayat et al. 1991	To evaluate hepatic intra-arterial infusion (HIAI) of fotemustine	Phase II Study Treatment: intraarterial fotemustine 100 mg/m² (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	Mulitvariate 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/m² of cisplatine was continuously infused by means of a power injector preceding embolization by manual injection of polyvinyl alcohol particles	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
					(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 catheterassociated 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	Retrospective evaluation (of patients treated within 2 different Phase II studies) Treatment: Chemoembolization	53 patients with uveal melanoma CE n=19 IE n=34	Overall survival (OS) Progression-free	Median OS CE: 9.8 months Low-dose IE: 13.0 months High-dose IE: 20.4 months Median Liver PFS CE:	No cutaneous melanoma patients	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(2-chloroethyl)-1-nitrosourea or immunoembolization (IE) with granulocyte-macrophage colony-stimulating factor (GM-CSF) for hepatic metastases	with BCNU or with GM-CSF		survival (PFS)	6.4 months Low-dose IE: 4.2 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	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	Presence or absence of extrahepatic metastases not mentioned	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				survival	progression-free survival: 185 days		
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/m² 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	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	No cutaneous melanoma patients	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		ethiodized oil. Gelatin sponge particles were used as a transiently occlusive agent.			PD 3.3 month		

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)	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	No cutaneous melanoma patients	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		delivered via the hepatic artery			PD n=1 1 year survival 80%		

5.5.5. Literatur

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

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

5.6.1. 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		QoI		
Mesh Term	melanoma	Quality of life		

5.6.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(“melanoma”[tiab] OR “melanoma”[MeSH]) AND (“Quality of life” OR “QoI” 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.

Datenbank	Suchstrategie	Datum	Treffer
			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)

5.6.3. Auswahlkriterien

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 Tumorentitiäten 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:	

Auswahl der Literatur	
- Reviews zu QoL bei Melanompatienten unter Therapie - Adjuvante Therapienstudien die QoL als Endpunkt enthalten - Palliative Therapienstudien die QoL als Endpunkt enthalten	

5.6.4. Evidenztabelle

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 questionaire, QWB-SA QOL Results: no significant improvements in	Detailed description of studies and results	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					QoL for any alternative for treating MM		
Cornish et al. 2009	To systematically review the available literature on health-related quality of life (HRQOL) and melanoma	Systematic review Inclusion criteria: (HR)QOL assessment in cutaneous melanoma	13 selected studies	HRQOL in patients with cutaneous melanoma	- 20 different instruments were used within the 13 studies - 3 distinct periods of HRQOL impact: diagnosis, treatment and follow-up - systemic drugs decreased patients´ HRQOL during treatment.	Results of QoL measurements within the studies are not presented in detail. Methodological quality of included studies was measured by 14 not validated criteria	1a-

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	QoL evaluation within a phase III trial QoL instrument: EORTC QLQ-C30	QoL Assessment no. of forms received (expected) Baseline n=725 (850)	HRQOL at baseline HRQOL during	HRQoL compared with the healthy reference population significant decrease	No assessment of long term QoL Data (Group 2)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) before and during the first 12 months of adjuvant treatment with IFN-a-2a	Time points: baseline, month 3, 6 and 12 Treatment: Group 1: IFN-a-2a 18 months Group 2: IFN-a-2a 60 months	all timepoints n=282 (850)	treatment	of 9 of 15 QLQ-C30 subscales peaked at 3 months		
Brandbert et al. 2011	To compare 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	QoL evaluation within a phase III trial QoL instrument: EORTC QLQ-C30 Time points: baseline, month 3, 6 and 12 Treatment: Arm A: Observation Arm B: 1 year intermediate Dose IFN-a-2b Arm C: 2 years intermediate Dose IFN-a-2b	QoL Assessment no. of forms received > 80% all timepoints n=282 (850)	HRQOL during treatment compared to baseline HRQOL differences between groups	significant interactions between randomisation arm and time after randomisation for almost all EORTC QLQ-30 variables Arm A improved or remained at baseline levels ARM B+C significant negative impact on HRQoL of IFN treatment. the impact were	-	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					reversible when treatment was stopped.		
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 III melanoma	QoL evaluation within a phase III trial QoL instrument: EORTC QLQ-C30 Time points: baseline, month 3, 12, 24, 36, 48, 60. Treatment: Group 1 observation (n = 629) Group 2 PEG-IFN-alpha-2b (n = 627)	QoL Assessment no. of forms received (expected) Baseline Gr. 1: n=521 (629) Gr. 2: n=520 (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	HRQOL at month 3	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) -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	Analysis was restricted to the first 3 years, as limited data existed at years 4 and 5. Conflict of interest 5 of 18 authors received funding, honoria or had consultant/advisory role (Schering Plough)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(P<.0001) over time: Appetite loss Fatigue		
Garbe et al. 2008	To evaluate adjuvant Interferon alpha and DTIC in terms of overall survival, recurrence-free survival and occurrence of adverse events. Health-related quality of life (QoL) was measured by a questionnaire.	QoL Evaluation within a RCT QoL Instrument: EORTC QLQ-C30 Time points: Baseline + 6 months Treatment: Arm A: Interferon alpha (n=146) Arm B: Interferon plus Dacarbazine (n=148) Arm C: Observation (n= 147)	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) 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 =	Baseline HRQOL data not presented	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 dose, 60 months Group 2: Observation (OBS)	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 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)	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
Loquai et al. 2011	To evaluate the impact on quality of life (QOL) in patients treated	Retrospective evaluation QoL Instrument:	30 patients	QOL changes	impairment in most QOL single dimensions	Small sample size	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	with once weekly 2µg/kg PEG-IFN-α2b and to examine whether there is a difference in patients' and physicians' perception of QOL	EORTC QLQ-C30 Time points: Baseline, every 3 months Treatment: 2µg/kg PEG-IFN-α2b		Patients questionnaires compared to physician assessment	QOL documented by physicians was significantly higher than QOL from the patients' questionnaires in all QOL dimensions		
Ratai et al. 2005	to evaluate the impact of interferon (IFN) treatment on patients' quality of life (QoL) after radical surgery of cutaneous melanoma	Comparative Study QoL Instrument: EORTC QLQ-C30 Time points: Baseline und during treatment Treatment: Group 1: INF-alpha-2b Group 2: Observation	220 patients Group 1 n=110 Group 2 n=110	QoL	The IFN-alpha-2b treatment significantly affected patients' physical condition, mental health, and social life. In spite of several adverse effects, the patients assessed their QoL as good	Allocation to groups not indicated Baseline data not presented Timepoints of assessment not indicated	4
Trask et al. 2004	To assess the the longitudinal course of depression, fatigue, and QoL	Observational study QoL Instruments: -BSI	16 patients	Depression QoL Fatigue	6-month post high-dose assessment: significantly increased somatic	Small sample size data presented in detail	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	before and during interferon therapy	-FACT-BRM -RPFS -BDI Time points: Baseline, 1, 2, 3, 6 months post treatment Treatment: high dose interferon-alpha			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		
Cohen et al. 2002	To prospectively assess QoL in patients with malignant melanoma participating in a phase Ib immunotherapy cancer clinical trial of an autologous tumour-derived vaccine	QoL Evaluation within a Phase Ib study QoL Instruments: -SF-36 (RAND scoring method, 8 scales, range 0 (worst) to 100 (best). Physical Component Summary (PCS) and Mental Component Summary (MCS)	QoL assessment Baseline n=29 Week 3 n=28 Follow up n=27 of 30 evaluable patients with stage III or IV malignant melanoma	Changes of PCS, MCS and IES over time Association between IES, PCS and MCS Scores	QoL remained stable during treatment, no significant time effect for the PCS score, MCS scores or the IES scores significant negative association between IES scores at baseline and mental health scores at	Missing data at all 3 timepoints. 2 of 3 missing assessments at follow up due to progressive disease. Mixed model regression analyses, analyses using the last observation carried forward and analyses using a complete cases	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Scores, computed by using items from the 8 subscales -Impact of Event Scale (IES) Time points: baseline, week 3 and follow-up Treatment: vaccine			each time point (< 0.002 for all).	approach were performed.	
Bender et al. 2000	To describe short- and long-term changes in cognitive function and quality of life in patients with melanoma receiving interferon (IFN) alpha-2b	Pilot Study QoL instrument: FACT-G scale Time points: baseline, 3, 6, 9, 12 and 15 months 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	18 melanoma patients (part of ECOG EST 1690 trial) baseline Group A: n=6 Group B: n=6 Group C: n=6 15 months Group A: n=2 Group B: n=3 Group C: n=2	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 diminished overall quality of life	Limitations: small sample size Baseline characteristics (e.g. gender, age) are not presented	4 Poor quality case control study

Palliative Therapiestudien die QoL als Endpunkt enthalten

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Robinson et al. 2012	To determinepatient-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
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,	QoL Evaluation within a cohort study QoL instrument: EORTC QLQ-C30 Treatment: Arm A: BSC (n=34)	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	Initial protocol: random assignment. Due to lack of patients consent for randomization the protocol was changed to treatment assignment based	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	disease control rate and quality of life	Arm B: BSC+CVD (n=83)			fatigue Arm B, not significant reduction in the Global Health status in both arms, not significant	on patients choice	
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 (BM), and to assess safety and quality of life	QoL Evaluation within a randomized phase III study QoL instrument: EORTC QLQ-C30 Time points: baseline and after induction period Treatment: Fotemustine versus DTIC	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. disease progression and performance status were the main factors for QoL impairment.	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, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties	1b
Chiarion-Sileni et al. 2003	To analyse the health related	QoL Evaluation within a randomized	Available QoL scores	HRQOL difference HRQOL at baseline	between treatment arms over time:		1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	quality of life (HRQOL) of advanced melanoma patients, in a randomised trial comparing bio-chemotherapy (bio-CT) versus chemotherapy (CT)	phase III study QoL Instrument: Rotterdam Symptom Checklist (RSCL) Time points: Baseline, Cycle 1, 2, 3, 4, 5 and 6 Treatment: CT: cisplatin and DTIC alone Bio-CT: cisplatin, DTIC, IL-2 and IFN a-2b	Baseline n=140 (of 178) Cycle 6 n=16 (of 57)	as prognostic factor	statistically significant difference in the overall quality of life score (P=0.03) , decrease of 6.28 points in the bio-CT arm no significant difference between treamtents: activity level (P=0.20) physical symptom distress (P=0.08) psychological distress (P=0.25) (values always slightly inferior in the bio-CT arm) deterioration over time: bio-CT arm: significantly in all domains (most important reduction		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					in the activity level) CT arm: significant only for the activity level and the physical symptom distress (P<0.001). 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 mulitvariate analysis.		
Kiebert et al. 2003	To report detailed HRQL results of a phase III clinical trial comparing temozolomide (TMZ) to dacarbazine (DTIC) in patients with metastatic	QoL Evaluation within a Phase III study QoL Instrument: EORTC QLQ-C-30 Time points: baseline, week 12,	Available HRQL scores Baseline TMZ n=110 Baseline DTIC n=110 Week 12 TMZ n=50 Week 12 DTIC n=31 Week 24 TMZ n=22	HRQL differences -Between groups -Over time	between groups: baseline: no significant differences 12 weeks: TMZ group significantly better physical functioning, less fatigue and sleep	At week 24 not enough data for interpretations. More missing data in the DTIC group. Limited external validity: Privilege of receiving the new,	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma	24 Treatment: Group 1 DTIC Group 2 Temozolomide	Week 24 DTIC n=8 (of 305 advanced melanoma patients)		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 emotional well-being, and less	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
					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	QoL evaluation within a phase III study QoL instrument: EORTC QLQ C30 (+3) Time points: baseline, at each visit Treatment: Group 1 DTIC Group 2 DTIC + IFN-alpha	41 (of 57) advanced melanoma patients completed at least 1 questionnaire Baseline n=38 Timepoint of tumor assessment n=27	QoL -between groups -over time	-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) -for both groups the level of symptoms worsened over time, but patients' functioning ability appeared to be stable	Limitations: missing data	1b
Middleton et al. 2000	To compare temozolomide and	Randomized phase III study	QoL Scores available	QoL (secondary objective)	TMZ group: significant better	QoL data are not shown in detail	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	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.	QoL Instrument: EORTC QLQ-C30 Timepoints: baseline, week 12 Treatment: Group 1 Temozolomide (TMZ) Group 2 DTIC	Baseline n=251 Week 12 TMZ group n=51 DTIC group n=31 of 305 patients with advanced metastatic melanoma	-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)	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	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)	
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	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
		Treatment: DTIC 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.	QoL assessment within a Phase III study QoL instrument: linear analog self assessment (LASA) scales, GLQ-8 by physician: QL Index questionnaire Time points: Baseline, week 12 Treatment: Group 1: DTIC Group 2 DTIC + IFN-alpha-2a	176 advanced melanoma patients Number of QoL data not indicated	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

Ausgeschlossene Studien

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*LoE*
Adamina et al. 2008	*To assess the safety and immunogenicity*	*multi-centre phase I/II open labeled*	*20 resected AJCC stages IIb-IV*			*QoL data are not presented*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of heterologous prime-boost immunotherapy of melanoma patients with Influenza virosomes, and recombinant Vaccinia virus. Quality of life will be assessed with a dedicated FACT-BRM 4 questionnaire	study LQ instrument: FACT-BRM 4 questionnaire	melanoma patients			excluded	
Beguerie et al. 2010	Tamoxifen vs. non-tamoxifen treatment for advanced melanoma: a meta-analysis	metaanalysis	9 randomized controlled trials	Secondary outcome quality of life (Response, mortality, toxicity, treatment-related mortality)	None of the trials reported QoL	excluded	
Noorda et al. 2007	To assess the long-term health-related quality of life (HRQL) of melanoma survivors who had undergone isolated limb	Comparative Study QoL Instrument: mailed questionnaire SF-36 Time point: after ILP, at least 6	QoL assessment n=51 (89%) of 51 patients after isolated limb perfusion median follow up	SF-36 scores	SF-36 scores of the patient group were equal to or better than that of the general population, significantly for bodily pain, general	Assessment after therapy, no baseline data Study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	perfusion (ILP) of the extremities, and to identify the patient-, tumour- and ILP-related factors associated most strongly with the patients' self-reported HRQL.	*months disease free* *Comparison: normative sample of the Dutch general population of SF-36 scores*	*after ILP 14 years (range 3-25 years)*		*health perceptions, and the physical and mental health component scores*		
Petrella et al. 2007	*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*	*systematic review*	*1 systematic review, 5 RCTs, 12 Phase II trials, 1 QoL report*			*excluded (only 1 QoL report)*	
Quirt et al. 2007	*To examine the role of temozolomide in patients with metastatic melanoma*	*systematic review*	*Two randomized phase III trials and three randomized phase II trials*		*only 2 studies with QoL data*	*excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	Outcomes: response rate, progression-free survival, overall survival, quality of life, and adverse effects						
Schallreuter et al. 1991	A quite promising clinical trial was conducted using the new nitrosourea fotemustine	phase II study	19 patients		quality of life of the patients during and after chemotherapy was not severely affected	no QoL assessment study excluded	
Verma et al. 2006	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	systematic review	37 randomized controlled trials, 2 meta-analyses, and 1 systematic review were identified that investigated interferon, levamisole, vaccine, or chemotherapy as adjuvant therapy			only Q-TWiST data, no QoL data presented study exluded	
Sigurdardottier et al. 1993	To assiss the QoL of patients with melanoma before the start of	quality of life (QoL) study QoL instruments:	89 patients		Before treatment the patients reported a relatively low symptom	No assessment under therapy study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	treatment	*- EORTC QLQ-C36 - study-specific melanoma (MM) module -Hospital Anxiety and Depression (HAD) scale*			*burden, good physical and social functioning, moderate psychological distress and a high overall QoL rating 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*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 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 toxicity data of E1684 and E1690* *QoL data of the trials are not presented* *Study excluded*	

5.6.5. Literatur

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Kilbridge KL, Cole BF, Kirkwood JM, et al. Quality-of-life-adjusted survival analysis of high-dose adjuvant interferon alpha-2b for high-risk melanoma patients using intergroup clinical trial data. J Clin Oncol 2002;20:1311-1318
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5.6.6. 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.

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

5.7.1. 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				

5.7.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1.Suche			
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])	30.05.11	1553 (Auswahl 19)
Embase	(melanoma and (treatment or therapy) and (brain or cerebral or CNS)).ti,ab.	11.05.11	1247 (Dedubliziert: 346, 0 dazu)

Datenbank	Suchstrategie	Datum	Treffer
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)

5.7.3. 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 Tumorentitiäten Kombination mit Radiotherapie	
Anzahl nach Abstractscreening, vorgesehen für Bewertung		22
Anzahl ausgewählter Studien nach Handsuche (Durchsicht der Literaturlisten)		0

Auswahl der Literatur	
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	9
Anzahl ausgewählter Volltexte	13 (davon 1 Asco Abstract

5.7.4. Evidenztabelle

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 alone (n=136)	676 HLA-A*0201-positive patients with previously treated unresectable stage III or IV melanoma 82 patients with brain metastases	Median Overall survival Overall Response Rate	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; p<0.001). 5.7% (n=23) vs. 11% (n=15) vs. 1.5% (n=2), sign., p=0.04	Outcomes of patients with brain metastases not reported separately	4
Avril et al. 2004	To compare fotemustine and dacarbazine (DTIC)	RCT Treamtent:	229 patients with metastatic melanoma		Patients with brain metastases n=43 Arm A Fotemustin	Outcomes of patients with brain metastases not	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	in in patients with disseminated cutaneous melanoma	Arm A: Fotemustine Arm B: DTIC	43 patients with brain metastases (Arm A n=22, Arm B n=21)	Response	vs. Arm B DTIC CR n=0 versus n=0 PR n=1 versus n=1 SD not reported PD not reported	reported in detail. Author contacted, no reply	
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 more than 4 years	Lack of control group	4
Amaravadi et al. 2009	To evaluate the combination of the oral alkylating agent temozolomide and the oral multikinase inhibitor sorafenib	Phase II study Treatment: Sorafenib 400mg twice daily + temozolomide	167 patients with metastatic melanoma 53 patients with brain metastases	Response rates	Evaluable patients (Arm D with brain metastases) n=52 CR rate: 0% PR rate: 15%	Response assessed according RECIST criteria, CT every 8 weeks Lack of control	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	in advanced melanoma patients		(Arm D)		SD rate: 48% PD rate: 37%	group	
				6-month PFS rate Median PFS Median OS	23% 3.5 months 8 months		
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 efficacy of the combination of temozolomide and lomustine in melanoma metastatic to the brain	Phase I/II study Treatment: temozolomide + lomustine	26 patients with brain metastases	CNS Response CR+PR SD PD Median OS	Evaluable patients: n=20 n=0 n=10, 50% n=10, 50% 2 months	Response assessed according WHO criteria, CT or MRI after 3.+ 6. cycle (28days/cycle) only 10% of patients received more than 2 cycles of therapy	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						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 Lack of control group	4
Bafaloukos et al. 2004	To evaluate the efficacy and toxicity of temozolomide-	Analyses of patients with brain metastases within 2	25 patients with brain metastases	CNS Response	Evaluable patients: n=24	Response assessed according WHO criteria, CT or MRI	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	based chemotherapy in patients with cerebral metastases from melanoma.	Phase II studies Treatment: temozolomide + docetaxel n=10, temozolomide + cisplatin n=9, temozolomide alone n=6		CR PR SD PD Median OS 1-year survival rate	n=0 n=6 n=5 n=13 4.7 months 20.9%	every second cycle (28 days/cycle) Lack of control group	
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
Chang et al. 1994	To investigate the sequential	Phase II study	34 patients with brain metastases	Response	Evaluable patients: n=34	Tumour response was defined	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	administration of dacarbazine and fotemustine in the treatment of cerebral metastases from malignant melanoma	Treatment: DTIC + fotemustine		CR PR SD Median OS	 n=2 n=2 n=9 duration of complete response: 12, 36+ months 4.5 months	according to World Health Organisation criteria Lack of control group	
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
	metastases			*1 year survival*	*without brain metastases)* *20%*		

5.7.5. Literatur

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Avril MF, Aamdal S, Grob JJ, et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J Clin Oncol 2004;22:1118-1125

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Hwu WJ, Lis E, Menell JH, et al. Temozolomide plus thalidomide in patients with brain metastases from melanoma: a phase II study. Cancer 2005;103:2590-2597

Jacquillat C, Khayat D, Banzet P, et al. Final report of the French multicenter phase II study of the nitrosourea fotemustine in 153 evaluable patients with disseminated malignant melanoma including patients with cerebral metastases. Cancer 1990;66:1873-1878

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Schadendorf D, Hauschild A, Ugurel S, et al. Dose-intensified bi-weekly temozolomide in patients with asymptomatic brain metastases from malignant melanoma: a phase II DeCOG/ADO study. Ann Oncol 2006;17:1592-1597

Vestermark LW, Larsen S, Lindelov B, et al. A phase II study of thalidomide in patients with brain metastases from malignant melanoma. Acta Oncol 2008;47:1526-1530

Weber JS, Amin A, Minor D, et al. Safety and clinical activity of ipilimumab in melanoma patients with brain metastases: retrospective analysis of data from a phase 2 trial. Melanoma Res 2011;21:530-534

6. AG Radiotherapie

6.1. 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?

6.1.1. 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		

6.1.2. 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 (1Studie dazu, Hedblad et al. 2011)
Cochrane Library	s.o.	31.01.12	42 (0 dazu)
Embase	s.o.	23.01.12	3475 (0 dazu)

6.1.3. 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**

6.1.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Wasif et al. 2011	To study the surgical management of desmoplastic melanoma (DM), identify prognostic factors, and impact	Retrospective cohort study	1735 patients with desmoplastic melanoma 143 (8%) of patients in the cohort received adjuvant	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
	of treatment options		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 exicision margin, higher tumor thicknes, 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 desmoplastic	Retrospective cohort study (1976 – 1999)	44 patients with DMM 14 patients with postoperative RT	Local recurrence Local control in re current DMM	Overall: n=21 (48%) Surgery +RT (15 pts)	Possible selection bias, Imbalance of groups, small sample size	4 Cohort study with

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	malignant melanoma (DMM)	Treatment: Surgery alone Surgery + RT, median dose 50 Gy	after local recurrence 1 patient with preoperative RT	Distant metastasis	n=15 Surgery alone (7pts) n=3 nonirradiated patients 35% irradiated patients 40%		imbalance 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. 2002	To perform a	Retrospective	150 patients with	Local recurrence	n=7 (7%)	Lack of control	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	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	Retrospective evaluation Treatment:	174 Stage I-III melanoma patients received postoperative	Local recurrence rate	n=20 (11%) (Group A and B)	Lack of control group No baseline characteristics	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	and postoperative hypofractionated radiation therapy	TD 30-36 grays (Gy), 5-7 fractions, twice weekly	radiation therapy Group A n=32: primary tumor site (Group B n=142: lymph node involvement)	3-years metastasis free survival	60% (Group A)	presented	
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-	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 ecur ttion for	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 r ecur. N=2 Nodal relapse n=2 D+N n=1	Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	regional relapse		nodal relapse		Distant met. N=21		
Storper et al. 1993	To elucidate the 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	Retrospective evaluation Treatment: -surgery (SE), n=26 -primary external beam irradiation (XRT), n=10 -adjuvant external beam irradiation (SE+XRT), n=8	44 melanoma patients with recurrent disease	Survival	SE 19% XRT 20% SE+XRT 37%	Imbalance of prognostic factors between groups Site of RT not mentioned	4
Phipps et al. 1992	To examine the effect of immediately preoperative adjuvant radiotherapy in the surgical treatment of primary cutaneous malignant	Retrospective evaluation (1958-1970) Treatment: All patients: 400 cGy external beam radiotherapy, 52 patients additional single-fraction	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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma	2000 cGy Surgery within 24h					
Elsmann et al. 1991	To facilitate clinical decisions the authors report on their results using soft X-ray therapy of primary melanomas	Retrospective evaluation (1974-1989) 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	83 melanoma patients LMM n=64 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	Local recurrence Survival	n=1 (skin metastasis) RT after total excision n=1 (recurrent tumor nodule) RT without total excision 60%, (melanoma deaths 9.6%, other diseases 30.1%) Follow-up median 42 months	Lack of control group	4
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*
Zygogianni et al. 2011	*To assess the potential impact of radiotherapy (RT) on local control, quality of life and overall survival*	*Review*	*Pubmed 1978 – 2010*			*Non systematic Review, excluded*	
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	*To analyze relevant*	*Retrospective*	*2 917 melanoma*	*Response at 3*	*CR n=7 (64%)*	*<20 patients RT*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
al. 1999	endpoints (tumor response, local tumor control, survival) and to identify prognostic factors for achievement of these endpoints in long-term follow-up (FU)	evaluation Treatment: linac 6-10 MV photons or 4-18 MeV electrons	patients 121 received RT, thereof 11 patients with relapsed/residual MM (UICC IIB)	months Recurrence rate In-field local relapse Regional in-transit metastases	PR n=4 (36%) n=3 (27%) n=2 (18%) n=1 (9%) of 11 patients	primary tumor, study excluded	
Tsang et al.	To report the experience with radiotherapy for lentigo maligna	Retrospective evaluation	54 patients with lentigo maligna			No patients with lentigo maligna melanoma study excluded	4
Umebayashi et al 1995	To answer whether or not the proton beam can provide useful treatment for cutaneous melanoma	Case series Treatment: proton beam, total dose of around 100 Gy, fractionated into single doses of approximately 10 Gy	7 patients with 5 primary melanomas and 3 metastatic lymph nodes	Regression primary melanoma	100% n=1 90% n=2 80% n=1 85% n=1	<20 patients, study excluded	
Rounsaville et al. 1988	Radiotherapy in the management of cutaneous melanoma: effect of time, dose, and	Review				Non systematic Review, excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	fractionation						
Von Rottkay et al. 1987	Radiation therapy in malignant melanoma using accelerated fractionation. Remission and preliminary results of local tumor control	Retrospective evaluation (1982-1985)	14 patients at different clinical stages			<20 patients, different stages, study excluded	
Blake et al. 1985	To report the results of treatment of malignant melanoma by fast neutrons	Retrospective evaluation Treatment: 156OcGy in 12 fractions (4 weeks) or 1395cGy in 6 fractions (2 weeks)	7 patients with primary melanomas (of 48 melanoma patients with 87 tumors)	Response	CR n=6 (86%) of 7 primary melanomas	<20 patients, study excluded	
Overgaard et al. 1980	Radiation Treatment of malignant melanoma	Retrospective evaluation (1970-1980) Treatment: Different fractions and dose schedules	36 patients with 24 skin lesions and 25 lymph node metastases	Response CR PR No response Progression CR PR	skin lesions n=24 n=7 n=10 n=6 n=1 lymph node metastases n=25 n=5 n=10	Baseline characteristics missing primary melanomas and skin metastases are not distinguished study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				No response *Progression*	*n=8* *n=2*		
Tonak et al. 1976	*To present the treatment results of 195 melanoma patients (clinical stages I and II)*					*published before 1980, study excluded*	
Von Lieven et al. 1976	*To investigate the correlation between the total dose needed for a local healing and the period of treatment*					*published before 1980, study excluded*	
König et al. 1970	*Problems in the radiological treatment of malignant melanomas of the skin. Report on 136 patients followed-up over long period of time*					*published before 1980, study excluded*	
Stein et al. 1965	*The avoiding of a combination-effect in combined surgical-radiological treatment of*					*published before 1980, study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	malignant skin tumors						
Hellriegel et al. 1963	*To present radiotherapentic improvements and results in malignant melanomas*					*published before 1980, study excluded*	
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*	

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6.2. 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?

6.2.1. PICO, Suchwörter

PICO - Schema (Intransitmetastasen)			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients with satellite or intransit metastases	radiotherapy	no radiotherapy	PFS, OS

Suchwörter (Instransitmetastasen)				
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			

6.2.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie (Instransitmetastasen)	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
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)

Datenbank	Suchstrategie (Instransitmetastasen)	Datum	Treffer
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)

Datenbank	Suchstrategie (Fernmetastasen)	Datum	Treffer
Embase	s.o.	23.01.12	3032 (0 dazu)
Gesamttreffer			6419

6.2.3. 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 Tumorentitiäten Nicht systematischer Review Publikation vor 1980
Anzahl ausgewählter Volltexte	23
Bermerkungen: Da zum Thema keine ranomisierten 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	

6.2.4. 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 treatment of malignant melanoma	RCT Treatment RT vs RT+Hyperthermia (HT) RT; high voltage photons or electrons	70 patients, 134 lesions, skin lesions: n=93	 Response Overall 5-year Survival Rate	128 evaluable tumors, RT vs RT + HT CR: 35% vs 62% , sign., p=0.003 PR: 37% vs 27% n.s. NR: 28% vs 11% n.s. 68 evaluable patients: 19%	Randomisation based on lesions, not on patients Response assessment was not blinded response was not analyzed separately for node and cutaneous lesions	4 1b (question RT vs RT + HT)
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	Retrospective evaluation	28 patients, 35 sites, bone and soft tissue	Response	Clinical response bone metastases 67%	Response was defined as relief of symptoms	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	radiation therapy in patients with metastatic melanoma	Treatment (most patients): TD 30 or 20 Gy, fraction size 3 or 4 Gy	metastases n=20, brain metastases n=8			Lack of response and survival data	
Seegenschmiedt et al. 1999	To analyze different endpoints and prognostic factors in patients with locally advanced, recurrent or metastatic melanoma	Retrospective evaluation Treatment: median TD 48 (range 20 – 66) Gy, fraction size 2–6 Gy	121 patients of a melanoma registry with 2,917 patients Stage IV n=53 (distant LN, SK, ST mets n=7, visceral organ mets n=46)	Response Suvival Rate (mean follow up 7.8 years)	Stage IV (n=53), at 3 months 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%)	Detailed analyses, large cohort, 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	4
Engin et al. 1993	To present the experience with hyperthermia combined with radiation in advanced melanoma patients between	Retrospective evaluation Treatment: RT mean TD 37 (range 13 – 66) Gy, mean fraction size	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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	1980–1988	3.6 Gy (range 2 – 5.5) combined with hyperthermia					
Pyrhönen et al. 1992	To present 15 patients with histologically proven recurrent or metastatic cutaneous melanomas treated with large fractions between April 1987 and May 1991	Case Series Treatment: Electron beams at appropriate energies (6–15 MeV). A total dose of 40 Gy was given in 8 fractions (fraction size 5 Gy) over 23 days.	15 melanoma patients, 89 treated lesions skin n=68 (76%) transplanted skin n=3 (3 %) subcutaneous n=11 (12%) lymph nodes n=7 (8%)	Response	Evaluable lesions (n=89) CR n=61 (69%) PR n=25 (28%) No response n=3 (3%)		4
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	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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		2850 cGy (range, 500 to 4000 cGy), fraction size 200-800 cGy					
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 permament implants, different doses	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 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	Baseline characteristics are not presented in detail, clinical stages not indicated	4
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 >	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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		600					
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 three San Francisco radiation oncology departments	Retrospective evaluation Treatment: TD range 600 – 7700 cGy, fraction size 180 – 1000	81 patients 29 patients (51 sites) with measurable tumor (Lymph node, skin, liver, mucosa, spleen) 15 patients (28 sites) with bone metastes	Response	Measurable tumor: CR 4 of 51 sites (8%) PR 22 of 51 sites (43%) Bone metastases: 24 of 28 sites (86%)	Definition response in bone metastases: marked regression or elimination of pain	4
Mameghan et al. 1988	To assess the acute skin reaction after treatment and to measure the response of the	Case Series Treatment: Radiotherapy alone (15 lesions)	12 melanoma patients with 32 lesions subcutaneous tissue n=26	Response	All lesions (n=32) CR n=14(44%) PR n=10(31%) No response		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma	Heat therapy alone (6 lesions) Combined radiation and heat therapy (11 lesions)	Lymph node n=5 Cheek n=1		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		
Konefal et al. 1987	To retrospectively analyze the results of 67 cutaneous or lymph node metastatic lesions, focusing on dosetime fractionation and tumor response	Retrospective evaluation (1970-1985) Treatment: TD 18-66 Gy, fraction size 1.5 - 8 Gy, intervals daily to weekly	35 melanoma patients with 67 cutaneous or lymph node metastatic lesions, 30 cutaneous lesions	Response	All lesions (n=67) Overall Tumor Control n=14 CR n=16 PR n=23 No response n=28	Overall tumor control indicates that lesions were controlled at the time of patient´s death or at last follow-up PR was defined as >50% reduction of tumor size	4
Overgaard et al. 1987	To present the experience with hyperthermia and radiotherapy in metastatic	Retrospective evaluation Treatment: - Radiation alone	36 patients, many patients with disseminated disease, 118 lymph node	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	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma patients	(TD 15-30 Gy) n=62 sites - Simultaneous heat plus radiation n=26 - Sequential radiation plus heat n=27 - heat alone n=3	and cutaneous metastases			treated with radiation alone. PR was defined as >50% reduction of tumor size	
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 fractions median 10, range 1-27.	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 separately	4
Blake et al. 1985	Treatment of malignant melanoma by fast neutrons	Retrospective evaluation Treatment: 75 MeV neutron beam, TD 156O or	48 patients, 87 primary, recurrent or metastatic tumors	Response Recurrence	All sites n= 87 CR n=62 (71%) n=8 (9%)	Baseline characteristics are not presented in detail, clinical stages not indicated,	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		1395 cGy in 12 or 6 fractions		Complications	n=19 (22%)	response for primary, recurrent or metastatic lesions was not analyzed separately	
Khan et al. 1984	To evaluate the results of different modes of treatment the records of 182 melanom patients, referred to the Regional Radiotherapy Centre, Newcastle upon Tyne between January 1975 and December 1980 have been reviewed	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 regimes and tumor doses	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 PR 6 (75%) Median duration of remission 7 months (range 1-72)		4
Johanson et al. 1983	To report the the experience of the	Retrospective evaluation	23 patients with recurrent melanoma		n= 23 patients	clinical stages not indicated,	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	Princess Margaret Hospital with large dose per fraction (800 rad) radiotherapy in the curative and palliative treatment of nodular melanoma	(1975-1980) Treatment: TD 2400 rad, fraction size 800 rad, given on day 0, day 7, and day 21		Response	CR, no local recurrence n=7 CR, local recurrence n=2 PR n=5 SD n=3 no response n=6	response was not analyzed separately	
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 fraction irradiation		22 patients, 24 sites, visceral sites n=2				
Katz et al. 1981	To determine if results in the irradiation of soft tissue, visceral, and bone metastases were comparable to	Retrospective evaluation Treatment: TD range 1000 to 6000 rad, fraction size	86 patients 16 patients with visceral metastases (20 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	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	those previously reported in the literature	200 – 1000 rad	32 patients with bone metastases (48 lesions) 8 patients with skin metastases (14 lesions)			the local tumor-associated symptoms	
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 schemes.	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

6.2.5. Literatur

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6.3. 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?

6.3.1. 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		

6.3.2. Datenbanken, Suchstrategien, Trefferzahlen

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)

6.3.3. Auswahlkriterien

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 Tumorentitiäten
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	7

6.3.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Eigentler et al. 2011	To identify prognostic factors in patients with brain metastases (BM) from malignant	Retrospective survival analysis Treatment: SRS + Surgery	692 patients	Median Survival (from date of diagnosis of brain metastases)	Entire cohort (n=672) 5 months SRS + Surgery vs.	Retrospective study large cohort SRS vs. Surgery was not compared	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma	(n=122) WBRT + Chemotherapy (n=92)			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 1.6, 95% CI 1.1-2.4, p=0.01 - Single BM: SRS or surgery vs. WBRT and/or chemotherapy, HR	Funding: in part by an educational grant from Essex/Schering-Plough.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 metastasis surgery (n=63) vs. SRS (n=31): HR 1.0, 95% CI 0.6 – 1.8	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
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 cerebral metastases from melanoma.	Retrospective survival analysis Treatment: surgery+RT (n=158) surgery (n=47) radiotherapy (n=236) supportive care	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. surgery vs. RT vs. supp.care 8.9 vs. 8.7 vs. 3.4	Retrospective study Large cohort results of univariate analyses not shown, only 578 of 686 patients included missing data not adressed Funding:	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		alone (n=210)			vs. 2.1 months multivariate analysis 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)	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 control rates	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 23.1% (95% CI 10-	Early termination of study, small sample size Independent tumor assessment Funding: not mentioned	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				(objective responses + stable disease) after 7 weeks time to cerebral progression	36%) vs. 37.8% (95% CI 22-54%), p=0.16 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 multivariate analysis negative impact on	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
					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*
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*	*Retrospective*	*51 patients*		*Standard vs. high*	*Lack of comparison*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	potential benefit from escalation of the whole-brain radiotherapy (WBRT) dose beyond the "standard" regimen 30 Gy in 10 fractions	*analysis, Cohort study* *Treatment: WBRT* *10x3 Gy (n = 33)* *40 Gy/20 fractions (n = 11)* *45 Gy/15 fractions (n = 7)*		*6 months survival (OS)* *12 months OS* *6 months local (intracerebral) control (LC)* *12 months LC*	*dose* *27% vs. 50% (p = 0.009)* *4% vs. 20%* *23% vs. 50%* *0% vs.13%.*	*group → study excluded*	
Redmond et al. 2008	*To investigate which patient- or treatment-specific factors influence survival of patients with melanoma brain metastases*	*Retrospective analysis, Prognosis study* *Treatment: GKS*	*59 patients*		*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)*	*Lack of comparison group → study excluded*	
Mathieu et al. 2007	*to assess clinical outcomes and*	*Retrospective analysis, Prognosis*	*244 patients*	*median survival*	*5.3 months*	*Lack of comparison group → study*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	identify prognostic factors for survival and cerebral disease control after Gamma knife radiosurgery	study Treatment: GKS		Sustained local control	86.2% of tumors	excluded	
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	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%	Lack of comparison group → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(Linac)-based stereotactic radiosurgery (SRS)				*Addition of WBRT to maintain control of brain metastases in a subset of patients did not improve survival*		
Christopoulou et al. 2006	*To investigate the effect of gamma knife surgery on the local control of cerebral metastases from melanoma and to assess survival*	*Retrospective analysis* *Treatment: GKS*	*29 patients*	*local control* *median survival from gamma knife surgery*	*61.5% of 96 metastases regressed by more than 50% of the pretreatment volume, 25% regressing by more than 90% and 13.5% completely* *5.7 months*	*Lack of comparison group → study excluded*	
Gaudy-Marqueste eta l. 2006	*To assess retrospectively a strategy that uses Gamma-Knife radiosurgery in the management of patients with brain metastases of*	*Retrospective analysis* *Treatment: GKS*	*106 patients, 221 brain metastases*	*Median survival from the time of GKR* *Control rate* *complete response* *partial response*	*5.09 months* *83.7%* *14% (14 BMs)* *42% (41 BMs)*	*Lack of comparison group → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	malignant melanoma			stabilization	43% (43 BMs)		
Koc et al. 2005	To evaluate retrospectively the effectiveness of Gamma Knife radiosurgery for intracranial metastatic melanoma and to identify prognostic factors related to survival	Retrospective analysis Treatment: GKS	26 patients, 72 brain metastases	Overall median survival after GKS 1-year survival	6 months 25%	Lack of comparison group → study excluded	
Meier et al. 2004	to determine the factors influencing survival in a retrospective review of patients with melanoma brain metastases to permit more specific recommendations regarding therapy	Retrospective survival analysis Treatment: WBRT (n=54) surgery (n=37) SRS (n=17) chemotherapy (n=38)	100 patients	median overall survival 6-month survival 1-year survival 2-year survival	Entire cohort (n=100) 4.8 months 36% 14% 5% WBRT vs. surgery vs. radiosurgery vs. chemotherapy vs. temozolomide	< 20 patients in one of the treatment groups → study excluded Only 63 patients included in multivariate analysis due to missing data	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					5.5 vs. 10.6 vs. 10.3 vs. 6.6 vs. 10.1 months		
Morris et al. 2004	To determine the outcome of patients with metastatic malignant melanoma (MMM) treated with palliative whole brain radiotherapy (WBRT)	Retrospective analysis Treatment: WBRT	112 patients	median survival after WBRT	51 days (range 3-1386)	Lack of comparison group → study excluded	
Radbill et al. 2004	To identify associated prognostic indicators for patients receiving gamma knife (GK) radiosurgery in the initial treatment of intracranial melanoma metastases	Retrospective analysis Treatment: GKS	51 patients, 188 brain metastases	median overall survival from time of GKS	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)	Lack of comparison group → study excluded	
Stone et al. 2004	To evaluate overall survival in patients with brain	Retrospective survival analysis	91 patients	Overall Survival	A survival benefit of 7.3 months (p = 0.05) was found to	< 20 patients in one of the treatment groups	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastases from malignant melanoma	*Treatment:* *SRS+WBRT (n=8)* *Surgery + WBRT (n=16)* *WBRT (n=59)*			*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.*	*→ study excluded*	
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*	*Retrospective*	*64 patients, 122*	*Median survival*	*10.6 months*	*Lack of comparison*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	radiosurgery is an alternative option to neurosurgical excision in the management of patients with brain metastases.	*analysis* *Treatment: Stereotactic radiosurgery*	*brain metastases*	*1 year local control*	*81%*	*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)* *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,*	*< 20 patients in one of the treatment groups → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					and 1.1 months (0.1–3.0 months) for the group that received no therapy		
Gonzales-Martinez et al. 2002	to evaluate retrospectively the effectiveness of stereotactic radiosurgery for intracranial metastatic melanoma and to identify prognostic factors	Retrospective analysis Treatment: stereotactic radio surgery	24 patients, 115 lesions	mean survival after radiosurgery	5.5 months no difference in terms of survival between patients who underwent WBRT or chemotherapy and those who did not significant difference ($p < 0.05$) in mean survival was observed between patients receiving immunotherapy or those with a Karnofsky Performance Scale (KPS) score of greater than 90	Lack of comparison group → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 3- month 6- month 12-month	8 months 75 +/- 9% 53 +/- 10% 29 +/- 10% n=5 (9.8%) 95 +/- 3% 90 +/- 5% 84 +/- 7%	Lack of comparison group → study excluded	
Yu et al. 2002	To identify important prognostic factors predictive of survival and tumor control in patients	Retrospective analysis Treatment: GKS	122 patients, 332 intracranial melanoma metastases	median overall survival from time of radiosurgery	7.0 months	Lack of comparison group → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	with metastatic melanoma to the brain who underwent gamma knife radiosurgery						
Zacest et al. 2002	to review the outcome of patients who underwent surgery for treatment of cerebral metastatic melanoma	Retrospective analysis Treatment: surgery	147 patients	median survival from the time of surgery	8.5 months	Lack of comparison group → study excluded	
Ellerhorst et al. 2001	To obtain a description of the population offered WBRT	Retrospective analysis Treatment: WBRT	87 patients	median survival	19 weeks	Lack of comparison group → study excluded	
Konstadoulakis et al. 2000	To evaluate the prognostic parameters and treatment modalities of malignant melanoma patients with brain metastases	Retrospective analysis Treatment: Surgery surgery + radiotherapy (n=2) surgery + chemotherapy	136 patients	1-year survival rate	surgery 28.3% radiotherapy and/or chemotherapy 6.67% no treatment 3.45% (p=0.006)	Subgroups < 20 patients→ study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		(n=17)					
Lavine et al. 1999	To analyze the effectiveness of Leksell gamma unit therapy for metastatic melanoma to the brain	Retrospective analysis Treatment: GKS	45 patients, 59 Leksell gamma unit treatment sessions	Median overall survival from the time of gamma knife treatment improved or stable neurological symptomatology local tumor control rate	8 months (range, 1-20 months) 78% 97%	Lack of comparison group → study excluded	
Friehs et al. 1998	To determine the effectiveness of gamma knife radiosurgery in patients with malignant melanoma metastases	prospective multicenter study Treatment: GKS	45 patients, 96 lesions	median overall survival tumor control	4.2 months 86% of lesions	Lack of comparison group → study excluded	
Sampson et al. 1998	To identify demographic factors associated with the development of clinically significant	Retrospective survival analysis Treatment: Surgery (n=52) Surgery+WBRT	702 patients	median overall survival	Entire cohort (n=702) 3.7 months surgery vs. surgery+WBRT vs. WBRT vs.	no multivariate analysis included → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	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	*(n=87) WBRT (n=180) Chemotherapy (n=205) Symptomatic treatment (n=178)*			*chemotherapy: 8.8 vs. 6.4 vs. 3.9 vs. 1.3 months*		
Fletcher et al. 1998	*To reviewe the results of surgical resection*	*Retrospective analysis* *Treatment: surgery*	*77 patients, different sites, brain n = 12*			*<20 patients with brain metastases → study excluded*	
Grob et al. 1998	*To evaluate the effectiveness of radiosurgery without whole brain radiotherapy in the palliative treatment of melanoma brain metastases*	*Retrospective analysis* *Treatment: radiosurgery*	*35 patients*	*Median overall survival* *local control rate at*	*22 months (solitary brain metastasis) 7.5 months (single brain metastasis + metastases elsewhere) 4 months (multiple brain metastases) 98.2% (55/56*	*Lack of comparison group → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				3 months	metastases)		
Mori et al. 1998	To evaluate results after stereotactic radiosurgery (SR) for patients with metastastic melanoma to identify patient outcomes and factors for survival	Retrospective analysis Treatment: SR alone n=9 SR+WBRT n=51	60, 118 melanoma brain metastases	Median survival after SR local control rate of evaluable tumors (n = 72) disappearance shrinkage stable	7 months 90% 11% 44% 35%	< 20 patients in one of the treatment groups → study excluded	
Seung et al. 1998	To evaluate the efficacy and toxicity of gamma knife radiosurgery in the treatment of melanoma metastases to the brain	Retrospective analysis Treatment: GKS	55 patients, 140 lesions	median overall survival	35 weeks 35 weeks for patients with solitary metastases versus 33 weeks for those with multiple metastases	Lack of comparison group → study excluded	
Gupta et al. 1997	To report the experience of 31 patients who presented with cerebral metastasis of cutaneous melanoma	Retrospective analysis Treatment: Surgery (n=17) Surgery + radiotherapy (n=6)	31 patients	median overall survival	4 months	< 20 patients in one of the treatment groups → study excluded	

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*LoE*
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 metastases*	*Retrospective analysis* *Treatment: Surgery alone n=12 Surgery + WBRT n=22*	*34 patients, 34 brain metastases*		*Overall survival was significantly improved in the 22 patients who received adjunctive cranial irradiation versus that in the 12 patients who had surgery alone*	*< 20 patients in one of the treatment groups → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 tomographic brain scans performed on 41 patients with*		*41 patients*			*No survival + efficacy data → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cerebral metastases from malignant melanoma was undertaken						
Hagen et al. 1990	To report treatment results of patients with brain metastasis from melanoma	Retrospective analysis Treatment: Surgery + postoperative radiation n=19 Surgery alone n=16	35 patients		Group A had a longer interval to CNS relapse compared with group B, but survival was similar.	< 20 patients in one of the treatment groups → study excluded	
Oredsson et al. 1990		Retrospective analysis Treatment: Surgery	40 patients	median survival 3-year survival 5-year survival Neurological improvement surgical mortality rate	8 months 25% 15% 25 patients less than 5% Quality of life as judged by Karnofsky	Lack of comparison group → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					index was improved after surgery and maintained on an acceptable level for the remaining time of survival		
Guazzo et al. 1989		Retrospective analysis Treatment: Surgery	31 patients	Significant and life-threatening complications relief of symptoms:	5 patients (17%) 64% had complete remission of symptoms while a further 20% were substantially improved	Lack of comparison group → study excluded	
Mendez et al. 1988		Retrospective analysis Treatment: Surgery, Radiotherapy	55 patients with neurological signs and symptoms secondary to metastases to the brain	6 month survival	58% if surgical excision was possible	< 20 patients in one of the treatment groups → study excluded	
Rate et al. 1988	To review the records of all patients receiving palliative	Retrospective analysis Treatment:	77 patients with brain metastases	median survival from the initiation of radiotherapy	14 week	Lack of comparison group → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	radiotherapy for malignant melanoma metastatic to brain, to bone, or with spinal cord compression	Radiotherapy					
Retsas et al. 1988		Retrospective analysis Treatment: Different treatments	100 patients	Median survival	2.5 months	Lack of comparison group → study excluded	
Wornom et al. 1986		Retrospective analysis Treatment: surgery	65 patients, 94 metastatic lesions (brain, lung, abdomen, distant subcutaneous sites, and distant lymph nodes)	Median survival after excision of brain metastases Relief of symptoms	8 months 77% of brain metastases	Lack of comparison group → study excluded	
Ziegler et al. 1986	To examine the records of 72 patients who received various regimens of radiotherapy for cerebral metastases	Retrospective analysis Treatment: WBRT 300 cGy (conventional	72 patients		No difference in response could be attributed to dose schedules, either overall or in the subgroups of patients who had	Lack of comparison between different treatments → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	from malignant melanoma	fractionation, CF) vs. 500-600 cGy (high-dose-per-fraction, HDF) to a total of 3000 cGy			solitary or multiple brain metastases		
Choi et al. 1985		Retrospective analysis Treatment: WBRT	194 patients with intracranial metastatic melanoma			Lack of comparison group → study excluded	
Stridsklev et al. 1984	To analyze patients who completed whole-brain irradiation treatment for brain metastases from malignant melanoma	Retrospective analysis Treatment: WBRT	39 patients	Median survival clinical improvement objective regression of the brain metastases	2 months n=21 (53.8%) 6 of 15 evaluable patients (40%)	Lack of comparison group → study excluded	
Madajewicz et al. 1984	To review 8 years of Roswell Park Memorial Institute's (RPMI) experience with the management of	Retrospective analysis Treatment: None (n=15)	125 patients with brain metastases (73% multiple metastases)	median survival	The median survival of the untreated group of patients was 3 weeks as compared with that of 6 weeks for the	< 20 patients in one of the treatment groups, no multivariate analysis→ study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	malignant melanoma CNS metastases (1972-1980)	*Steroids (n=17) radiotherapy (n=23) surgery (n=20) chemotherapy*			*patients 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*	*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
		brain metastasis treated with RT (n = 17) 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	Retrospective analysis	63 patients	Response	73% to corticosteroids	< 20 patients in one of the treatment	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	received radiotherapy for melanoma metastatic to brain (63 patients	*Treatment: corticosteroids, radiotherapy, surgery (n=8)*			*42% to radiotherapy*	*groups → study excluded*	
Carella et al. 1980	*To determine the response to whole brain irradiation*	*Retrospective analysis* *Treatment: WBRT*	*60 patients*	*Median survival*	*Study 1 patients 10 weeks (range 1-200) vs. Study II patients 14 weeks (range 1-76)* *significant benefit from radiation therapy in terms of symptomatic and neurologic function improvement. Symptomatic improvement was observed in 76%, with 31% completely improved*	*Lack of comparison group → study excluded*	
Cooper et al. 1980		*Retrospective analysis* *Treatment:*	*30 patients, 35 courses*		*Marked improvement in neurologic status occurred in*	*Lack of comparison group → study excluded*	

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*LoE*
		WBRT			*approximately 35%. Slight to moderate improvement was evident in an additional 35%.*		
Hafstrom et al. 1980		*Retrospective analysis* *Treatment: Surgery*	*25 patients*	*median survival*	*5 months*	*Lack of comparison group → study excluded*	
Pennington et al. 1975		*Retrospective analysis* *Treatment:* *Radiotherapy, chemotherapy, surgery and immunotherapy*	*57 patients*			*Publication <1980 → study excluded*	

6.3.5. Literatur

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6.4. 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?

6.4.1. 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

6.4.2. 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	04.11.11	455

Datenbank	Suchstrategie	Datum	Treffer
	"lymph nodes"[tiab] OR "nodal "[tiab] OR "lymphoid tissue"[MeSH])		
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)

6.4.3. 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

6.4.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Burmeister et al. 2012	To compare adjuvant radiotherapy with observation alone in patients at high risk of lymph-node field relapse who had undergone therapeutic lymphadenectomy for metastatic melanoma in regional lymph nodes	Multicenter randomized study Treatment: Group A: surgery alone n=127 Group B: surgery + RT (TD 48Gy, 20 fractions) after lymphadenectomy, n=123	250 patients after lymphadenectomy	**Lymph node field relapse** Relapse-free survival Overall survival	Surgery alone vs. Surgery + RT 34 patients vs. 20 patients relapsed (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)	Jadad Score 3 Limitations: high number of ineligible patients Funding: National Health and Medical Research Council of Australia, Cancer Australia, Melanoma Insitute Australia and the Cancer Council of South Australia	1b
Gojkovic-Horvat et al. 2011	To determine the efficacy of and criteria for postoperative radiotherapy (PORT) in patients with palpable melanoma metastases to the	Retrospective cohort study Treatment: Group A: surgery alone, n=64 Group B: surgery +	101 patients, 103 nodal dissections	Recurrence	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%)	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
	groin	RT (TD range 50 – 72 Gy, fraction size 2 – 3 Gy), n=37		2-year regional control rates 2 years overall survival	(p=0.431) 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,	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
					better survival p=0.005 control rates / regions: Axillary 90 vs. 70% inguinal 80 vs. 72% cervical 85 vs. 50% Subgroup extracapsular extension: RT <50Gy vs. RT <50Gy 5 year regional control 80 vs. 35%, p=0.03		
Strojan et al. 2010	To review experiences in the treatment of regionally advanced melanoma to the neck and/or parotid with adjuvant radiotherapy.	Retrospective cohort study Treatment: Group A: surgery alone, n=40 Group B: surgery + RT (median eqTD2 60 Gy, range 47.8-78.8, fraction size 5	83 patients after surgery on metastases to the neck and/or parotid gland lymph nodes, no distant metastases	2-year regional control rates 2-year distant metastasis-free survival rates 2-year survival	Surgery alone vs. Surgery + RT 56% (CI 40-72%) vs. 78% (CI 63-92%) (p =0.015) 55% (CI 40-70%) vs. 40% (CI 25-56%), n.s. 51% (CI 36-66%) vs.	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,	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Gy, range 2-6 Gy), n=43		rates (all deaths considered as events)	58% (CI 42-73%), n.s.	nonradical surgery, less systemic immunotherapy with interferon) a risk factor score was used for 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%,	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
					p<0.0001 inguinal 69 vs. 69%, n.s. multivariate analysis: DMFS and DSS both were influenced by the 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	Retrospective cohort study	64 patients with nelanoma neck node metastasis		Surgery alone vs. Surgery + RT	retrospective study, short median follow-up (2.5	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	regional control of melanoma neck node metastasis.	Treatment: Group A: surgery alone, n=24 Group B: surgery + RT (TD 24 – 36 Gy, fraction size 6 Gy) n=40		2-year ipsilateral regional recurrence rate 2-year disease-free survival (DFS) 2-year overall survival (OS).	46% vs. 18%, n.s. (p=0.16) multivariate analysis: significant reduction of the RR rate after correction for the number of involved nodes (p=0.04) 29% vs. 18%, n.s. (p=0.30) 58% vs. 26%, n.s. (p=0.07)	years), small sample size,-Imbalance of prognostic factors between the groups	
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	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	retrospective study, large series, imbalance of groups: the surgery plus RT group includes significantly less patients with microscopic than	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		(range 30 – 60 Gy, most patients: fraction size 5.5 Gy, 2x/week) n=129			radiotherapy multivariate analysis: ulceration in the primary tumor: only significant independent predictor of regional recurrence (p = 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)	macroscopic disease and significantly more patients with extensive surgery	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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. Groups were treated in 2 different german centres using the same follow up schedule. missing data, e.g. median follow up, p-values	3b
Shen et al. 2000	To examine the incidence of cervical recurrence among patients who did not receive	Retrospective cohort study Treatment: Group A: surgery	217 patients with head and neck melanoma after regional lymph node dissection	Cervical recurrence rate	Surgery alone vs. Surgery + RT 14% (25/183) vs. 15% (2/13), n.s.	Baseline characteristics for the surgery+RT group were not indicated, no	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	postoperative radiotherapy after surgical management of nodepositive head and neck melanoma	alone, n=196 Group B: surgery + RT (treatment Schedule not indicated) n=21		5 years overall survival 5 years disease free survival	32% 21% mulitvariate analysis: extranodal disease: only independent predictor for cervical recurrence	statistical analyses for this group due to small sample size, retrospective study	
O'Brien et al. 1997	To analyze the influence of the number of positive nodes, extracapsular spread, and the use of adjuvant radiotherapy on regional control and survival	retrospective 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)	143 patients after neck or parotid dissection, 152 lymphadenectomy sites	Local recurrence 5 years survival	Surgery alone vs. Surgery + RT 18.7% (20 of 107) vs. 6.5% (3 of 45), p=0.055 35% vs. 40%, n.s.	retrospective study, imbalance of groups, difficult to compare data for recurrence with other studies as they do not refer to patients but to irradiated sites.	3b
Creagan et al. 1978	To assess the role	RCT	56 patients after		Surgery alone vs.	Limitations:	2b poor

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of postoperative radiation therapy directed to the regional node area in patients undergoing lymphadenectomy for metastatic melanoma	Treatment: Group A: surgery alone, n=29 Group B: surgery + RT (TD 5000 rad, fraction size 2500 rad) n=27	lymphadenectomy	Time to recurrence Survival	Surgery + RT 9 months vs. 20 months, n.s. (p=0.07) 22 months vs. 33 months, n.s. (p=0.09)	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	quality RCT

6.4.5. Literatur

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6.5. Frage VI.6. Fraktionierung

Frage VI.6. Hat das Fraktionierungsschema einen Einfluss auf die Effektivität der Radiotherapie bei Melanompatienten?

6.5.1. 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		

6.5.2. 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]))	14.07.11	216 (Auswahl 9)
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation) and fraction*).ti.	14.07.11	3 (Overgaard, Chang, Sause – alles Dubletten, 0 dazu)
Embase	(melanoma and (radiotherapy or radiation or irradiation) and fraction*).ti.	11.05.11	49 (Katz – Dublette)
Update Suche			
Medline	s.o.	31.01.12	221 (0 dazu)
Cochrane Library	s.o.	31.01.12	3 (0 dazu)
Embase	s.o.	23.01.12	52 (0 dazu)

6.5.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	276
Einschlusskriterien	RCT´s Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kombinationstherapien

Auswahl der Literatur	
	Kollektive mit gemischten Tumorentitiäten Arbeiten älter als 1980
Anzahl nach Abstractscreening, vorgesehen für Bewertung	9
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	7
Anzahl ausgewählter Volltexte	2

6.5.4. 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	RCT Treatment:	14 patients, 35 skin and lymph node metastases	Response	Group A vs. Group B: no significant differences	Randomization scheme not described,	2b low quality RCT

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	schedules in recurrent or metastatic malignant melanoma	Group A: 9 Gy X 3, 2 fractions per week Group B: 5 Gy X 8, 2 fractions per week			CR n=11 (65%) vs. n=13 (72%) PR n=5 (29%) vs. n=5 (28%) NC n=1 (6%) vs. n=0 (0%)	assessment not blinded, lesions not patients were randomized, very heterogeneous population, small sample size	

6.5.5. Literatur

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7. AG Nachsorge

7.1. Frage VII.3. Selbstuntersuchung im Rahmen der Nachsorge - Adaptation

Frage VII.3. Sollte die Selbstuntersuchung ein Bestandteil der Nachsorge sein?

7.1.1. 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

7.1.2. Empfehlung, Hintergrundstext 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	S. 122 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	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:	S. 51 Suivi Stade I AJCC Standards […] ■ éducation du patient à 'autodépistage d'un nouveau mélanome et à l'autodétection d'une récidive. *Nachsorge* *Stadium I nach AJCC* *Standards* *[…]* ■ *Anleitung des Patienten zur Selbstuntersuchung auf ein neues Melanom und zur selbständigen Erkennung eines Rezidivs.* Stades IIA et IIB AJCC Standards […] ■ éducation du patient à

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
			l'autodépistage d'un nouveau mélanome et à l'autodétection d'une récidive. *Stadien IIA und IIB* *Standards* *[…]* ■ *Anleitung des Patienten zur Selbstuntersuchung auf ein neues Melanom und zur selbständigen Erkennung eines Rezidivs.* Stades IIC et III AJCC Standards […] ■ éducation du patient à l'autodépistage d'un nouveau mélanome et à l'autodétection d'une récidive. *Stades IIC et III AJCC* *Standards* *[…]* ■ *Anleitung des Patienten zur Selbstuntersuchung auf ein neues Melanom und zur selbständigen Erkennung eines Rezidivs.*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
Hintergrundtexte	S. 121 - 122 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 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.	S. 370 (Guideline Evidence Review) Patient self examination The questions *In the follow-up of patients with skin cancer, what is the usefulness of education for self examination?* The nature of the evidence Twelve papers were identified representing eleven studies (with one RCT reported at two stages of follow-up) as follows: • 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 Only one study originates from the UK. Seven studies are from the US, one study is from Australia and two studies	S. 51 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. Pour les mélanomes de stade I AJCC qui présentent globalement un faible risque de récidive, l'examen clinique annuel ou biannuel 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). Les autres examens d'imagerie (à la recherche de métastases à distance) n'ont pas apporté la preuve qu'ils pouvaient influer sur la survie en partie du fait de l'absence de thérapeutique

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
	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] 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 concern over travelling times, costs, brevity of consultations, and poor continuity. 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	are from Italy. Generalisability to the UK is therefore limited. 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. Summary of the supporting evidence for the recommendations Self examination (SE) versus physician examination There is consistent evidence that expert physician examination has greater 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	efficace à ce stade. 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 *evidence-based* 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. CONFRONTATION 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

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
	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. Evidence summary 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 LoE: IV References: 14-16 Self-examination may be combined, if appropriate, with routine follow-up by the patient's preferred health professional	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. Factors affecting SE 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 examination are: • skin awareness • habitual sun protection • previous benign skin biopsy • family cancer history	stades II et III AJCC (option, accord d'experts). L'examen clinique complet et l'éducation à l'autodépistage du patient restent le standard. 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. S. 51 *BEGRÜNDETES URTEIL DER EXPERTEN* *[…]* *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 Selbstuntersuchung.* *Bei Melanomen im Stadium I nach AJCC, die insgesamt ein geringes Rezidivrisiko haben, wird die jährliche oder zweijährliche klinische*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
	LoE: IV References: 14-16	• 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 The same level of evidence suggests that older patients may be less likely to perform SE. Rates of SE 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	*Untersuchung die Erkennung eines eventuellen zweiten Melanoms zum Ziel haben.* *Für Patienten in den Stadien II und III nach AJCC kann eine Lymphknoten-Sonographie des Abflussgebietes als Option ins Auge gefasst werden (Expertenmeinung).* *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.* *Durch das Fehlen von Studien zum Thema Nachsorge und Nachsorge-Intervalle scheint es nicht möglich, aus der Literatur evidenzbasierte Schlussfolgerungen zu ziehen.* *Daher beruhen die gegebenen Empfehlungen nur auf Expertenmeinung und spiegeln einen Konsensus für eine minimale Nachsorge basierend auf vollständiger klinischer Untersuchung und Anleitung*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		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. 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. Benefit of SE Case control study evidence suggests that SE is associated with a marginally significant reduced risk of melanoma	*des Patienten zur Selbstuntersuchung wider.* *GEGENÜBERSTELLUNG* *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.* *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.*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		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 and performance of SE are associated with thinner melanoma tumours. • 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	

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		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 dermatological assessment for both common and atypical naevi and concluded that SE of melanoma risk is not reliable. • 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.	

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		• 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 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. • 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	

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		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, awareness and confidence increased in both groups at immediate follow-up ($p < 0.0001$) but there were no significant differences in scores	

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		between the photography group and the brochure group. • 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 auf NMSC.	Keine Literaturangaben zu Fragen der Selbstuntersuchung; Angaben sind

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
			daher nur konsensbasiert.

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LL GB NICE 2006

Siehe Evidence Table 5.3, S. 375 – 379 des Guideline Evidence Review

7.2. 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?

7.2.1. 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.)		

7.2.2. 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
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
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.			

7.2.3. 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
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 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		

Auswahl der Literatur
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.) identifiert wurden, sind in der Tabelle „I.6, I.7, I.8, VII.6_kurz“enthalten.

7.2.4. 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 10-year recurrence-free survival was 78.9% (95% confidence interval 73.1-90.5); in stage	Very large and multi-center patient cohort	1b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					I, 89.0%; stage II, 56.9%; and stage III, 36.0%. HR for recurrent CM: - Stage IA: constantly low level HR </= 1:125 per year - stage IB: higher HRs >/= 1:40 for the first 3 years and generally in stages II to III 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-up HR of all 3 stages did not differ		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					significantly. Of all patients 2.3% developed secondary melanomas, with a consistently low HR < 1:220 per year		
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	Sensitivity Specificity Positive predictive value (PPV) negative predictive value (NPV) Survival relapse-free survival overall survival 2- and 4-year survival rates	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%. 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%	No information about the examiner (blinded for the results of the other examination?)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(95% CI: 99.6-100.0%. B-scan was highly superior to physical examination (P = 0.001). Out of 242 proven melanoma metastases, 24.8% were detected by both methods simultaneously. Survival curbes: see full-text		
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	Systematic review (without meta-analysis)	72 articles included Given separately for every included study (see original article)	Various	first recurrence: - 20-28% local or in-transit recurrences - 26-60% regional recurrences - 15-50% distant metastases Ultimately	Systematic literature search, but no meta-analysis (no summary of effect measures)	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	follow-up.				- 3-5% local or in-transit recurrence - 5-13% regional nodes - 3-10% distant metastates 62% of patients detected their first recurrence themselves frequency of late recurrences (DFS>10 years) between 1% to 25% Incidence of subsequent PM: 2% to 7% Optimum frequency and length of follow-up services: no true evidence for follow-up surveillance in		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					localised melanoma according to the articles In no study any benefit in DFS or OS associated 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		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients: 98.5%, 90.9%, 98.5% and 90.9% sensitivity, specificity, PPV and NPV of PET-CT for 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	Prospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					superior with regard to detection of metastases compared with clinical investigations alone (P<0.0001) 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.	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	Big patient cohort	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	Secondarily, to estimate the effect of prognostic factors on development of recurrence or SPM				that requires far fewer visits (3,000 fewer visits per 1,000 patients) than recommended by current guidelines. AJCC substage= predictor of 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	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	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	sensitivity of MRI not determined because of the low incidence of brain metastases. Small population	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	and brain MRI.			value (NPV) positive predictive value (PPV) False-positives (FP) False negatives (FN)	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: Brain metastases in 1 patient (2%). NPV: 100% specificity: 100% PPV of an elevated serum S-100B: 50% (S-100B level>0.10 µg/L). Of the 23 patients with a true positive PET/CT scan, 6 (26%) received		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					surgical treatment with curative intent; 17 (74%) received palliative treatment or supportive care. 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).		
Brown RE et al. (2010)	to determine the clinical efficacy of routine CXR for recurrence surveillance in melanoma.	Diagnostic study	1,235 patients with invasive cutaneous melanoma ≥1.0 mm in Breslow thickness and without clinical evidence of regional or distant metastases	Sensitivity Specificity PPV NPV	210 patients (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	post hoc analysis on data from a prospective, randomized, multiinstitutional study on melanoma (Sunbelt Melanoma Trial) no information about reference standard	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					falsely positive (FP). 0.9%(n = 38) of all CXR obtained were true positives (TP). Sensitivity and specificity: 7.7% and 96.5%, respectively.		
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 factcors for survival (Cox regression analysis): - patient's age - sex - tumor localization, - pT - pN. median time to first recurrence: 24 months. 5-recurrence-rate: 81.6%	Retrospective review (prospective database) Large patient cohort	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					late recurrences-rate (>10-years): 6.5% independent factors for time to recurrence. (Cox regression analysis) - age at primary - treatment - pT - pN - type of recurrence were found to be independent factor influencing survival after a first recurrence: - type of recurrence (advanced age at diagnosis of recurrence male sex marginally significant)		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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	disease-specific mortality Overall survival (OS) Survival after recurrence (SAR) Adjusted survival time by using sjourn time	disease-specific mortality: 69.6% (n=78). Overall 10-year survival rate: 36.1% 10-year SAR survival rate: 25.4% 10-year OS probability for detection in early phase: 42.6% for early phase vs. 25.6% for advanced phase (P = 0.012) Adjustment for 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	Adjustment for important confounding factor Estimated sojourn time (no evidence base available) Missing data in 10 of 112 patients for Cox proportional hazard model	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 survival: age, gender, location, ulceration On CS analysis:	Very large patient cohort Only available study which gives data for this outcome (conditional survival) CS is a function of the traditional survival estimates, adjusted to reflect	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- survival differences until 8 years after treatment - 10-year survival rates: low-risk :95.4% high-risk: 91.7% P = 0.51 On Multivariate analysis: age, gender, location, ulceration: no longer predictive after 8 years	the probability of survival conditioned on living to a certain point in follow-up the low-risk category: T2-T3, N0 high-risk category T4N0 or T2-4N1-3	
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 compliance, anxiety and depression, as	RCT	142 melanoma patients free of recurrent disease	Patient satisfaction measured by questionnaire Adherence to guidelines Health status measured by SF-36 Anxiety and	cluster-adjusted mean summary satisfaction score: - at baseline no significant difference between groups - at follow-up significantly lower in the intervention group 26.4 (95% CI:	Reliable randomization design; blinding not possible Study took place in Scotland; transferability to German health care system?	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	well as health status.			depression measured by the Hospital Anxiety and Depression Scale HADS	24.9–27.9) vs 33.5 (95% CI: 32.5–34.4), 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 SF-36 scores and HADS score: no statistically significant differences between groups at either baseline or follow-up.		
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)	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Tarhini AA et al. (2009)	To asses the effect of elevated serum S100B level at baseline and during therapy.	Progostic study	Sera from 670 patients with high risk melanoma (≥stage IIB disease) banked at baseline and 3 additional time points were tested for S100B	Overall survival (OS) RFS	median OS time: 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	Patients were included in an intergroup trial E1694 was a randomized comparison of heGM2ganglioside vaccine (GMK) versus HDI that accrued 880 patients. No information about staging	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					significant prognostic factors for RFS and OS. Lower S100B 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	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
					examination and LN sonography: - stage 14289€/4391$ and 18035€/131423$ - stage II: 500€/512$ and 1333€/9712$ - stage III: 168€/171$ and 1250€ /9112$, respectively. Cost for CR to detectof one 1 recurrence: - stage I: 22886€/20 512$) (stage II and III: see full-text) Total costs amounted to 990.8€/2208$ per patient (stage I) and up to 1841€/ 4009$ per patient		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(stage III)		
Egberts et al. (2009)	to investigate whether a serial analysis of protein S-100B in serum with a luminescence immunoassay compared with routine LDH assessment could be of value as an indicator of melanoma progression	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 patients progressing to stage IV: S-100B: 53.8% vs. LDH: 23.1% (P=0.008) Specificity 98% for both S-100B and LDH PPV: S-100B% 73% vs. LDH: 64%	Treatment bias: Patients were treated with different adjuvant therapies	2b
Moore Dalal et al. (2008)	to determine the effect of the method of detection of initial recurrences and timing of visit on	Prognostic study	198 Clinical stage I/II patients who developed recurrence after SLNB and who were evaluable for	Method of recurrence detection Prognistic factors of survival	Median follow-up after first recurrence: 17 months. Self-detection of		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	post-recurrence survival in patients undergoing SLN biopsy		longterm follow-up		recurrences in 55% of patients, 78% were seen earlier than their scheduled visit. Self-detected physical diseases: -24% in-transit -23% nodal Physician detection in 45%, in 46% by a scheduled radiographic test (CXR 16%; CT 29%; PET 1%). method of detection significantly predicted post-recurrence survival ($p<0.05$) Multivariate analysis		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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		
Hengge et al. (2007)	to analyze the follow-up of 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.	Economic analysis	526 melanoma patients stage I-III	Recurrence Method of examination Direct medical costs per metastasis QALYs	Detection of 57 recurrences in stages I-III (5-year follow-up period), 61% detected by physician and 39 % by patients. Detection of 25 SPM. The total costs for melanoma follow-up in stages I-III for the 5-year term at the tertiary care university center accounted for	Retrospective data Patients kept only about 75% of follow-up appointments (real costs possibly even higher) Costs were calculated according to standardized average fees (GOÄ 2004)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					725,095 € ($870,114) - Clinical examinations represented 21,437 € ($145,724) - technical examinations accounted for 286,656 € ($343,987) laboratory costs totaled 317,002 € ($380,402) respectively		
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	Prognostic study	4484 patients diagnosed with a first PM, 385 had >=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	Retrospective design (prospective database)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	to these patients.				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		
Machet et al. (2005)	to study the value of adding ultrasound lymph node examination (7.5 MHz) to the routine clinical examination recommended by French guidelines in melanoma follow-up.	Diagnostic study	373 patients enrolled in a follow-up protocol	Sensitivity specificity	Sensitivity of clinical examination and ultrasound 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)	No information about design (prospective/retrospective)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 cases per 100,000 per year from 1–4 years, for 5–10 years, 10–15 years, and 15–20 years after diagnosis, respectively. presence of 1st CM on the face, neck, and trunk →	Retrospective design Large patient cohort For cumulative risk and monthly hazard diagrams see original article	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					increased risk for 2nd CM (in both univariate and multivariate models): stage IV disease → lower risk of 2nd CM		
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	Recurrence detection Time to detection of recurrence Modes of detection	Detection of recurrences: - in 71% on scheduled follow-up examinations - in 17% by patients themselves, in 13% of these recurrences diagnosis was established during subsequent regular follow-up examinations - in 12% by physicians not participating in the melanoma follow-up schedule	Descriptive study Standardized follow-up procedures Detailed description of procedures and of follow-up of study drop-outs Data about yield of different imaging methods vs. physical examination not listed here (see original article)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					In 2,3% of patients, SPM were identified. Modes of detection: see full-text		
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 years.	Prognostic study	See fulltext	Survival Relative risks	Median survival: 6.4 months (95% confidence interval, 6.1 to 6.9 months.) F factors conferring the greatest increased risk of death: - number of metastatic sites (RR = 1.12) - 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		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(RR = 1.19). Prior immunotherapy (RR = 0.84) and female sex (RR = 0.87)were associated with prolonged survival. response to protocol treatment (RR = 0.57) was a significant prognostic factor: Prognostic for poorer survival: - increased number of sites of metastasis (RR = 1.30) - abnormal LDH (RR = 1.89) - abnormal alkaline phosphatase (RR = 1.76) - abnormal platelets		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(RR = 1.63) - GI metastases (RR 5 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	411 melanoma patients with PM with a tumour thickness >= 1.5 mm (237 patients stage II, 148 patients stage III, 26 stage IV)	Sensitivity Specificity False-negatives (FN) True-negative (TN) True-positives (TP) False-positives (FP) Positive predictive value (PPV) Negative predictive value (NPV) efficiency of protein S100 as a diagnostic test	Serum protein S100 cut-off value at 0.13 µg/l: FN: n=28 TN: n=355 TP: n=13 FP: n=15 PPV: 46 NPV: 93 Test efficiency (< 2): 1.39. The protein S100 values of the metastasis group were significantly higher (P =0.0.001). S100: sensitivity: 0.32, specificity: 0.96 cut-off value of 0.08 µg/l (outcomes for this cut-off: see full-text):lower	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
					specificity, PPV and test efficiency sensitivity: 41%		
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	Of 2,600 patients: 4.3% of patients with SPM mean tumor thickness: 1,72 mm for PM vs. 0.58 mm for SPM 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 initial primary melanomas tended to be thicker (by an average of 3.8 mm, p = 0.008).	Retrospective design Predominantly male patients	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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	115/528 patients had relapses. 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. Time between relapse and last follow-up examination: ≤ 2 months in 9% of cases, ≤ 3 months in 23% and ≤ 4 months in 34%.	Retrospective design For cost analysis see full text of paper	2b
De Giorgi et al. (2010)	To identify main risk factors associated	Prognostic study	40 patients with MPM	Thickness of SPM	Overall mean thickness of	Retrospective design	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	with MPM and to investigate the association between regular follow up and tumour thickness of a SPM			Odds ratio of having MPM	melanoma: 0.517 mm for first melanoma and 0.64 mm for SPM (P = 0.12). 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) OR of having a diagnosis of MPM in comparison with SPM: - 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	Prognostic factors	41 melanoma patients with	Disease-free-survival	Thickness of subsequent vs.	Posthoc analysis from a multi-	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	incidence of multiple primary melanoma (MPM) and other cancer types among patients with melanoma. The risk for secondary nonmelnoma malignancies was also assessed.		multiple melanoma and no evidence of distant metastasis and no palpable nodal metastasis. (Patients with synchronous lesions not included)	overall survival	primary melanomas: median 0,32 mm versus 1,50mm, p<0,0001) 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. 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	institutional prospective randomized trial Loss-to-follow-ups not commented Patients with melanoma <1mm excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					detection of secondary melanomas within the first year in 29,3% of patients, detection of subsequent melanoma within 60 days in 9,8 % after primary melanoma. Median time to development of second primary: 29 months. Nonmelanoma malignancies in 6,1% of patients		
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	Time to recurrence Sites of recurrence Survival	Sites of first recurrence: 52% regional nodes, 17% local recurrences, 8% in-transit metastases, 23% to a distant organ.	Retrospective design Population not described in detail	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Diagnosis of recurrences: 67% within 24 months, 81% within 36 months Survival after the diagnosis of recurrence was independent of: - thickness of the primary tumor - duration of DFI (local, in-transit or regional nodal) diagnosis of distant organ metastasis: shorter survival local recurrence, in-transit metastasis, and regional nodal metassis: comparable survivals		
Romano et al.	implications for	Prognostic study	340 patients AJCC	Relapse-free	5-year RFS for stage	Retrospective	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(2010)	follow-up guidelines		stage III who recurred	survival Overall survival Mode of relapse detection 5-year survivals	IIIA, IIIB, and IIIIC patients was 63%, 32%, and 11%, respectively Site of first relapse: - local/in-transit 28% - regional nodal 21% - systemic 51% 1st relapses detected by patient or family, physician, or by screening radiologic tests in 47%, 21%, and 32% of patients, respectively. Factors associated for better OS (multivariate analysis): - younger age - 1st relapse being	design estimated site-specific risk of first relapse for each substage	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					local/in-transit or nodal, asymptomatic, or resectable. estimated 5-year survivals for stages IIIA, IIIB, and IIIC from time of 1st 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	Retrospective design	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					recurrences patients with LR/ITR (n=26): - 3% local recurrences - 5% in transit recurrence - 2% both LR/ITR - 56% concurrent regional LN metastases. LR/ITR was associated with: - 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	Prognostic study	118 patients with stage II or III	Mode of recurrence detection Time to recurrence	Median time to recurrence: 14 months (range, 2-88 months)	Retrospective analysis of prospective database	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with stage II and sentinel lymph node-positive stage III melanoma.			Overall survival Costs	Types of recurrence: 9% local, 40% in transit, 16% regional lymph node basin, 35% distant Mode of detection: - self-detection in 37% asymptomatic patients - 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 Median survival after recurrence: 22 months (locoregional	Small patient cohort	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					disease) vs. 7 months (distant disease) no difference in survival among symptomatic vs. asymptomatic patients no significant difference in survival between a 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	Retrospective design Part of the cohort very old (starting 1959) For Kaplan-Meier	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					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 thickness, ulceration and tumour mitotic rate were important predictors of recurrence.	curves for time to first recurrence see original article Time between relapse and last follow-up not measured	
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	median survival of stage M1c: 6.0 months. Survival was longer for stage M1a and M1b and shorter in older patients. No significant		2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					differences were found in survival based on gender. 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 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	Prognostic study	1,007 consecutive patients for scheduled follow-up visits. (876 stage I, 35	Disease-specific survival	The mean serum concentration of S-100B protein was significantly related to clinical stage	Follow-up diagnostic procedures not stated in article Study included in	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma.		stage II, 96 stage III)		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 whom the metastases had been resected compared with patients with subcutaneous and/or LN metastases (P=0,004) or disseminated	Mocellin et al. 2008 The three-stage system for classification of malignant melanoma	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastases (P < 0,001). 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)		
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 high risk melanomas (Clark levels IV/V, thickness>0,75 mm)	Diagnostic study	50 patients	Sensitivity Specificity Predictive values	FDG-PET: Sensitivity=100%, specificity=95% Conventional imaging: Sensitivity=92%, specificity=82% S100 : Cut-off-levels were 0,1µg/l and 0,2µg/l: Sensitivity=85%,	Selection criteria not described No information about time interval between blood sample and imaging procedures Small patients cohort	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					specificity=55% when measured by RIA, Sensitivity=77%, specificity=61% when measured by LIA NPV=91% (RIA) and 88% (LIA) PPV=39% (RIA), 40% (LIA) At a cut-off level of 4,0µg/l, TK showed a sensitivity of 70% and a specificity of 41%.		
Poo-Hwu et al. (1999)	To evaluate the follow-up protocol instituted in 1987 at the Yale Melanoma Unit to improve upon the detection of disease recurrence in patients with	Retrospective prognostic study	373 patients followed according to the protocol schedule. AJCC Stage I-III	Recurrence-free interval Overall survival Modes of detection	median time interval to recurrence: - stage I:22.0 (range, 2.0-60.5) months - stage II 13.2 (range, 2.4 -71.0) months - stage III: 10.6	Detailed follow-up procedure given Retrospective design	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	American Joint Committee on Cancer Stage I-III cutaneous melanoma.				(range, 2.3-53.8) months 51% locoregional recurrences detected by patients, 64% distant metastases detected by physicians physician-detected recurrences: - 57% by history or physical examination - 18% by abnormal chest X-ray - 23% by CT scan or MRI - 2% by elevated LDH median survivals: 34 months for locoregional vs. 13 months for distant		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					recurrences All 19 patients with MPM were identified by physician-performed physical examination.		
von Schoultz et al. (1996)	To asses the potential prognostic value of serum concentrations of S-100ß	Serum levels of S-100ß 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 satelilites within 5 cm), 24 patients: stage II (in-transit metastases and/or regional lymph node metastases), 66 patients: stage III (distant metastases)	Overall survival	Significant correlateion of serum concentrations of S-100ß to clinical stages. They were significant higher in men than in women (p<0,001). Association between OS rate with serum levels of S-100. observed/expected death ratio was markely increased with increasing levels of S-100ß (P<0,001). A	No information about number of blood samples taken Poor information about population No information about study design (prospective/ retrospective?) Disease classification different from AJCC was used study included in Mocellin et al. 2008	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					fivefold increase in relative hazard was indicated by a value of S-100ß >0,6µg/l (P<0,001) and when its cut-off level was used S100ß had additional prognostic value independent of clinical stage (P<0,001).		
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 diagnostis of reccurence: 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 guidelines for the	Prognostic study	295 patients with metastatic	disease-free interval	independent significant predictor	Incomplete patient records (of 295	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	follow-up of patients with primary cutaneous melanoma		malignant melanoma(clinical Stage I).	predictors of disease-free interval recurrence rate	of DFI: tumor thickness (p = 0.0015) (not significant: sex, age, elective regional LN-dissection, tumor location) diminution of DFIfrom 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)	patients, only 177 were included in multivariate analysis) For details of survival and recurrence statistics, see original article	
Alvarado et al.	to assess the	Prevalence study	146 patients with	incidence rate of	Recurrences in 75%	Limitation of study	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(2011)	frequency of the 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.		primary melanoma who had adequate follow-up evaluation for at least 5 years. (109: stage I or II disease, 33: patients stage III, 4: stage IV)	metastases Survival Time to recurrence	of patients 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	and bias not described Patients with mucosal melanoma included	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					most common sites of first recurrence: lymph nodes (n=41, 37%), 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	Reference standard not described	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					performed. In total: 3 FP and 2 TP Total cost per diagnosis:$312 990.		
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).	Conclusion about infrequence 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
					Statistical variate analysis failed to identify possible factors significantly associated with late recurrence		
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 asses the frequency of patient detection of both first primary	Prevalance study	112 patients with recently diagnosed SPM	FPM and SPM-detection rate	Patients deteced 59% of the FPMs vs. 46% of the SPMs themselves	Only patients with SPMs were interviewed	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanomas (FPMs) and second primary melanoms (SPMs)				significant predictors for a patient-de-tected FPM: - females gende - greater Breslow tumour thickness - younger age (OR 4,9; 3,2 and 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)	(both in situ and invasive melanomas were included.) Excluded were patients who had multiple primary melanomas or who developed a 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	Prevalence study	211 patients with a first melanoma recurrence (FMR) were interviewed	Median time to detection of an FMR Sites of recurrence	median time to detection of FMR: 28 months (range, 2-322)	risk of bias (in group B, only patients with unambiguous information in	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patient or doctor was analyzed			Modes of detection Mean survival	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-ray - 11% by LN ultrasound Detection of FMR: - in 154 patients by patient, partner, or relative - in 57 patients by a doctor mean survival time: 23.8 months.	patients records were included)	
Zogakis et al. (2007)	To estimate survival and time to first	Prevalence study	773 melanoma patients with	Overall survival	Recurrence in 8,9 % of patients with	Subgroup of sentinel-node-	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	recurrence in patients with negative sentinel nodes.		tumor-negative SLNs	Disease-free survival Time to first recurrence	tumor-negative SLNs 1-year, 3-year, and 5-year DFS rates: 98%, 91%, and 88%, respectively. 1-year, 3-year, and 5-year OS rates: 99.7%, 96%, and 92.7%, respectively. Significant differences in survival between patients with local/in-transit and nodal vs. distant first recurrence No significant difference in time to the development of local/in-transit vs. nodal vs.distant recurrence	negative patients Retrospective design	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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	Sensitivity Mode of detection	In 5.5% of patients, S100 was the first indicator of disease progression. 40.2% of relapses noted by the patients themselves, 27.6% diagnosed by a doctor. Imaging procedures lead to detection of melanoma recurrence in 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) S100 sensitivity: 37%.	Population not described. Small patient number in every stage specificity not given No information about time interval between imaging procedures and blood samples.	3b
DiFronzo et al. (2001)	To investigate whether routine reassessment and	cohort study	3310 patients with primary melanoma AJCC stage I/II	Rate of patients who developed SPM	114 patients with AJCC Stage I or II melanoma	Standard follow-up procedure is defined	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	careful education of postoperative patients would facilitate earlier diagnosis of a subsequent second primary melanoma, as reflected by reduced thickness of that lesion.				developed a SPM AJCC stages of SPM: - lower in 48% - same-stage in 50% mean tumor thickness for PM: 1.32 +- 1.02 mm, for SPM: 0.63 +- 0.52 mm level of invasion of SPM vs. PM - decreased in 60% - remained the same in 27% - increased in 13% of patients. significant differences in stage, tumor thickness, and level of invasion between PM and SPM (paired t test)		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 melanomas detected? (vi) Do patients alter their behaviour after attending a melanoma follow-up clinic?	Prevalence study	1568 patients with stage I melanoma	Risk of recurrence First site and detection of recurrences Changes in behaviour (see full text)	Overall 19% developed recurrences 79% of recurrences occurred during the first 3 years. <8% after the 10-year interval. patients detected their recurrences more often than doctors at follow-up clinics The first site of recurrence was: - local 17% - in transit 6% - local nodes 56% - distal 22%	Large patient cohort No standardized follow-up protocol	3b
Johnson et al. (1998)	To characterize the subgroup of patients with	cohort study	60 with with multiple primary melanomas, and	Time to diagnosis of second melanoma	In 30% MPM were diagnosed concurrently within	Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	multiple melanomas.			Tumor thickness of second melanoma	1 month, in 63% > 1 month apart, and in 7% concurrently and subsequently (>2 primaries). median time interval between subsequent diagnoses of 2nd PM: 63 months (range 2-456) in patients with > 2 PM: median time interval between subsequent lesions: 42 months (range 2-456). Appearance of subsequent primary - 42% within 3 years - 17% between 3-7 years - 42%> 7 years - 19% > 10 years - 6% > 15 years	Small patient cohort	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					After initial diagnosis mean tumor thickness from the 1st primary lesion to the subsequent lesion(s) decreased from 0.98 to 0.90 mm.		
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)	Overall survival (= disease specific survival in this study) Survival after first recurrence	5-year survival: 45% (95% CI 39%, 51%) 10-year survival: 37% (95% CI: 31%, 43%). - 42 patients with local recurrences: 5-year survival rate of 26% (95% CI: 13%, 39%). - 93 with regional recurrences: 5-year survival rate of 18% (95% CI: 10%, 26%). - 41 with distant	Retrospective design Patient cohorts only includes patients with melanoma > 4 mm thickness No attempts to recover patients lost to follow up Patients who died of other diseases were excluded	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastases: 5-year survival rate of 5% (95% CI: 0%, 11%).		
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	Mean time to first recurrence: 22.27 months (median 13.5 months). 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. Recurrences significantly earlier (mean 18.18 months, median 10.5 months) in males than in females (mean 26.78 months, median 17.5 months).	Retrospective design with incomplete patients records (only 675 of 840 patients "histologically evaluable"). Patient cohort contains melanoma in situ (105 lesions not invasive).	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Pathway of first recurrence: 81.19%: lymphatic 17.33%:hematic 1,48%: unknown		
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)	Time to relapse 5-year-survival Questionnaire results (subjective value of follow-up to patients)	82% of first relapses occurred within 3 years and none has yet been seen after 7 years. Actuarial 5-year-survival (doctor-diagnosed vs. patient-diagnosed recurrences): 18 vs. 20 % (P>0,8) For time to first relapses over year of follow-up, see fig. 1 in original article.	Retrospective design No standard follow-up protocol	3b
Kang et al. (1992)	To examine the natural history and	cohort study	41 patients with multiple cutaneous	Interval between melanoma	In 39% the MPM were diagnosed	Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	impact of regular follow-up evaluation of multiple primary cutaneous melanoma		melanoma	diagnoses Tumor thickness	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)	Small patient cohort	
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-table analysis on	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 in11 patients: - 4 local recurrences	Retrospective design No standard therapy and follow-up protocol Different excision margins have been used	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	206 evaluable patients.				- 4 LN metastases - 3 distant disease. - Actuarial 5-year CSS: 96.1% - 10-year CSS:92.3% - 15-year CSS: 92.3%. cancer-specific DFS after 5 years: 95.2%, after 10 years: 86.9%, after 15 years: 86.9%.		
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	Recurrence rate Site of first recurrence Time to first recurrence	Time to first recurrence depended upon: - thickness of the tumor - whether ELND was performed or not Times to recurrence for 50% respectively 95% of the recurrent patients in months:	Retrospective design Different follow-up schedules over time Large patient cohort	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- 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		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months for > 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
					With subsequent melanomas a greater proportion were found by the dermatologist. Risk factors: see full-text		
Zissimopoulos et al. (2009)	To evaluate 111In-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	35 patients with malignant melanoma 20 female, 15 male, mean age 46±7, range 32-51 years Treatments in some patients: Interferon alpha, IL-2	Positive- rate	During 3 years of the follow-up period, 26/35 of the patients had clinical recurrence. (17 patients: regional lymph node metastases, 9 distal metastases) In 111In-O Scintiscan 20/26 patients had positive scans with 56 lesions, 6 had negative scans. CT	Selection criteria not given Small sample size No information about false positives and false negatives. Positive CT: only number of metastases is given but not number of patients No information about interval between CT and	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					images showed only 31 lesions.	111In-O Scintiscan No information 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

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Dancey et al. (2004)	to assess patient opinions on follow-up. to ascertain whether GPS would be willing to follow melanoma patients up in a primary care setting	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 difficult to attend the clinic 53% expressed some degree of anxiety at attending the outpatient department 12%: recurrence, 52% of them detected it themselves 60% of patients would be happy to consider routine follow-up with their GP 70% of local GPs would be unhappy to monitor their		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients.		
Johnson et al. (1999)	to determine the value of follow-up in two subgroups of patients with a thin melanoma less than 0.76 mm and 0.76-1.5 mm thick.	Prevalence study	306 patients: 178 with a melanoma < 0.76 mm (group 1) and 128 with a melanoma of 0.76 - 1.5 mm (group 2)	Recurrence rate	Recurrences in 4 patients (2.2%) in group 1 and 16 (12.5%) in group 2 group 1: all patients presented with untreatable, widespread metastatic disease, detected by a clinician in the follow-up clinic. 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	Standardized follow-up procedure	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					in the follow-up clinic.		
Mooney et al. (1998)	To asses the impact on survival by components of a surveillance program (physical examination, blood tests, and chest radiograph) used to detect recurrences in patients with cutaneous melanoma	Prognostic study	1004 patients AJCC Stage I or II	Method of detection Survival 5-, 10- and 15-year survival	Physical examination detected 72% constitutional symptoms indicated 17% and chest radiograph 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.	Retrospective design No information about verification/reference test	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					No statistically significant difference in OS between patients with asymptomatic pulmonary recurrences and those with symptomatic pulmonary metastases The 5-year, 10-year, and 15-year OSrates, 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.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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%. 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.	No level of evidence was assigned because of unique study design and hypothetical cohort of patients	

7.2.5. 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
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)			
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)			
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
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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8. AG Begleittherapie

8.1. Frage VIII.1. Misteltherapie

Frage VIII.1. Beeinflusst eine Misteltherapie das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?

8.1.1. 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		

8.1.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(“melanoma” OR “melanoma”[MeSH Terms] OR “skin cancer”) AND (“mistletoe” OR “viscum	28.09.10	41

Datenbank	Suchstrategie	Datum	Treffer
	album" OR "mistletoe"[MeSH Terms])		
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

8.1.3. Auswahlkriterien

Auswahl der Literatur		
Gesamttreffer		97
Einschlusskriterien	Klinische Studien zur Misteltherapie bei Melanomapatienten, alle Stadien Vergleichsarm: Beobachtung oder Standardtherapie, Sprachen: e,dt	
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

8.1.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Kleeberg et al. 2003 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 (thickness >3 mm) or regional lymph node metastasis	To clarify whether claims of the efficacy of Iscador M were justified	Prospective, randomised phase III adjuvant trial	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 value of Iscador: 102 controls vs. 102 pts in the Iscador group. Stage IIb: 48%/49% Stage III: 52%/51% Baseline characteristics were well balanced	 Disease free Interval rate (DFI) Overall Survival (OS)	Iscador M1 versus control HR 1.32 (0.93, 1.87) HR 1.21 (0.84, 1.75) The data support, but do not provide significant proof of earlier warnings about a potential negative effect of mistletoe extracts in melanoma patients, since the observations did not reach significance.	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. Funding: In part by grant DKG 80-1	1b Individual RCT

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Augustin et al. 2005 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 Misteltoe (Viscum album L.) Extract	To evaluate the therapeutic safety and efficacy of Fermented European Misteltoe Extract (FME)	Mulicenter, comparative, epidemiological cohort study	686 Patients, 329 treated with FME vs. 357 controls from 35 centers; UICC/AJCC tumor stage (II/III) % 91,5/8,5 vs 95.0/5.0 Treatment group: 83,3% patients received FME P 16,7% received FME M, Q or others median duration of therapy: 30 months	Prim. endpoint Tumor-related survival Sec. endpoint Overall Survival Disease-free-survival Brain metastasis-free survival	Significant reduction of tumor-related mortality hazard in the FME group Tumor-related mortality rate 8,9% FME group vs. 10,7% control group Adjusted hazard ratios (FME vs. control): HR Tumor-related survival = 0,41 HR Overall survival = 0,64 HR Disease-free Survival = 0,73 HR Brain metastasis-free survival = 0,33	Limits: Not randomized design Thus, baseline characteristics were well balanced Potential biases were well addressed by using a standardized parallel goups study design, independent auditing of data quality, multivariate adjusted endpoint criteria for potential confounders and other measures. Funding: The study was supported by an educational grant of the Research Institute Hiscia, Arlesheim (Switzerland) (Iscador)	2b Individual Cohort Study

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
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 HospitalFreiburg, 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 Melanoma Registry.	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

Ausgeschlossene Studien

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*LoE*
Stumpf et al. 2003 *Retrospective Study of Melanoma Patients Treated*	*to analyze survival time and survival rate of all patients with malignant*	*Retrospective Study*	*284 melanoma patients of the Tumorambulanz Herdecke were included,*	*Survival time* *Survival rate*	*Survival time and survival rate were comparable to controls of literature*	*Poor quality → study excluded* *Limits: retrospective*	*4* *poor quality cohort study*

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
with Mistletoe Extracts	melanoma who had been counseled at the Tumorambulanz Herdecke		94 patients with sufficent data were analysed, 66 of this patients received mistle toe treatment. This 66 patients were compared with patient data from the literature			design, heterogeneous patient collective: patients with and without metastases, clinical stage was not indicated, Comparison with literature data based on clark level Different treatment regimens (Iscador M, Iscador P and others) Funding: The study was partially initiated and financed by Helixor GmbH&Co	
Grossarth-Maticek et al. 2007 Efficacy and Safety of the Long-term Treatment of Melanoma with a Mistletoe	To investigate if the long-term application of the mistletoe preparation Iscador show any effect in prospective controlled	Study 1: Randomised matched-pair study (22 pairs) Study 2: Non-randomised matched-pair study	Study population consisted of 1499 melanoma patients of different german centres Melanoma patients without metastases,	Overall survival Progression free survival Self regulation	Overall survival: No difference between Iscador and control group Significant better progression free survival in Iscador	Poor quality → study excluded Recruitment period was between 1973 and 1988 Two studies were analysed seperately	4 poor quality cohort study

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Preparation (Iscador)	studies on survival, tumor progression, and psychosomatic self-regulation of patients with melanoma	(32 pairs)	receiving conventional therapies were matched to melanoma patients with same characteristics to receive additionally 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	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 (significant) Funding: No statement included Affiliation of Corresponding author: Institut Hiscia, CH-Arlesheim (Iscador)	
Schuppli R. 1990	To assess the therapeutic effect of	Controlled study	High risk melanoma patients	Overall survival	Risk factor Survival Iscador group: 3,4	Poor quality → study excluded	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Adjuvant treatment of malignant melanoma with Iscador P c Hg.]	*Iscador plus Hg on overall survival*		*114 patients treated with BCG alone* *84 patients treated with BCG and Iscador P c Hg*		*Contol group: 2,3*	*The study was conducted at the Department of Dermatology, Universitiy Basel, 1981-1988* *Limits:* *Study reporting of low quality* *No baseline charachteristics, (groups balanced?)* *Statistical methods were not reported* *Funding:* *No statement included*	*poor quality cohort study*

8.1.5. Literatur

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9. AG Versorgungsqualität und Qualitätsindikatoren

9.1. Frage IX.1. Klinische Studien - Adaptation

Frage IX.1. Welchen Patienten sollte eine Teilnehme an klinischen Studien empfohlen werden?

Die Frage wurde letztendlich Konsens-basiert beantwortet

9.1.1. 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**
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 Patienten durch Studienteilnahme	Keine Erwähnung	*Nur relevant für medikamentöse Therapien*

9.1.2. Empfehlung, Hintergrundstext 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)	LL Kanada Cancer Care Ontario 2007
Schlüsselempfehlungen	S. 128 Patients can be informed that they are unlikely to be disadvantaged by participation in an RCT. Grade of Recommendation: A		Keine Erwähnung	Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma: Updated Guideline Recommendations 2009 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.
Hintergrundtexte	S. 127 20. Clinical Trials The clinical trial is an instrument designed to assess	Patient-centered care C. Evidence S. 41	Keine Erwähnung	Keine Erwähnung

	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
	the effectiveness of potentially new or altered interventions 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] 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] The randomised clinical trial (RCT), which involves random	Clinical trials One high-quality systematic review investigated patient outcomes related to mortality and morbidity among participants and nonparticipants in clinical trials. RCTs of different specialities 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. The same review found no evidence of greater risk arising from trial participation. A previous, poorer-quality systematic review than the one		

	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
	allocation of patients to their treatment or control group, is becoming the 'gold standard' for assessment of new management processes. 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. 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] However, in our community some people are concerned about RCTs, believing that	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 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. An audit of skin cancer MDT activity undertaken in the South West of England found that many trusts did not have		

	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
	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 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	sufficient infrastructure to ensure that patients are offered trial entry. 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 proportion of patients with cancer are involved in clinical trials. Trial participation was less likely in settings outside of large cancer centres.		

	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
	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 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] Evidence summary Outcomes for patients who participate in RCTs on average			

	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
	do not differ from those of patients who receive similar treatments and do not participate in a trial. LoE: I Reference: [2]			

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10. 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 eexamination
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	senitinel 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