S3-LEITLINIE LUNGENKARZINOM

Evidenzbericht zur Therapie des nicht-kleinzelligen Lungenkarzinoms im Stadium III

PD Dr. Susanne Unverzagt

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Inhalt

Zusammenfassung

In diesem Evidenzbericht wird die Evidenz aus systematischen Übersichten und aktuelleren randomisierten Studien zu fünf Fragestellungen in der Therapie von Patienten mit nicht-kleinzelligem Lungenkarzinom (NSCLC) im Stadium III zusammengefasst.

Die Fragestellungen umfassen die Therapieauswahl und Prognose auf Grundlage von Ergebnissen aus histologischen und molekularen Analysen (Fragestellung 1), adjuvante und neoadjuvante Chemo- und Chemoradiotherapien (Fragestellungen 2a und 2b), minimal invasive Eingriffen (Fragestellung 3) und Konsolidierungstherapien (Fragestellung 4).

Auf Grundlage von systematischen Recherchen in zwei Datenbanken (Medline und CENTRAL) in den Monaten September bis November 2020 wurden insgesamt 3301 Referenzen gescreent, 137 Volltexte gelesen und Informationen aus 38 Veröffentlichungen in fünf Evidenztabellen extrahiert und mit Evidenzgraden (EG) bewertet.

Zu Fragestellung 1 wurden zehn systematische Übersichten bei Patienten mit NSCLC in verschiedenen Stadien eingeschlossen. Von diesen bewerten sieben Studien eine Therapiewahl bei EGFR-positiven Patienten und jeweils eine Übersicht die Therapiewahl bei Patienten mit einer ALK- oder ROS-1 Mutation sowie in Abhängigkeit von den histologischen Ergebnissen. Es konnte mit hoher Qualität der Evidenz gezeigt werden, dass EGFR-Inhibitoren bei Patienten mit EGFR-positivem lokal fortgeschrittenem oder metastasiertem NSCLC in der Erstlinientherapie sowohl das krankheits- als auch das progressionsfreie Überleben bei gleichbleibendem Gesamtüberleben verbessern können (EG 1a). Für die Zweitlinientherapie existieren in Abhängigkeit von den Ergebnissen histologischer und molekularer Untersuchungen Therapien, welche das progressionsfreie Überleben verlängern (EG 1a). Zur Therapie des ALK-positivem NSCLC (Stadium III/IV) existieren Therapien, welche sowohl das Gesamt- als auch das progressionsfreie Überleben verlängern können (EG 2a-). Zusätzlich wurden Ergebnisse aus 2 systematische Übersichten zur prädiktiven Güte histologischer und molekularer Marker extrahiert (EG 1a-).

Zu Fragestellung 2a wurden eine systematische Übersichtsarbeit und sechs randomisierte Studien zur Wirsamkeit einer adjuvanten Chemotherapie in Ergänzung zur Operation (oder Operation und Strahlentherapie) bei Patienten mit NSCLC in den Stadien I bis III eingeschlossen. Zusammenfassend konnte bei hoher Qualität der Evidenz (EG 1a) ein deutlicher Vorteil einer adjuvanten Chemotherapie im Anschluss an die Operation unabhängig von der strahlentherapeutischen Behandlung auf das Gesamt- und rekurrenzfreie Überleben nachgewiesen werden. Die Wirksamkeit einzelner Therapiekombinationen wird in der Evidenztabelle beschreiben. Zu Fragestellung 2b wurden zwei systematische Übersichten unter Einschluss von Patienten in allen Stadien, zwei randomisierte Studien zu Patienten im Stadium IIIA und zwei Kohortenstudien mit Konfounderadjustierung eingeschlossen. Diese zeigen bei hoher Qualität der Evidenz (EG 1a-) einen deutlichen Überlebensvorteil mit weniger oder später einsetzenden Rekurrenzen durch neoadjuvante Therapien. Die Studien und die systematische Übersichtsarbeit zur Induktionstherapie zeigen widersprüchliche Ergebnisse: während eine systematische Übersicht auf Grundlage zweier retrospektiver Studien, von denen insgesamt 297 eine Induktionstherapie erhielten, einen Vorteil im Überleben nach 5 Jahren (aber nicht nach 1-4 Jahren) zeigte, konnte dieser in zwei konfounderadjustierten Auswertungen von Daten der US-amerikanischen National Cancer-Datenbank nicht bestätigt werden (EG 2b).

Für Fragestellung drei zu minimal invasiven Operationen wurden Ergebnisse aus einer systematischen Übersicht auf der Grundlage vergleichender randomisierter und nichtrandomisierter Studien bei NSCLC-Patienten der Stadien I bis III sowie einer randomisierten Studie und einer retrospektiven vergleichenden Kohortenstudie mit Konfounderadjustierung unter Einschluss von Patienten im Stadium III extrahiert. Die niedrige bis moderate Evidenz der systematischen Übersichtsarbeit weisen auf ein verbessertes Gesamt- und krankeitsfreies Überleben mit multiport- video-assistierten thrakoralenOperation (m-VATS) bei Patienten im Stadium I-III hin (EG 2a-). Höhere Sicherheit existiert für das Auftreten von weniger Nebenwirkungen und postoperativer Schmerzen bei gleichzeitig geringerer Kosten nach mVATS im Vergleich zur offenen Lobektomie. Zum Einsatz einer RATS existiert bisher wenig Evidenz.

Zu Fragestellung 4 konnten fünf randomisierte Studien bei Patienten mit NSCLC im Stadium III identifiziert werden. In keiner der drei Studien zur Wirksamkeit einer Konsolidierungschemotherapie konnte eine Verlängerung des Gesamt- oder progressionsfreien Überlebens nachgewiesen werden, während zum Teil schwerwiegende Nebenwirkungen auftraten. Auch eine zielgerichtete Therapie mit Icotinib bei Patieten mit EGFR-positivem NSCLC konnte lediglich einen geringen (nichtsignifikanten) Überlebensvorteil bei geringer Toxizität zeigen. Im Gegensatz zu diesen Ergebnissen konnte die Wirksamkeit einer Konsolidierungstherapie mit Durvulumab auf das Gesamt- und progressionsfreie Überleben in einer randomisierten Studie mit hoher Qualität der Evidenz nachgewiesen werden. Die Anzahl von schweren Nebenwirkungen war in der Gruppe mit Durvulumab im Vergleich zur Kontrollgruppe mit Plazebo leicht erhöht.
Für die Fragestellungen 1 bis 3 liegt vorrangig zusammenfassende Evidenz für Patienten der Tumorgrade I bis IIIA vor, so dass die vorliegende Evidenz für die vorliegenden Fragestellungen aufgrund von Indirektheit abgewertet wurde, wenn die Abhängigkeit von Stadien nicht in Subgruppenanalysen oder im Rahmen einer Adjustierung berücksichtigt wurde (EG 1b).

Fragestellungen

Im folgenden werden die sich aus den Fragestellungen ergebenden Einschlusskriterien an die Studien (Patientenpopulation, zu untersuchende Intervention und Alternative, interessierende Endpunkte) in den Tabellen Tabelle 1 bis Tabelle 5 zusammengefasst.

Fragestellung 1: Ist die Histologie einschließlich molekularer Analysen im Stadium III für die Therapie-Wahl relevant?

Tabelle 1: PICO-Kriterien der Fragestellung 1 zur Wirksamkeit einer Therapie auf Grundlage der Histologie oder molekularer Analysen bei Patienten mit NSCLC im Stadium III

Patienten	Patienten mit NSCLC im Stadium III mit vorliegenden Ergebnissen zur Histologie bzw. molekularer Analysen
Intervention	Therapiewahl oder Prognose auf Grundlage von • Histologie (Adenokarzinom vs. Plattenepithelkarzinom) • molekularen Analysen (EGFR mutation, ALK translocation, ROS1 mutation)
Kontrolle	Therapiewahl ohne Informationen zu Histologie oder molekularer Analysen / andere Ausürägung der prognostischen Faktoren
Zielkriterien (Outcomes)	Kritische Endpunkte: • Überleben (OS, DFS), Lebensqualität • Nebenwirkungen (Grad 3 oder 4), Studienabbruch wichtige Endpunkte: Response
Studiendesign	Systematische Übersichten und RCTs mit Veröffentlichung der finalen Ergebnisse im Volltext ab 2000
ALK: anaplastic lymphoma kinase; DFS: Krankheitsfreies Überleben (disease-free survival); EGFR: epidermal growth factor receptor; NSCLC: Non-small cell lung cancer; OS: Overall survival (Gesamtüberleben); RCT: Randomisierte kontrollierte Studie; ROS1: Receptor tyrosine kinase	

Fragestellung 2a: Welche adjuvante Chemotherapie ist im Stadium III nach kompletter Resektion sinnvoll?

Tabelle 2: PICO-Kriterien der Fragestellung 2a zur adjuvanten Chemotherapie im Stadium III nach kompletter Resektion

Patienten	Patienten mit NSCLC im Stadium III nach kompletter Resektion
Intervention	Operation und adjuvante Chemotherapie: • Cisplatin plus (vinorelbine or navelbine or etoposide or pemetrexet or gemcitabine or paclitaxel or taxol or docetaxel) • Carboplatin plus (vinorelbine or navelbine or etoposide or pemetrexet or gemcitabine or paclitaxel or taxol or docetaxel) • Monochemotherapie • Platin plus all chemotherapeutic regimes • postoperative chemoradiotherapy (gleichzeitig) • sequential chemo radiotherapy
Kontrolle	Operation und Best supportive care, Plazebo oder einer anderen adjuvanten Chemotherapie
Zielkriterien (Outcomes)	Kritisch: Prognose: Überleben (OS, DFS), Lebensqualität Nebenwirkungen (Grad 3 oder 4), Studienabbruch
Studiendesign	Systematische Übersichten und RCTs mit Veröffentlichung der finalen Ergebnisse im Volltext ab 2000
DFS: Krankheitsfreies Überleben (disease-free survival); NSCLC: Non-small cell lung cancer; OS: Overall survival (Gesamtüberleben); RCT: Randomisierte kontrollierte Studie	

Fragestellung 2b: Welche neoadjuvante oder Induktions-Chemotherapie ist im Stadium III sinnvoll?

Tabelle 3: PICO-Kriterien der Fragestellung 2b zur Wirksamkeit einer neoadjuvanten Chemotherapie

Patienten	Patienten mit NSCLC im Stadium III vor einem geplanten chirurgischen Eingriff
Intervention	neoadjuvante oder Induktionstherapie Chemotherapie und Operation: • Cisplatin oder Carboplatin plus (Vinorelbine, Navelbine, Etoposid, Pemetrexet, Gemcitabine, Paclitaxel, Taxol oder Docetaxel) • Monochemotherapie • Platin plus alle anderen chemotherapeutischen Regime • preoperative gleichzeitige oder sequentielle Chemoradiotherapie
Kontrolle	Best supportive care, Plazebo oder einer anderen neoadjuvanten Chemotherapie und Operation
Zielkriterien (Outcomes)	Kritisch: Prognose: Überleben (OS, DFS), Lebensqualität Nebenwirkungen (Grad 3 oder 4), Studienabbruch Complete resection (R0) wichtig: Response
Studiendesign	Systematische Übersichten und RCTs mit Veröffentlichung der finalen Ergebnisse im Volltext ab 2000
DFS: Krankheitsfreies Überleben (disease-free survival); NSCLC: Non-small cell lung cancer; OS: Overall survival (Gesamtüberleben); RCT: Randomisierte kontrollierte Studie	

Fragestellung 3: Sind VATS oder RATS im resektablen Stadium III der Thoraktomie gleichwertig?

Tabelle 4: PICO-Kriterien Fragestellung 3 zur Wirksamkeit einer VATS und RATS im Vergleich zur Thoraktomie

Patienten	Patienten mit NSCLC (≥ 20 je Gruppe) im resektablen Stadium III
Intervention	Chirurgische Exploration mit minimal invasiven Eingriffen (Minimal invasive surgery): • VATS • RATS
Kontrolle	Thoraktomie (nicht minimal invasiv)
Zielkriterien (Outcomes)	Kritisch: Prognose: Überleben (OS, DFS), Lebensqualität Nebenwirkungen (Grad 3 oder 4, Wechsel zur offenen Operation, Blutverlust, Blutung nach den ISTS- Kriterien) Resection (R0 oder R1) wichtig: Response, postoperative Schmerzen, Operationszeit, Aufenthaltsdauer im Krankenhausl
Studiendesign	Systematische Übersichten auf der Basis vergleichender Studien und vergleichende Studien mit adäquater Konfounderadjustierung (oder Propensity-score Analysen) mit Veröffentlichung der finalen Ergebnisse im Volltext ab 2000
DFS: Krankheitsfreies Überleben (disease-free survival); NSCLC: Non-small cell lung cancer; OS: Overall survival (Gesamtüberleben); RATS: Robotic assisted thoracic surgery; RCT: Randomisierte kontrollierte Studie; VATS: Video assisted thoracic surgery	

Fragestellung 4: Ist eine Konsolidierungstherapie nach definitiver Therapie im Stadium III (bimodal oder trimodal) von Vorteil?

Tabelle 5: PICO-Kriterien der Fragestellung 4 zur Wirksamkeit einer Konsolidierungstherapie nach definitiver Therapie im Stadium III

Patienten	Patienten mit NSCLC im Stadium III nach definitiver (bimodaler oder trimodaler) Therapie
Intervention	Konsolidierungstherapie • Chemotherapie • Immuntherapie
Kontrolle	Best supportive care, Plazebo oder keine weitere Behandlung
Zielkriterien (Outcomes)	Kritisch: • Überleben (OS, DFS), Lebensqualität • Nebenwirkungen (Grad 3 oder 4), Studienabbruch wichtig: Response
Studiendesign	Systematische Übersichten und RCTs mit Veröffentlichung der finalen Ergebnisse im Volltext ab 2000
DFS: Krankheitsfreies Überleben (disease-free survival); NSCLC: Non-small cell lung cancer; OS: Overall survival (Gesamtüberleben); RCT: Randomisierte kontrollierte Studie	

Methoden

Systematische Suche

In den Monaten September bis November 2020 erfolgte durch Frau Unverzagt eine Suche in zwei elektronischen Datenbanken (Medline (Ovid), CENTRAL) nach geeigneten randomisierten kontrollierten Studien (RCTs), systematischen Übersichten und Metaanalysen. Dazu wurden Fragestellungen mit der Arbeitsgruppe NSCLC (Prof. Eberhardt) und Dr. Langer abgestimmt und anschließend geeignete Suchstrategien in Medline (Ovid) und CENTRAL entwickelt (siehe Anhang 1: Suchstrategien für elektronische Datenbanken). Alle identifizierten Referenzen wurden in eine gemeinsame Datenbank in Endnote exportiert.
Auf Grundlage des Berichtes wurden von der Arbeitsgruppe eine weitere relevante systematische Übersicht ergänzt.

Screenen

Alle Referenzen aus der systematischen Suche wurden von Frau Unverzagt auf der Grundlage des Titels, der Zusammenfassung und der Schlüsselwörter gescreent. Alle potentiell relevanten Titel wurden mit der Leitliniengruppe (Prof. Eberhardt) abgestimmt. Zusätzlich wurden alle potentiell relevanten zitierten Referenzen aus eingeschlossenen Studien überprüft.

Evidenztabellen und kritische Bewertung der Studien

Es wurden Evidenztabellen für die vorgegebenen Fragestellungen nach Vorgaben der AWMF erstellt. Diese Tabellen enthalten den Zeitraum oder Durchführung der Studien, das Hauptziel der systematischen Übersicht oder Studie, eine Beschreibung der Studienteilnehmer, der untersuchten Interventions-und Kontrollgruppen, eine Liste der untersuchten Endpunkte sowie die Ergebnisse zu den vordefinierten Endpunkten der Tabellen 1 bis 5. Alle Extraktionen erfolgten in englischer Sprache. Der Evidenzgrad jeder Studie wurde mit Hilfe der in Tabelle 6 zusammengefassten Oxford-Kriterien bewertet (1) und basiert vorrangig auf dem Design der Studie. Diese Evidenz wird bei Vorliegen schwerwiegender Studienlimitationen, Publikationsbias, geringer Präzision der Ergebnisse, bedeutsamer Heterogenität (Inkonsistenz der Ergebnisse der Einzelstudien) und eingeschränkter Übertragbarkeit der Ergebnisse abgewertet. Die Beurteilung der Konsistenz gepoolter Effekte basiert auf der der Heterogenität der Einzelstudien, welche auf der Basis des I^2-Wertes als gering (I^2< 30 %), moderat (I^2 zwischen 30 und 60 %) oder bedeutsam (> 60 %) eingestuft wurde.
Zusätzlich wurden die Schlussfolgerungen der Autoren der Studien extrahiert und es folgt eine Schlussfolgerung der Begutachterin, in welcher Gründe für die Evidenzbeurteilung erläutert werden.

Tabelle 6: Evidenzgrad der eingeschlossenen Studien nach den Oxfordkriterien (OCEBM) für Studien zur Wirksamkeit von Therapien oder zur diagnostischen Güte

Studientyp	**Evidenzgrad** (OCEBM 2009)
Systematische Übersicht (mit homogenen Ergebnissen) auf der Basis von RCTs (Ergebnisse zur Wirksamkeit) oder prospektiven Kohortenstudien (Ergebnisse zur prädiktiven Güte)	1a
Randomisierte Studie (Ergebnisse zur Wirksamkeit) oder prospektive Kohortenstudien	1b
Systematische Übersicht (mit homogenen Ergebnissen) von Kohortenstudien oder RCTs mit hohem Verzerrungsrisiko (Ergebnisse zur Wirksamkeit) oder retrospektiven Kohortenstudien bzw. Kontrollgruppen aus RCTs (Ergebnisse zur prädiktiven Güte)	2a
Retrospektive Kohortenstudien bzw. Kontrollgruppen aus RCTs (Ergebnisse zur prädiktiven Güte)	2b
CebM: Centre of evidence-based Medicine; RCT: Randomisierte kontrollierte Studie	

Bei einem hohen Evidenzgrad kann mit hoher Wahrscheinlichkeit davon ausgegangen werden, dass das Ergebnis der vorliegenden Studien nahe am wahren Interventionseffekt liegt. Diese Sicherheit nimmt mit geringerer Qualität der Evidenz ab.
Eine Bewertung der Studienlimitationen erfolgte durch die Autorin (SU) für randomisierte kontrollierte Studien (RCTs) auf der Grundlage des Cochrane-Risk of Bias-Tools (2). In die Bewertung gingen folgende Kriterien ein:

- Randomisierung: Erzeugung und verdeckte Zuweisung der Randomisierungsfolge
- Verblindung der Patienten, Behandler und Endpunkterfassung
- Ergebnisgesteuerte Berichterstattung
- Umsetzung des Intention-to-treat (ITT)-Prinzips (Auswertung von mindestens 90 % der eingeschlossenen Studienteilnehmer)
- Frühzeitiger Studienabbruch, ungleiche Verteilung klinisch relevanter Parameter zu Studienbeginn
- Zusätzlich wurden die von den Autoren genannten Limitationen, soweit diese sich auf die Ergebnisse zu den kritischen oder klinisch wichtigen Endpunkten dieser Leitlinie bezogen, wiedergegeben.

Zusätzlich erfolgte eine zusammenfassende Bewertung der methodischen Qualität aller systematischen Übersicht unter Nutzung der AMSTAR-II-Kriterien (3, 4) durch die Autorin (SU). In diesem Bericht wurde sich auf die hervorgehobenen kritischen Fragen sowie auf die Punkte 5. und 6. beschränkt.

1. Basieren Forschungsfrage und Einschlusskriterien auf den PICO-Kriterien?
2. **Wurden die Methoden vorher in einem Protokoll festgelegt und Abweichungen beschrieben?**
3. Falls zutreffend: Wird der Einschluss verschiedener Studiendesigns (neben RCTs) begründet?
4. **Erfolgte die systematische Suche in mindestens 2 bibliographischen Datenbanken und werden Datenbanken und der Zeitraum der Suche genannt?**
5. **Erfolgte die Auswahl der Studien durch 2 Autoren?**
6. **Erfolgte die Datenextraktion durch 2 Autoren?**
7. **Existiert eine Liste der ausgeschlossenen Studien (oder ein Flowchart) unter Angabe der Ausschlussgründe?**
8. Werden die eingeschlossenen Studien detailliert beschrieben?
9. **Erfolgte eine Beurteilung des Verzerrungsrisikos mit geeigneten Instrumenten** (z.B. QUADAS-2 (5))**?**
10. Wurden die Interessenkonflikte der eingeschlossenen Studien extrahiert?
11. Falls Metaanalysen erfolgten:
    a. **Wurden für Metaanalysen geeignete Methoden verwendet?**
    b. Wurde der Einfluss des Verzerrungsrisikos auf das Ergebnis der Metaanalysen beschrieben?
12. **Wurde der Einfluss des Verzerrungsrisikos auf das Ergebnis der systematischen Übersicht beschrieben?**
13. Wird die auftretende Heterogenität beschrieben und erklärt?
14. **Wird der Einfluss eines Publikationsbias diskutiert?**
15. Berichten die Autoren potentielle Interessenkonflikte bei der Erstellung der systematischen Übersicht?

Ergebnisse

Ergebnis der systematischen Suche

Auf der Grundlage der in Anhang 1: Suchstrategien für elektronische Datenbanken beschriebenen Strategien konnten insgesamt 3297 Referenzen identifiziert wurden. Zusätzlich wurden in den Referenzen der eingeschlossenen systematischen Übersichten drei weitere Arbeiten gefunden und eine systematische Übersichtsarbeit aus der Leitliniengruppe bewertet. Insgesamt 137 Volltexte wurden gelesen und anschließend wurden 39 Veröffentlichungen zu 15 systematischen Übersichten, 15 RCTs und drei Kohortenstudien eingeschlossen und extrahiert. Die Suche wird in Abbildung 1 zusammenfassend dargestellt.

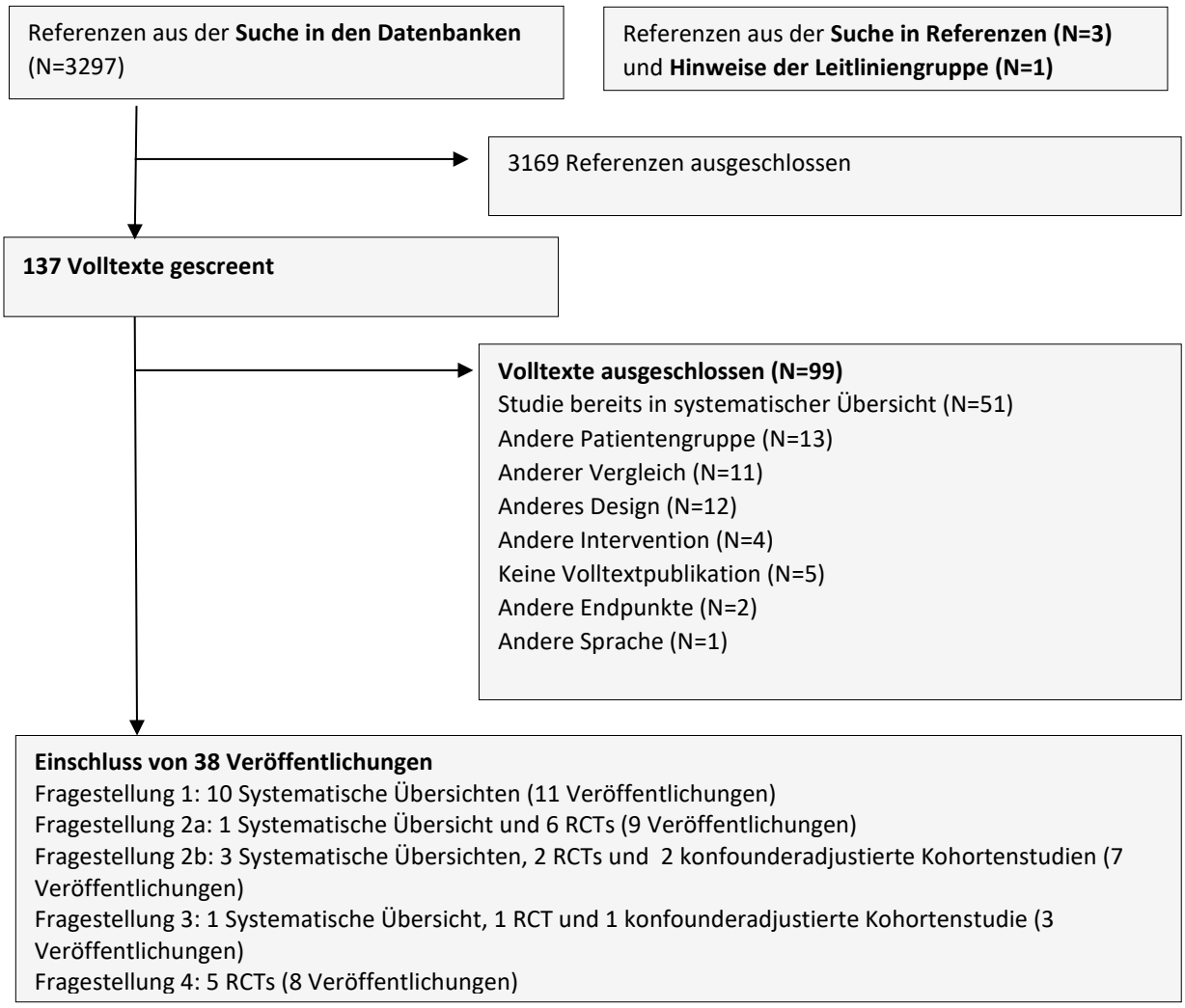

Abbildung 1: Flussdiagramm der systematischen Suche zur Behandlung des NSCLC im Stadium III

Zu Fragestellung 1 (Therapiewahl und Prognose auf der Grundlage histologischer oder molekularer Analysen) wurden nach Löschen der Duplikate 1740 Referenzen gescreent und anschließend 51 Referenzen im Volltext geprüft. Anschließend konnten zehn geeignete systematische Übersichten (11 Veröffentlichungen) eingeschlossen, extrahiert und bewertet werden (siehe Eingeschlossene Systematische Übersichten: Fragestellung 1). Von den zehn systematischen Übersichten untersuchen acht die Wirksamkeit einer Therapie auf der Grundlage histologischer und molekularer Analysen. Auf Wunsch der Leitliniengrundlage wurde die Fragestellung hinsichtlich der prädiktiven Güte erweitertund eine systematische Übersichtsarbeit zur prädiktiven Güte der Analysen eingeschlossen. Anschließend wurden die Referenzen aus der elektronischen Suche nach weiteren systematischen

Übersichten zur prädiktiven Güte gescreent und eine weitere Arbeit eingeschlossen. Es wurden 40 Referenzen im Volltext geprüft und anschließend ausgeschlossen (siehe Ausgeschlossene Studien: Fragestellung 1). Häufigster Ausschlussgrund für die geprüften Studien war der Einschluss der Studien in eine der eingeschlossenen systematischen Übersichten mit demselben oder einem breiteren Thema und einem längeren Suchzeitraum (28 Veröffentlichungen). Acht weitere Veröffentlichungen wurden aufgrund ihrer Methodik oder aufgrund des Einschlusses von nichtrandomisierten Studien ausgeschlossen. Zusätzlich wurde eine vorzeitig beendete randomisierte Studie ausgeschlossen, welche insgesamt acht Patienten in eine Interventionsgruppe mit Erlotinib randomisierte. Insgesamt zwei Veröffentlichungen wurden ausgeschlossen, da die Therapiezuweisung an die Probanden nicht auf Grundlage von molekularen oder histologischen Analysen erfolgte und eine weitere systematische Übersichtsarbeit liegt bisher nicht im Volltext vor.

Zu Fragestellung 2 (adjuvante und neoadjuvante Chemotherapie im Stadium III) wurden nach Löschen der Duplikate insgesamt 817 Referenzen gescreent und anschließend 14 bzw. s13 Referenzen für die Fragestellungen 2a (adjuvante Chemotherapie nach vollständiger Resektion) und 2b (neoadjuvante Chemotherapie) im Volltext geprüft.

Für die Fragestellung 2a konnten eine geeignete systematische Übersichten und sechs Studien (insgesamt 9 Veröffentlichungen) eingeschlossen, extrahiert und bewertet werden (siehe Eingeschlossene Studien: Fragestellung 2a). Es wurden drei Referenzen im Volltext geprüft und anschließend ausgeschlossen. Eine systematische Übersicht (6) wurde aktualisiert und diese Arbeit wurde extrahiert (Burdett 2015). Eine weitere Übersicht (7) schließt zwei in den Jahren 2008 und 2010 veröffentlichte systematische Übersichten und bereits in die systematischen Übersichten von Burdett 2015, Sim 2018 oder Cheng 2019 oder nicht im Volltext veröffentlichte Studien (ohne beschriebene Kontaktierung der Autoren) ein. Desweiteren wurde eine randomisierte Studie (8) aufgrund eines nicht-geplanten Vergleichs zu einer aktiven Kontrollgruppe (Uracil-Tegafur) ausgeschlossen (8) (siehe Ausgeschlossene Studien: Fragestellung 2a.

Für die Fragestellung 2b konnten drei geeignete systematische Übersichten, zwei RCTs und zwei konfounderadjustierte Kohortenstudien (insgesamt 7 Veröffentlichungen) eingeschlossen, extrahiert und bewertet werden (siehe Eingeschlossene Studien: Fragestellung 2b). Eine systematische Übersicht und drei RCTs wurde ausgeschlossen, da diese oder alle eingesclossenen Studien in einer anderen, methodisch höherwertigen systematischen Übersicht enthalten sind. Es wurden zwei Referenzen im Volltext geprüft und anschließend ausgeschlossen, da diese die Wirksamkeit einer neoadjuvanten Radiochemotherapie mit der einer neoadjuvanten Chemotherapie vergleichen und damit den Zusatznutzen einer neoadjuvanten Radiotherapie beschreiben (siehe Ausgeschlossene Studien: Fragestellung 2b).

Zu Fragestellung 3 wurden nach Löschen der Duplikate 432 Referenzen gescreent und die Volltexte von 43 Referenzen gelesen und anschließend drei Veröffentlichungen (1 systematische Übersicht, 1 RCT und 1 retrospektive Kohortenstudie) eingeschlossen, extrahiert und bewertet (siehe Eingeschlossene Studien: Fragestellung 3).Es wurden 40 Referenzen im Volltext geprüft und anschließend ausgeschlossen (siehe Ausgeschlossene Studien: Fragestellung 3). Zahlreiche geprüfte Studien wurden in die in die extrahierte und bewertete systematische Übersichtsarbeit von Ng 2019 (9) (11 Veröffentlichungen) eingeschlossen. Zusätzlich wurden systematische Übersichten mit älterem Suchdatum, deren Studien in die methodisch gute umfassende extrahierte systematische Übersichtsarbeit von Ng 2019 (9) eingeschlossen wurden (6 Veröffentlichungen) ausgeschlossen. Weitere Ausschlussgründe umfassen eine nicht geeignete Studienpopulation (Patienten im Stadium I/II und weniger als 20 Patienten im Stadium III in der Interventionsgruppe mit VATS) (13 Veröffentlichungen), eine andere untersuchte Intervention, welche speziell an Patienten in China mit häufigen Koinfektionen mit Tuberkulose angepasst war (1 Veröffentlichung), Vergleiche, welche nicht zur konventionellen Thoraktomie erfolgten (4 Veröffentlichungen), das ausschließliche Berichten von Ergebnissen für einen nicht geplanten Endpunkt (Immunfunktion in 1 Veröffentlichung), Veröffentlichungen auf chinesisch oder als Koferenzabstrakt (2 Veröffentlichungen) oder Designbetrachtungen, wenn die Methodik in systematischen Übersichten nicht hinreichend beschrieben wurde (2 Veröffentlichungen).

Zu Fragestellung 4 (Konsolidierungstherapie nach definitiver Therapie im Stadium III) wurden nach Löschen der Duplikate 309 Referenzen gescreent, 21 potentiell relevante Volltexte geprüft und anschließend vier RCTs (7 Veröffentlichungen) eingeschlossen, extrahiert und bewertet (siehe Eingeschlossene Systematische Übersichten: Fragestellung). Es wurden 14 Referenzen im Volltext geprüft und anschließend ausgeschlossen (siehe Ausgeschlossene Studien: Fragestellung 4). Ausschlussgründe betreffen das Designs einer Metaanalyse ohne Poolung der vergleichenden Effekte der eingeschlossenen Studien (1 Veröffentlichung), die Untersuchung der Wirksamkeit einer zielgerichteten Konsolidierungstherapie (2 Veröffentlichungen), nicht geplante Vergleiche zwischen einer Konsolidierungs- und einer Induktionstherapie (6 Veröffentlichungen) oder 2 verschiedenen Konsolidierungskonzepten (2 Veröffentlichungen), das ausschließliche Berichten von Ergebnissen zur Kosteneffektivität in den USA (1 Veröffentlichung) oder fehlenden Veröffentlichungen im Volltext (3 Veröffentlichungen).

Fragestellung 1: Ist die Histologie einschließlich molekularer Analysen im Stadium III für die Therapie-Wahl relevant?

Studiencharakteristika

Insgesamt sieben eingeschlossene systematische Übersichten bewerten die Wirksamkeit von EGFR-Inhibitoren bei EGFR-positiven Patienten (10-17), wobei bei einer der systematischen Übersichten Ergebnisse zur auf der grundlage histologischer Untersuchungen vorliegen (17) und eine weitere systematische Übersicht bewertet die Wirksamkeit von ALK-Inhibitoren bei Patienten mit ALK-oder positivem ROS-positivem nichtkleinzelligem Lungenkarzinom. Zusätzlich untersuchen 2 systematische Übersichten die prädiktive Güte von histologischen und molekularen Markern (18, 19).

Fünf systematische Übersichtsarbeiten (Cheng 2019, Greenhalgh 2016, Lee 2015, Lin 2018, Raphael 2019) (10-15) untersuchen die Wirksamkeit von EGFR-Inhibitoren in der Erstlinientherapie. Dabei schlossen Cheng 2019 und Raphael 2019 Patienten mit resektiertem NSCLC (Stadium IB bis IIIA) ein, während Greenhalgh 2016 Patienten mit lokal fortgeschrittenem und metastasiertem NSCLC (Stadium IIIB/IV) und Lee 2015 und Lin 2018 Patienten mit fortgeschrittenem NSCLC. Dabei fehlen bei Lin Angaben zur Stadieneinteilung, während die Ergebnisse in Lee 2015 vorrangig auf Patienten im Stadium IV basieren.

Während drei Übersichten (Cheng 2019, Lee 2015, Raphael 2019) zusammenfassende Ergebnisse für alle EGFR-Inhibitoren berichten, differenzieren Greenhalgh 2016 und Lin 2018 zwischen den verschiedenen Wirkstoffen. Es werden Ergebnisse für Erlotinib, Gefitinib, Afatinib, Dacomitinib, Cetuximab und Osertinib im Vergleich zu Chemotherapie oder Placebo berichtet. In Lee 2015 und Lin 2018 werden zusätzlich Ergebnisse zu verschiedenen Subgruppen (Exon 19 und EXON21L858R Mutation) berichtet. Die systematische Übersichtsarbeit von Lin 2018 kann auf der Basis einer Netzwerkmetaanalyse zusätzlich die Wirksamkeit der EGFR-Inhibitoren untereinander vergleichen. Die eingeschlossenen systematischen Übersichten schließen 4 randomisierte Studien mit insgesamt 1901 Patienten (Cheng 2019), 19 randomisierte Studien mit insgesamt 2317 EGFR-positiven Patienten (Greenhalgh 2016), 7 randomisierte Studien mit 1649 EGFR-positiven Patienten (Lee 2015) und 11 randomisierte Studien mit 3145 EGFR-positiven Patienten (Lin 2018) ein. Die unterschiedlichen Anzahlen ergeben sich aus den verschiedenen Einschlusskriterien und Suchzeiträumen (2010 bis 06/2019, bis 06/2015, 2004 bis 02/2014, 2009 bis 11/2017 und 01/2000 bis 10/2017), welche in Tabelle 8 detailliert dargestellt werden.

Eine weitere systematische Übersicht untersucht die Wirksamkeit von Gefitinib in der Erst- bis Drittlinientherapie bei Patienten mit fortgeschrittenem oder metastasiertem NSCLC (Stadium IIIB/IV) (Sim 2018) (16). Es werden insgesamt 35 randomisierte Studien mit 12089 Patienten eingeschlossen und Ergebnisse für Patienten mit EGFR-Mutation gesondert berichtet. Die Suche umfasste den Zeitraum bis 02/2017.

Zur Therapiewahl in der Zweitlinientherapie des fortgeschrittenen NSCLC (Stadien IIIB/IV) in Abhängigkeit von der Histologie und molekularen Untersuchungen existiert eine umfassende systematische Übersichtsarbeit (Vickers 2019) (17), welche im Rahmen einer Netzwerkmetaanalyse alle Therapieoptionen in Abhängigkeit von der Histologie (Plattenepithelkarzinom ja vs. nein), der PD-L1-Expression und der Mutation des EGFR-Rezeptors miteinander vergleichen. Es wurden 30 randomisierte Studien eingeschlossen, welche 17 verschiedene Therapieoptionen miteinander vergleichen. Die Suche umfasste den Zeitraum bis 09/2015.

Die Wirksamkeit von Therapien des NSCLC (Stadium III/IV) aufgrund einer ALK- oder ROS-1 Mutation werden in einer systematischen Übersichtsarbeit von Elliot 2020 (20) zusammenfassend untersucht. Auch hier ermöglicht die Netzwerkmetaanalyse einen Vergleich aller möglichen Therapieoptionen. Es wurden 13 randomisierte Studien zur Therapie mit Crizotinib, Ceritini, Alectinib, Brigatinib und Chemotherapie eingeschlossen und miteinander verglichen. Die Suche umfasste den Zeitraum bis 06/2019.

Insgesamt 2 systematischen Übersichten berichten Informationen zur prädiktiven Güte histologischer und molekularer Marker. Walls 2018 untersuchte einmal sehr weitgefasst die prädiktive Güte von Informationen bei Patienten in den Stadien I-III, welche routinemäßig zu Beginn einer Strahlentherapie

vorliegen (demographische Informationen des Patienten, Komorbiditäten, Charakteristika der Erkrankung, Tumormarker, radiologische Informationen, Chemotherapie). Diese Charakteristika enthalten Informationen zu molekularen Markern und zur Histologie. Wang 2017 untersucht die prognostische Güte einer ALK-Mutation bei allen Patienten mit NSCLC. Die systematischen Übersichten basieren auf einer systematischen Suche bis 07/2017 (Walls 2018) und 02/2017 (Wang 2017). Die Anzahl der eingeschlossenen Studien weicht aufgrund der unterschiedlichen Breite der eingeschlossenen Studien stark ab, so dass 255 Studien mit 71 933 Patienten (Walls 2018) bzw. 15 Studien (Wang 2017) eingeschlossen werden.

Bewertung der methodischen Qualität

Die methodische Qualität in der Durchführung der systematischen Übersichten wird in Tabelle 7 zusammenfassend dargestellt. Drei der systematischen Übersichten (Elliot 2020, Lin 2018, Vickers 2019) erlauben aufgrund der durchgeführten Metaanalysen einen Vergleich aller untersuchten Therapieoptionen. Ein Protokoll liegt für die 2 Cochrane-Reviews (Greenhalgh 2016 und Sim 2018) und 2 Netzwerkmetaanalysen (Elliot 2020, Vickers 2019) vor. Diese 4 Arbeiten weisen insgesamt einen hohen Qualitätsstandard auf. Die verschiedenen Stadien wurden allein in den Analysen von Vickers berücksichtigt, so dass diese mit dem Evidenzgrad 1a und die anderen 3 Arbeiten mit dem Evidenzgrad 1a- bewertet wurden. Die Abwertung der Evidenz für das Stadium III basiert auf der Zusammenfassung der Ergebnisse verschiedener Stadien ohne getrennte Ergebnisse für Subgruppen für das Stadium III. Die Übersichtsarbeiten von Lee 2015, Lin 2018 und Raphael wurden mit dem Evidenzgrad 2a bewertet. Die Abwertung der Evidenz basiert auf Indirektheit und Studienlimitationen oder Inkonsistenzen. Die systematische Übersicht Cheng 2019 wurde mit dem Evidenzgrad 2a- bewertet, die Abwertet basiert auf Studienlimitationen, Inkonsistenzen der Ergebnisse und Indirektheit.
Eine Bewertung der Evidenz für einzelne Endpunkte (Gesamtüberleben und progressionsfreies Überlegen) mit GRADE liegt für insgesamt 3 systematische Übersichten vor.
Die systematischen Übersichten zur prädiktiven Güte basieren auf nichtrandomisierten Kohortenstudien und wurden aufgrund ihrer methodischen Qualität, dem Einschluss nicht-vergleichender Studien und Indirektheit mit den Evidenzleveln 2a- (Walls 2018) und 1a-(Wang 2017) bewertet.

Tabelle 7: Methodische Bewertung der systematischen Übersichten zur Wirksamkeit einer Therapie auf Grundlage der Histologie oder molekularer Analysen bei Patienten mit NSCLC im Stadium III

Studie	Proto-koll	Suche	Doppelte Auswahl	Doppelte Extraktion	Ausge-schlossene Studien	Bewer-tung VZP	Meta-analysen	Einfluss VZP	Publikations-bias
Cheng 2019	☹	☺	😐	😐	😐[a]	☺	☺	☺	☹[b]
Elliot 2020*	☺	☺	☺	☺[c]	😐[a]	☺	☺	☺	☹
Greenhalgh 2016	☺	☺	☺	☺	☺	☺	☺	☺	☺
Lee 2015	☹	☺	😐	☺	😐[a]	😐	☹[d]	☹	😐
Lin 2018*	☹	☺	😐	☺	☺	😐	☺	☺	☺
Raphael 2019	☹	☺	☺	☺	😐[a]	☺	☺	☺	☹
Sim 2018	☺	☺	☺	☺	☺	☺	☺	☺	☹
Vickers* 2019	☺	☺	☺	☺	😐[a]	☹[e]	☺	☺	☹
Walls 2018	☹	☺	☺	☺	☺	☺	☺	☹	☹
Wang 2017	☹	☺	☺	☺	☹	☺	☺	☺	☺

☺: niedriges Verzerrungsrisiko, 😐: Bewertung ist teilweise unklar, ☹: hohes Verzerrungsrisiko
*: Netzwerkmetaanalysen
a: Darstellung der Gründe im Flowchart, aber fehlende Liste der ausgeschlossenen Studien mit Zuordnung zum Ausschlussgrund
b: Publikationsbias kann aufgrund fehlender Recherche in laufenden Studien nicht ausgeschlossen werden
c: Extraktion durch 1 Gutachter, Kontrolle durch 2. Gutachter
d: Keine statistische Beschreibung der Heterogenität, Fixed-effekt-Modell wurde trotz Heterogenität angewandt
e: Qualitätsbewertung war durch 1 Gutachter geplant
f: Extraktion durch 1 Gutachter, Kontrolle von 20% der Studien durch 2. Gutachter
g: Keine Information zur doppelten Qualitätsbewertung und detaillierte Beeschreibung der Qualität
h: Ausschließliches Auszählen signifikanter Ergebnisse, kein Poolen der Ergebnisse der Einzelstudien
VZP: Verzerrungspotential

Wirksamkeit und Sicherheit

Bei EGFR-positivem lokal fortgeschrittenem oder metastasiertem NSCLC konnte sowohl in einer zusammenfassenden Auswertung aller EGFR-Inhibitoren (Cheng 2019, Lee 2015, Raphael 2019) als auch für Erlotinib, Gefitinib, und Afatinib in der Erstlinientherapie ein verbessertes krankheits- oder progressionsfreies Überleben bei gleichbleibendem Gesamtüberleben bei hoher Qualität der Evidenz nach GRADE nachgewiesen werden (Greenhalgh 2016). Diese Ergebnisse wurden für Gefitinib in der Erstlinien- Zweitlinien- und Erhaltungstherapie bei moderater Qualität der Evidenz bestätigt (Sim 2018) (Evidenzgrad 1a- bis 2a).

Zur Therapiewahl in der Zweitlinientherapie des fortgeschrittenen NSCLC auf Grundlage von histologischen und molekularen Untersuchungen werden Ergebnisse für acht Subgruppen in Abhängigkeit von der Histologie (Plattenepithelkarzinom ja vs. nein), der PD-L1-Expression und der Mutation des EGFR-Rezeptors (Vickers 2019) berichtet. Die Autoren empfehlen für jede Subgruppe eine wirksamere Therapie im Vergleich zur Monotherapie mit Docetaxel mit einer allgemein höheren Wirksamkeit von Docetaxel und Ramucirumab. Bei EGFR-Mutation wird eine Therapie mit Erlotinib oder Gefitinib empfohlen, bei einer PD-L1 Expression und Nicht-Plattenepithelkarzinomen eine Behandlung mit Nivolumab (Evidenzgrad 1a).

Lin 2018 (Evidenzgrad 1a-) verglich die Wirksamkeit von EGFR-Inhibitoren der ersten, zweiten und dritten Generation und stellte eine höhere Wirksamkeit von Osimertinib im Vergleich zu Erlotinib und Gefitinib fest, welche vorrangig in bestimmten Subgruppen auftritt (Männer, Nicht-Asiaten, Raucher und Patienten mit Del 19-Mutation). Zu beachten ist, dass diese Ergebnisse auf einer Studie basieren, in welcher nur 219 Patienten mit Osimertinib behandelt wurden. Die Ergebnisse zur Verlängerung des progressionsfreien Überlebens, nicht aber des Gesamtüberlebens bei Einsatz von EGFR-Inhibitoren und EGFR-positivem NSCLC werden in den Veröffentlichungen von Lee 2015 bestätigt. Diese betonen die höhere Wirksamkeit bei Patienten mit Exon 19-Mutation, Nichtrauchern und Frauen (Evidenzgrad 2a).

In der Therapie des ALK-positivem NSCLC (Stadium III/IV) wurde eine Verbesserung des Gesamtüberlebens und progressionsfreien Überlebens mit Crizotinib, Ceritinib, Alectinib und Brigatinib im Vergleich zur Chemotherapie beschrieben, wobei Alectinib und Brigatinib wirksamer als Crizotinib und Ceritinib waren. Therapiebedingte Todesfälle traten sind selten auf (Elliot 2020). Die Evidenz wurde mit dem Evidenzlevel 1a- bewertet.

Walls 2018 berichtet die Anzahl signifikanter Parameter zur Vorhersage der Wirksamkeit und Toxizitäten während der Strahlentherapie von Patienten mit NSCLC (Kontrolle der Erkrankung, Auftreten von Gehirnmetastasen). Die Autoren schlussfolgern, dass zurzeit keine wirksamen validierten prädiktiven Parameter existieren. Wang 2017 berichtet Ergebnisse zur Wirksamkeit von Therapien auf das Therapieansprechen einer Chemotherapie, das Gesamt- und progressionsfreie Überleben bei Patienten mit und ohne ALK.Progression und weist auf eine hohe Abhängigkeit vom Rauchstatus hin (Evidenzgrad 1a- und 2a-).

Tabelle 8: Evidenztabelle zur Wirksamkeit und Sicherheit von Therapien auf der Grundlage histologischer oder molekularer Analysen bei Patienten mit NSCLC im Stadium III

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Cheng 2019 (10) Search from 01/2010 to 06/2019	**Systematische Übersicht** Efficacy of adjuvant EGFR-TKIs in the management of patients with resected NSCLC	Inclusion Criteria: • RCTs that compared the survival benefits of adjuvant EGFR-TKIs with CT or a placebo for patients with resected NSCLC Exclusion criteria: • pregnancy or lactating N=5 with n=1901 (41 to 973) patients 4 RCTs with low risk of bias, 1 with moderate risk of bias (no double-blinding) median age: 56-67 yrs stage IB to IIIA (N=3) stage IIIA N2 (N=1) stage IIIA: N=1 adjuvant CT: 0% (N=2) to 53% EGFR mutations: 17-100% (N=2)	**adjuvant EGFR-TKIs (erlotinib, gefitinib, icotinib)** (N=5): vs. **placebo** (N=2) **or adjuvant chemotherapy** (vinorelbine+cis platin) (N=3) median TKI treatment duration: 4.8 to 23.9 months	Primary: DFS Secondary: OS safety tolerability median follow-up: 2 to 4.7 yrs	**DFS:** EGFR-TKI vs. placebo: • unselected patients: no difference (HR 0.88; 95%CI 0.59 to 1.32; p=0.54) with substantial heterogeneity between studies (I^2=76 %) • patients with EGFR mutation: benefit for IG (HR 0.59; 95%CI 0.40 to 0.88; p=0.009) with moderate heterogeneity between studies (I^2=45 %) • patients with wild-type EGFR: no difference (HR 1.00; 95%CI 0.62 to 1.60; p=0.009) with substantial heterogeneity between studies (I^2=76 %) EGFR-TKI vs. CT: • patients with EGFR mutation: benefit for IG (HR 0.42; 95%CI 0.19 to 0.93; p=0.03) • patients with wild-type EGFR: no difference (HR 1.00; 95%CI 0.62 to 1.60; p=0.99) **Overall survival:** EGFR-TKI vs. placebo: • unselected patients: no difference (HR 1.09; 95%CI 0.80 to 1.49) with moderate heterogeneity between studies (I^2=52 %) • patients with EGFR mutation: no difference (HR 0.97; 95%CI 0.36 to 2.61) with moderate heterogeneity between studies (I^2=59 %) **Toxicities:** EGFR-TKI vs. placebo: • more adverse events (grade 3-4) with EGFR-TKIs (RR 2.72; 95%CI 2.23 to 3.33; p<0.00001) with low heterogeneity between studies (I^2=14 %) EGFR-TKI vs. CT:	**2a-** Abwertung aufgrund von Studien-limitationen, Inkonsistenzen und Indirektheit

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
					• less adverse events (grade 3-4) with EGFR-TKIs (RR 0.26 95%CI 0.18 to 0.38; p<0.00001) with substantial heterogeneity between studies (I^2=91 %)	
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** "In conclusion, patients with resected EGFR-mutant NSCLC treated with adjuvant EGFR-TKIs has an improved DFS compared with placebo or adjuvant chemotherapy. Adjuvant EGFR-TKIs were not effective among wild-type EGFR NSCLC. Treatment with adjuvant EGFR-TKIs resulted in more averse events than the placebo but fewer adverse events compared with adjuvant chemotherapy. Ongoing studies are needed to further confirm the possible benefits af adjuvant EGFR-TKI therapy in patients with NSCLC. " **Schlussfolgerung der Begutachterin:** Systematische Übersicht mit hoher Einschränkung der Qualität (keine Registrierung eines Protokolls, keine Angaben zu Screening und Extraktion sowie Ausschlussgründen je Studie, da keine Konferenzbände oder Register durchsucht wurden kann ein Publikationsbias nicht ausgeschlossen werden), basiert auf 5 Studien unter Einschluss von 1901 Patienten (2 Studien mit 176 Patienten schlossen nur Patienten im Stadium III ein) mit meist geringem Verzerrungspotential (1 Studie ohne vollständige Verblindung), Limitationen ergeben sich aus der teilweise substantiellen Heterogenität der Ergebnisse der einzelnen Studien (daher Abwertung aufgrund von inkonsistenzen), wobei aber die Aussage der Einzelstudien zum Vorteil einer EGFR-Therapie konsisten war, den Einschränkungen der Qualität der systematischen Übersichtsarbeit (daher Abwertung aufgrund von Studienlimitationen) und dem Einschluss von Studien mit Patienten der Stadien IB-IIIA ohne Subgruppeneinteilung für das Stadium III						
Elliott 2020 (20) CRD42017077046 Search until 06/2019	**Systematische Übersicht mit Netzwerk-analyse** Efficacy of individual anaplastic lymphoma kinase (ALK) inhibitors for NSCLC	Inclusion criteria: • RCTs on treatment-naïve or experienced participants with phase III or IV ALK-positive and/or ROS1-positive NSLC. • comparison of ALK inhibitors vs. all comparators Search in 3 databases N=13, one with cross-over design from 2103 and behind with 28 to 376 patients with ALK positive NSCLC median age: 45 to 61 yrs sex: 37% to 64% males	ALK inhibitors: crizotinib (N=8), ceritinib (N=2), alectinib (N=5), brigatinib (N=2) vs. CT (N=7) or another ALK inhibitor or the same ALK-inhibitor at a different dose (N=6) with allowed cross-over after	primary: treatment-related death secondary: OS, PFS, SAEs as reported by the study authors. .	**Treatment-related deaths** (11 RCTs): • rare, no difference stated • 11 deaths from 5 RCT: 10/917 with crizotinib vs. 1/765 with CT: RD 0.49; 95% CrI –0.16 to 1.46; OR 2.58; 95%CrI 0.76 to 11.37, • no deaths due to ceritinib (n = 304), alectinib (n = 415), or brigatinib (n = 137) with heterogeneous follow-up periods **Overall survival** (9 RCTs, n=2376): • improved OS with any ALK inhibitor vs. CT (HR 0.84, 95%CrI 0.72 to 0.97; n = 1611) with no heterogeneity between studies (I^2 = 0%) • difference was conserved among treatment-naive (HR 0.78; 95%CrI 0.62 to 0.97; I^2 = 0%;) but not experienced (HR 0.90, 95% CrI 0.73 to 1.11; I^2 = 0%) participants • improved OS with alectinib vs. CT (HR 0.57; 95% CrI 0.39 to 0.83) and crizotinib vs. CT (HR 0.68; 95% CrI 0.48 to 0.96) (1 RCT),	**1a-** Abwertung aufgrund von Indirektheit

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		no history of smoking: 46%–75% adenocarcinoma: 90%–100%, although 1 small RCT enrolled a higher proportion of participants with squamous NSCLC (64%) <u>Risk of bias:</u> low ROB for • sequence generation: 62% • allocation concealment: 54% • no double blinding: 100%, • independent review committee to ascertain disease progression for PFS in all RCTs • selective reporting: unclear for 23%, high in 2 RCTs • Other concerns: potential for cross-over between study groups • unclear reporting of outcome data by group allocation.	disease progression in N=6 RCTs		• Comparisons <u>between ALK inhibitors:</u> no differences shown **Progression-free survival** (12 RCTs, n=2583): • improved by all <u>ALK inhibitors compared to CT</u>: crizotinib RD 0.46 (CrI 0.39 to 0.54), ceritinib RD 0.52 (CrI 0.42 to 0.64), alectinib 300 BID: RD 0.16 (CrI 0.08 to 0.33), alectinib 600 BID RD 0.23 (CrI 0.17 to 0.30) and brigatinib RD 0.23 (CrI 0.15 to 0.35) • similar results among both treatment-experienced (HR 0.47, 95%CrI 0.39–0.57; I2 = 0%) and naive participants (HR 0.47, 95%CrI 0.40–0.56; I^2 = 0%) • improved by each individual <u>ALK inhibitor vs. placebo</u> (crizotinib: HR 0.46, 95%CrI 0.39–0.54; ceritinib: HR 0.52, 95%CrI 0.42–0.64; alectinib 300 BID: 0.16, 95%CrI 0.08–0.33; alectinib 600 mg BID: 0.23, 95%CrI 0.17–0.30; brigatinib: HR 0.23, 95%CrI 0.15–0.35) • Comparisons <u>between ALK inhibitors:</u> no difference between ceritinib and crizotinib, between alectinib and brigatinib, or between doses of alectinib (300 v. 600 mg BID). • alectinib and brigatinib better than crizotinib and ceritinib: • alectinib vs. crizotinib: RD 0.34 (CrI 0.17 to 0.70), alectinib vs. ceritinib RD 0.30 (CrI 0.14 to 0.64), brigatinib vs. crizotinib RD 0.49 (CrI 0.33 to 0.73), brigatinib vs. ceritinib RD 0.43 (CrI 0.27 to 0.70) **Serious adverse events** (9 RCTs, n>2074): • increased risk of <u>any ALK inhibitor vs. CT</u> (OR 1.67 [95%CrI 1.34–2.08]; I2 = 62%) among all patients. • consistent among both treatment experienced (OR 1.75 [95%CrI 1.23–2.46]; I2 = 73%) and naive participants (OR 1.42 [95%CrI 1.10–1.89]; I^2 = 18%)	

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
					• increased by crizotinib vs. CT (OR 2.08; 95% CrI 1.56 to 2.79) and alectinib vs. CT (OR 1.60; 95% CrI 1.00 to 2.58), but not ceritinib vs. CT (1.25; 95% CrI 0.90 to 1.74) • Comparisons <u>between ALK inhibitors:</u> fewer SAEs with ceritinib vs. crizotinib (OR 0.60, 95%CrI 0.39–0.93) • no other differences between crizotinib and alectinib or between ceritinib and alectinib shown	
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** " Treatment-related deaths were infrequent among ALK-positive NSCLC. Among patients with ALK-positive NSCLC, progression-free survival was improved by crizotinib, ceritinib, alectinib, and brigatinib compared with chemotherapy, while alectinib and brigatinib were significantly better than crizotinib and ceritinib. Overall survival was improved only by alectinib; however, the findings are likely confounded by crossover between treatment groups and should be interpreted with caution. Few studies have enrolled participants with ROS1 mutations, and additional research is need in this area." **Schlussfolgerung der Begutachterin:** Systematische Übersicht und Netzwerkanalyse zum Vergleich der Wirksamkeit aller untersuchten ALK-Inhibitoren mit geringen Einschränkungen der Qualität (keine Untersuchung von Publikationsbias, aber Suche in Registrierungen laufender Studien), basiert auf 13 Studien mit moderatem Verzerrungspotential (alle Studien ohne vollständige Verblindung, Verzerrung der Angaben zum Gesamtüberleben durch cross-over nach Progression in 6 Studien, daher Abwertung aufgrund von Studienlimitationen) Einschluss von mehr als 2600 Patienten, Limitationen für den primären Endpunkt (behandlungsbedingte Todesfälle) ergeben sich aus inkonsistentem Berichten in den Studien; insgesamt erfolgte ausschließlich eine Abwertung aufgrund von Indirektheit (Einschluss von Patienten im Stadium III und IV) aufgrund der Netzwerkmetaanalyse (Aufwertung des Evidenzgrades)						
Greenhalgh 2016 (11) Search until 06/2015	**Systematische Übersicht** clinical effectiveness of single -agent or combination EGFR therapies in locally advanced or metastatic EGFR positive NSCLC	<u>Inclusion criteria:</u> • Parallel RCTs comparing EGFR-targeted agents (alone or in combination with cytotoxic agents or BSC) with cytotoxic • CT (single or doublet) or BSC in CT-naive patients with locally advanced or metastatic (stage IIIB or IV) EGFR positive NSCLC unsuitable for treatment with curative intent	single -agent or combination **EGFR-TKIs** erlotinib (N=8) gefitinib (N=7) afatinib (N=2) cetuximab (N=2) vs. cytotoxic **CT** agents alone or in combination (e.g. platinum-based CT,	<u>Primary:</u> OS <u>Secondary:</u> PFS, Response, toxicity, quality of life follow-up 15.9 to 59 months	**Overall survival:** • no difference between EGFR-TKI and platinum-based CT: o <u>erlotinib</u> (N=3, n=429): 54 per 100 (95%CI 46 to 63) with erlotinib vs. 56 per 100 patients with CT died (HR 0.95; 95%CI 0.75 to 1.22) with no heterogeneity between studies (I^2=0%) o <u>gefitinib</u> (N=2, n=489): 66 (95%CI 58 to 73) with gefitinib vs. 67 per 100 patients with paclitaxel+carboplatin died (HR 0.95; 95%CI 0.77 to 1.18) with no heterogeneity between studies (I^2=0%) o <u>afatinib</u> (N=2, n=709): 44 (95%CI 37 to 52) with afatinib vs. 46 per 100 patients with CT died (HR 0.93; 95%CI 0.74 to 1.17) with no heterogeneity between studies (I^2=0%)	**1a-** Abwertung aufgrund von Indirektheit GRADE: erlotinib: high (OS, PFS) gefitinib: high (OS, PFS) afatinib: high (OS, PFS)

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		Search in 4 databases N=19, n=9414 (113 to 1217) 7 RCTs exclusively recruited EGFR positives, 2 reported subgroup analyses for these patients n=2317 EGFR positives (165 to 364), of whom 3 RCTs were exclusively in Europe, 10 in Asia1700 were of Asian origin median age: 56-65 years more females than males Risk of bias: double-blinding of 4 RCTs, 11 RCTs describe independent verification of PFS 15 RCTs were partially or totally funded by a pharmaceutical company, 3 RCTs were terminated early (1 for non-inferiority, 2 for benefit)	vinorelbine), or **Placebo** (N=4) or **best supportive care** (BSC)		○ cetuximab+CT vs. CT (N=2, n=81); HR 1.62 (95%CI 0.54 to 4.84) and HR 1.48 (95%CI 0.77 to 2.82) • benefit vs. placebo: ○ erlotinib (N=1): HR 0.48 (95%CI 0.27 to 0.85) **Progression-free survival:** • benefit with eEGFR-TKIs vs. platinum-based CT for ○ erlotinib (N=4, n=595): 33 per 100 (95%CI 27 to 40) with erlotinib vs. 73 per 100 patients with CT had progression or died (HR 0.30; 95%CI 0.24 to 0.38) with substantial heterogeneity between studies (I^2=73.8%) ○ but no difference vs. vinorelbine (HR 0.55; 95%CI 0.21 to 1.46) ○ gefitinib (N=2, n=485): 57 (95%CI 50 to 64) with gefitinib vs. 89 per 100 patients with paclitaxel+carboplatin had progression or died (HR 0.39; 95%CI 0.32 to 0.48) ○ afatinib (N=2, n=709): 29 (95%CI 24 to 35) with afatinib vs. 56 per 100 patients with CT had progression or died (HR 0.42; 95%CI 0.34 to 0.53) with substantial heterogeneity between studies (I^2=90.4%) • benefit for CT vs. placebo for ○ benefit for erlotinib+CT vs. CT+placebo (HR 0.25; 95%CI 0.16 to 0.39) • no difference for cetuximab (N=2, n=81) **Tumour response:** • benefit with eEGFR-TKIs vs. platinum-based CT for ○ erlotinib (N=5, n=593): RR 2.26 (95%CI 1.85 to 2.76) with moderate heterogeneity between studies (I^2=57.1%) ○ erlotinib +CT (N=1, n=97): RR 5.74 (95%CI 2.86 to 11.5)	

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
					○ gefitinib (N=4, n=648): RR 1.87 (95%CI 1.6 to 2.19) with moderate heterogeneity between studies (I^2=57.5%) ○ afatinib (N=2, n=709): RR 2.71 (95%CI 2.12 to 3.46) with no heterogeneity between studies (I^2=0%) • no difference between erlotinib and vinorelbine, cetuximab+CT and CT **Adverse events (grade 3 or 4):** • Commonly reported for afatinib, erlotinib, and gefitinib monotherapy: rash and diarrhoea. • Consistenlly worse with CT: myelosuppression, fatigue and anorexia were also associated with some chemotherapies. **Quality of life and symptom improvement**: • For each of erlotinib, gefitinib, and afatinib, 2 RCTs showed improvement in one or more indices for EGFR-TKIs vs. CT	
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** " Erlotinib, gefitinib, and afatinib are all active agents in EGFR M+ NSCLC patients, and demonstrate an increased tumour response rate and prolonged progression-free survival compared to cytotoxic chemotherapy. We also found a beneficial effect of the TKI compared to cytotoxic chemotherapy. However, we found no increase in overall survival for the TKI when compared with standard chemotherapy. Cytotoxic chemotherapy is less effective in EGFR M+ NSCLC than erlotinib, gefitinib, or afatinib and is associated with greater toxicity. There were no data supporting the use of monoclonal antibody therapy." **Schlussfolgerung der Begutachterin:** Systematische Übersicht ohne Einschränkungen der methodischen Qualität, basiert auf 19 Studien unter Einschluss von 9414 Patienten (davon 2317 EGFR positiv), Verzerrungspotential betrifft vorrangig fehlende Verblindung in 15 RCTs, fehlende unabhängige Beurteilung von PFS in 8 RCTs sowie teilweise bzw. vollständige Finanzierung durch die Pharmaindustrie in 15 RCTs), enthält eine Evidenzbewertung nach GRADE (Bewertung der Evidenz der Ergebnisse zu OS und PFS mit hoch trotz fehlender unabhängiger Begutachtung von PFS (Erlotinib, betriff alle 4 RCTs, Gefitinib in 1 von 2 RCTs) und teilweise hoher Heterogenität zwischen Studienergebnissen, welche Gesamtbewertung nicht beeinflussen.						
Lee 2015 (5, 12, 13) Search from 01/2004 to 02/2014	**Systematische Übersicht** Impact of different EGFR mutations and	Inclusion criteria: • RCTs that compared EGFR TKIs against platinum-based combination CT in adult patients with	**EGFR-TKIs** (n=950): gefitinib (N=2) erlotinib (N=3) afatinib (N=2) for PFS	most updated results on **PFS** (independent reviews) (13) **OS**	**Progression-free survival** (N=7, n=1649 patients) (13)**:** • Treatment with EGFR TKIs was associated with a 63% reduction in the risk of disease progression or death (HR 0.37; 95% CI 0.32 to 0.42; p<0.001)	**2a** Abwertung aufgrund von Studien-limitationen

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
	clinical characteristics on PFS and OS in patients with advanced EGFR-mutated NSCLC treated with EGFR TKIs as first-line therapy	• good performance status who did not receive any systemic therapy for their • histologically or cytologically confirmed, newly diagnosed advanced NSCLC • with sensitizing EGFR mutations, inclusion of published manuscripts, conference abstracts and additional data and individual patient data with longest available follow-up Search in 4 databases N=7 with 1649 (154-364) patients, subgroup analyses base on individual patient data from 2 RCTs, 4 RCTs recruited only patients with the two common EGFR mutations, exon 19 deletions and exon 21 L858R substitution exon19 deletions: 772 (56%) Exon 21 L858R substitution: 686 (44%) <65 yrs: 49-79% ECOG 0 or 1: 94-100%	and gefitinib (N=3) erlotinib (N=3) for OS vs. **CT** (n=699)	(individual patient data, median follow-up: 35 months) (12)	• Compared with CT, treatment with EGFR TKIs demonstrated 50% greater benefit in exon 19 deletions vs. in exon 21 L858R substitution: ○ subgroup with <u>exon 19 deletions</u> (n=872): HR 0.24; 95%CI, 0.20 to 0.29; p<0.001) ○ subgroup with <u>exon 21L858R substitution</u> (n=686): HR 0.48 (95% CI 0.39 to 0.58; p<0.001) • Improvement in PFS with EGFR TKI treatment compared with chemotherapy did not differ by tumor histologic subtype (adenocarcinoma vs. other histologic types) • 348 patients in 4 RCTs who were randomly assigned to CT: longer median PFS survival of patients with exon 21 L858R substitution vs. those with exon 19 deletions: 6.1 vs. 5.1 months (HR, 0.70; 95% CI 0.56 to 0.89; p=.003). • 362 patients who were randomly assigned to EGFR TKIs: shorter median PFS of patients with exon 21 L858R substitution vs. those with exon 19 deletions: 10.0 vs. 11.8 months (HR, 1.39; 95% CI 1.10 to 1.76; p=0.006) **Overall survival:** (N=6, n=1231 patients) (12): • 780 deaths (65.4 vs. 61.3%) with no difference between treatment groups (median OS 25.8; 95% CI 23.8 to 27.5 months vs. 26.0; 95% CI 23.6 to 28.9 months; HR 1.01, 95% CI 0.88 to 1.17; p=0.84) • no differences between subgroups of different EGFR mutations: ○ <u>exon 19 deletions</u>: median OS 27.4, 95% CI 25.1 to 29.3 months vs. 25.9; 95% CI 23.2 to 29.5 months; HR 0.96, 95% CI 0.79 to 1.16; P=0.68; ○ <u>exon 21 L8585R:</u> median OS 24.1; 95%CI 21.6 to 26.8 months vs. 25.9; 95% CI 22.5 to 29.6; HR 1.06, 95% CI 0.86 to 1.32 months; p=0.59 • no differences in treatment effects between patients with adenocarcinoma and non-adenocarcinoma	und Indirektheit

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		Stage IIIB: 12.6 % IV: 80.3 % Postoperative recurrence : 6.9 % sian: 5 RCTs with 100% women: 61-73% adenocarcinoma: 92-100% never-smoker: 92-100% risk of bias: 100% open-label RCTs, low in 6 RCTs, unclear in 1 unpublished RCT			Patients with **documented disease progression** (n=1004): 65.9% in the EGFR-TKI arm received CT vs. 73.8% in the CT arm received EGFR-TKI as salvage therapy with no differences between EGFR mutation subgroups: o exon 19 deletion crossover of 64.0% vs. 71.1% o exon 21 L858R crossover of 67.7% vs. 77.2% • more patients in the EGFR-TKI arm received no systemic treatment at disease progression vs. in the CT arm (9.1% vs 0.6%). • Following disease progression patients from the EGFR-TKI arm had shorter OS compared to CT arm: 12.8; 95% CI 11.4 to 14.3 months vs. 19.8; 95% CI 17.6 to 21.7 months) • patients who progressed and received EGFR-TKI as a second or subsequent line of therapy had longer median OS (21.5; 95% CI 19.1 to 24.9 months) vs. those who received chemotherapy (15.9, 95% CI 14.2 to 17.5 months), no treatment (4.1; 95% CI 3.0 to 5.9 months) or other/unknown therapies (4.9; 95% CI 3.5 to 5.8 months)	

Zusammenfassende Beurteilung

Schlussfolgerungen der Autoren der Studie: "In conclusion, EGFR TKIs significantly prolong PFS in all patients with advanced NSCLC with EGFR mutations compared with chemotherapy. The relative benefits of EGFR TKIs compared with chemotherapy were greatest in patients with exon 19 deletions. Greater PFS benefit with EGFR TKIs compared with chemotherapy was also seen in never smokers and women. These findings have important implications for clinical trial design and interpretation, economic analyses, and future drug development for EGFR-mutated, advanced NSCLC."(13)

"In conclusion, despite statistically significant relative PFS benefit, OS did not statistically significantly differ between gefitinib or erlotinib vs chemotherapy in advanced NSCLC with common EGFR mutations. This result is likely due to effective subsequent therapy with EGFR-TKI at disease progression in patients randomly assigned to chemotherapy. Upfront EGFR-TKI treatment is still recommended over chemotherapy as firstline treatment in this population." (12)

Schlussfolgerung der Begutachterin:

Systematische Übersicht mit moderater Einschränkung der Qualität (keine Registrierung eines Protokolls, keine Angaben zu Screening und Bewertung des Verzerrungspotentials, wenige Angaben zum Verzerrungspotential sowie Heterogenität der Effekte zwischen den Studien) (daher Abwertung aufgrund von Studienlimitationen), basiert auf 7 (PFS) bzw. 6 RCT (OS) Studien unter Einschluss von 1649 bzw. 1231 Patienten. Zusätzlich wurde die Wirksamkeit in Abhängigkeit verschiedener Charakteristika der Patienten auf der Grundlage individueller Patientendaten aus 4 bzw. 6 Studien verglichen und es wurden Gründe für die verschiedenen Ergebnisse zu PFS und OS (Behandlung nach Progression) gesucht. Insgesamt 12.6 % der Patienten im Stadium IIIB wurden angeschlossen, 80 % im Stadium IV (daher Abwertung aufgrund von Indirektheit)

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)

Lin 2018 (14) Search 01/2009 to 11/2017	**Systematische Übersicht und Netzwerk-metaanalyse** Efficacy of EGFR-TKIs in terms of PFS and toxicity, primary focus on superiority of osimertinib to first-generation EGFR TKI	Inclusion criteria: RCTs that compared EGFR TKIs with standard platinum-based CT or compared different first-line EGFR TKIs in patients with newly pathologically confirmed advanced NSCLC with actionable EGFR mutations
		Search in 3 databases
		N=11 with 3145 (154 to 556) patients
		median age: 57 to 65 yrs
		more females (53 to 72%)
		1 non-Asian RCT, 6 only conducted in Asia, all other mainly Asian
		mostly never-smoker (62-71%), PS 0-1 (86-100%) and adenocarcinoma (87-100%)
		19Del and L858R accounted for > 90% of patients
		Quality of RCTs: high (Jadad-score >3)
			EGFR TKIs: gefitinib (N=2, n=200) erlotinib (N=4,n=404) afatinib (N=3) dacomitinib (N=1, n=227) osimertinib (N=1, n=279)
			
			vs.
			standard platinum-based **CT** (N=7, n=702) or first-line **EGFR TKIs**: (standard of care: gefitinib, erlotinib) (N=4, n=789)
				PFS
				OS
				toxicity
					Progression-free- survival:
					• EGFR-TKI had longer PFS vs. CT:
					  ○ gefitinib and erlotinib (=standard of care) : HR 0.63 (95%CI 0.55 to 0.72)
					  ○ dacomitinib: HR 0.50 (95%CI 0.37 to 0.69)
					  ○ afatinib: HR 0.61 (95%CI 0.51 to 0.73)
					  ○ osimertinib: HR 0.45 (95%CI 0.33 to 0.62)
					• no difference between gefitinib and erlotinib (=standard of care) (N=6): HR 0.94 (95% CI 0.76 to 1.15)
					• higher benefit with osimertinib vs. standard of care (HR 0.71; 95%CI 0.54 to 0.95)
					• no difference between dacomitinib (HR 0.80; 95%CI 0.60 to 1.06) or afatenib (HR 0.96; 95%CI 0.86 to 1.17) and standard of care
					• rank of efficacy remained unchanged in females, males, non-Asians, never smokers, ever or current smokers, and those with 19Del and L858R mutations but not in the Asian subgroup
					• osimertinib was associated with improvement PFS in
					  ○ men (HR=0.79, 95% CI, 0.68–0.92)
					  ○ non-Asians (HR=0.63, 95% CI, 0.40–0.98)
					  ○ smokers (HR=0.73, 95% CI, 0.56–0.95) and
					  ○ Del19 mutation (HR 0.69, 95% CI, 0.54–0.90)
					
					Adverse events:
					• first- and second-generation TKIs (gefitinib, erlotinib, afatinib, dacotinib) shared similar common AEs (predominately rash and diarrhea)
					• third-generation TKI (osimertinib) was not associated with a significant incidence of rash
					• permanent discontinuation rate due to toxicity was low
					• for all EGFR TKIs (13% with ositerminib)
					• Toxicity-related death was rare (none with ositerminib)
						2a Abwertung aufgrund von Studien-limitationen und Indirektheit

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** "In summary, our study supported osimertinib as a first-line treatment for NSCLC patients with an activating EGFR mutation. The analysis suggested that only some subgroups (men, non-Asians, and smokers) would really benefit from osimertinib compared with gefitinib or erlotinib." **Schlussfolgerung der Begutachterin:** Systematische Übersicht mit Netzwerkmetaanalyse zwischen EGFR-Inhibitoren sowie EGFR-Inhibitoren und Chemotherapie in der Erstlinientherapie bei Patienten mit fortgeschrittenem NSCLC mit ausführlichen Subgruppenanalysen, moderate Einschränkung der Qualität (keine Registrierung des Protokolls, fehlende Informationen zur Durchführung des Screenen und zur Durchführung und Ergebnissen der Qualitätsbewertung, daher Abwertung aufgrund von Studienlimitationen), basiert auf 11 Studien mit insgesamt 3145 Patienten ohne nähere Informationen zur Stadieneinteilung (daher Abwertung aufgrund von Indirektheit), berichtet werden ausschließlich Ergebnisse zum progressionsfreien Überleben und Zusammenfassung der Toxizitäten (ohne Häufigkeiten), Ergebnisse zu EGFR-Inhibitoren der 2. und 3. Generation basieren für 2 Substanzen auf Ergebnissen aus je 1 Studie (daher Abwertung aufgrund fehlender Präzision), zusammenfassend erfolgte eine Abwertung der Evidenz aufgrund von Studienlimitationen trotz der Durchführung der Netzwerkmetaanalyse (Aufwertung des Evidenzgrades)						
Raphael 2019 (15) Search from 01/2000 until 10/2017	**Systematische** Übersicht Efficacy and safety of adjuvant TKIs in NSCLC patients	Inclusion criteria: RCTs evaluating the survival and/or safety associated with adjuvant TKI in resected NSCLC patients ≥ 18 years, stage IB to IIIA NSCLC (any histology), particularly patients harboring an EGFR activating mutation. Exclusion criteria: TKI in inoperable NSCLC patients and studies with no survival data N=6 with 1860 patients, of them 599 with with an activating EGFR mutation (ie, exon 19 deletion/ exon 21 L858R) N=4 studies included only patients with EGFR mutation	**any TKI used in lung cancer** (first, second, or third generation) for a period ≥ 4 months **vs.** **no treatment, placebo or adjuvant CT** CT before or parallel to TKI), 3 studies used gefitinib, 2 erlotinib, 1 icotinib, With administration between 4 month and 2 years	Primary: DFS (median and 2-yr DFS) in patients harboring activating mutations Secondary: DFS in patients with any EGFR mutational status, OS (median OS) in patients with any EGFR mutational status and in patients harboring activating mutations toxicity profile in all patients	**Disease-free survival:** In patients with EGFR activating mutations: • 48% reduction in the risk of disease recurrence in IG (N=5, n=560; HR: 0.52, 95% CI: 0.35-0.78) with moderate heterogeneity between studies (I^2=52%) • 47% reduction in the risk of 2-year disease recurrence in IG (N=6, n=599, RR: 0.53, 95% CI: 0.43-0.66) with no heterogeneity between studies (I^2=0%), NNT with a TKI to have one less recurrence over 2 years: 4 (95% CI: 3-6) Subgroup analysis: • 57 % reducation of disease recurrence with adjuvant TKI compared to CT (N=2, n=324, HR: 0.43, 95% CI: 0.19-0.93, I^2=76%) with benefit in 2-year DFS: RR: 0.5, 95% CI: 0.31-0.8,I^2=56%, NNT 3 (95%CI 2-6) • 38 % reduction in patients treated with additional TKI after surgery and CT (N=3 studies, n=236, HR: 0.62, 95% CI: 0.33-1.17, I^2=46%) with benefit in 2-year DFS (N=4, n=275, RR: 0.51, 95% CI: 0.35-0.74, I^2=0%), NNT 5 (95%CI 3-9) In patients with any EGFR mutation: 35% reduction in the risk of disease recurrence with the use of TKIs (N=5, n=1860, HR: 0.65, 95% CI: 0.43-1.00), with substantial heterogeneity between studies (I^2=84%)	**2a** Abwertung aufgrund von Inkonsistenz und Indirektheit GRADE: DFS/OS: low due to study limitations and inconsistency Toxicity: moderate

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		Risk of bias: generally low, but no blinding in 4 studies			**Overall survival:** • In <u>patients with an actvating EGFR mutation</u>: • no OS benefit in IG (N=4, n=338 participants, HR: 0.64, 95% CI: 0.22-1.89) with substantial heterogeneity between studies (I^2=73%) • in <u>patients with any EGFR mutational status</u>: • no OS benefit (N=4, n=1638, HR: 0.8, 95% CI: 0.48-1.33) with substantial heterogeneity between studies (I^2=77%) <u>Toxicity:</u> • increase in grade ≥3 or higher • skin toxicity (N=6, n=1831, OR: 6.07, 95% CI: 4.34-8.51) with no heterogeneity between studies (I^2=0%), NNH: 7) • diarrhea (N=6, n=1,831, OR: 4.05, 95% CI: 2.44-6.74, I2=0%, NNH: 20) • nausea/vomiting (N=4, n=1545, OR: 2.59, 95% CI: 1.03-6.51, I^2=45%, NNH: 100)	
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** " Adjuvant TKIs appear to decrease the risk of recurrence in NSCLC patients harboring an EGFR mutation but do not improve OS. However, OS data are still immature and longer follow-up is needed for a definitive assessment of this outcome measure. There is currently not sufficient evidence (low level of evidence) to recommend routine use of adjuvant TKIs. Further results from ongoing well-designed trials will define the role of adjuvant TKI in NSCLC patients harboring an EGFR mutation and provide stronger conclusions." **Schlussfolgerung der Begutachterin:** Systematische Übersicht zur Wirksamkeit einer adjuvanten Chemotherapie mit EGFR-Inhibitoren bei Patienten mit resektierten NSCLC der Stadien IB bis IIIA mit einer geringen Einschränkung der Qualität (keine Registrierung des Protokolls, fehlende Untersuchung auf Publikationsbias), basiert auf 6 Studien (davon 4 aus Asien) mit insgesamt 1860 Patienten (davon 599 mit EGFR-Mutation, 2 Studien mit 162 Patienten schlossen aussschließlich Patienten im Stadium III ein – daher Abwertung aufgrund von Indirektheit), berichtet werden Ergebnisse zum krankheitsfreien und Gesamtüberleben und zur Toxizität (ohne Häufigkeiten), die Qualität der Evidenz wurde von den Autoren mit GRADE bewertet. Es erfolgte eine Einschätzung der Evidenz mit gering für DFS und OS (Abwertung aufgrund von Studienlimitationen (fehlende Verblindung in Mehrheit der Studien, unklare Verblindung der Zuweisung der Intervention) und Inkonsistenz der Ergebnisse und moderat für die Toxizitäten (Abwertung aufgrund der beschriebenen Studienlimitationen). Zusammenfassend wird die Qualität der Evidenz daher mit 1a-bewertet.						
Sim 2018 (16)	**Systematische Übersicht** Effectiveness and safety of	<u>Inclusion criteria:</u> RCTs assessing gefitinib, alone or in combination with other treatment,	**Gefitinib** (at any dose, alone or as	**Primary:** OS, PFS, TTF, toxicities (NCI CTCAE) **Secondary:**	**Overall survival:** no difference for all patients (except for EGFR positives) • <u>Gefitinib vs. placebo</u>: 4 RCTs: no difference in 1st-line (HR 0.84; 95%CI 0.62 to 1.14) or second-line treatment (HR	**1a-** Abwertung aufgrund von Indirektheit

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Search until 02/2017	gefitinib as first-line, second-line or maintenance treatment for advanced NSCLC	compared to placebo or other treatments in the first- or successive-line treatment of patients with NSCLC (age≥ 18 yrs, stage IIIB/IV)) Exclusion criteria: cross-over and quasi-randomized studies, compassionate use Search in 3 databases and other resources 35 RCTs, 12 089 patients 17 multicenter phase III trials and 18 phase II trials Risk of bias: adequate sequence generation in 17 RCTs adequate allocation concealment in 11 RCTs adequate blinding of patients and investigators in 8 RCTs low risk of bias according to incomplete outcome data in 28 RCTs low risk of bias on selective reporting in all RCTs 3 RCTs were stopped early	combination therapy to CT) mostly continued until disease progression, unacceptable toxicity or withdrawal vs. **Control** (placebo, best supportive care, or CT or gefitinib at different doses)	median OS and PFS, 1-year survival, Tumour response (RECIST), QoL (FACT-L, LCS, TOI, PSI)	0.89; 95%CI 0.79 to 1.01) and maintenance therapy (HR 1.14; 95%CI 0.61 to 2.14), but better 1-year survival after 2nd line treatment (HR 1.28; 95%CI 1.05 to 1.57), higher benefit of maintenance therapy in EGFR positives (1 RCT; HR 0.39; 95%CI 0.15 to 0.98) • Gefitinib vs. CT in 1st-line treatment: 2 RCTs, 275 patients: mean OS ranged from 2.2 to 5.9 vs. 3.5 to 8 months (HR 0.98; 95%-CI 0.91 to 1.46), no influence of EFGR mutation (HR 0. 97, 0.77 to 1.21) and Asian origin • Gefitinib vs. CT in 2nd-line treatment: 2 RCTs, 1607 patients: mean OS ranged from 7.5 to 7.6 vs. 7.1 to 8 months (HR 1.02; 95%-CI 0.91 to 1.15), no influence of EFGR mutation (HR 0.83; 95%CI 0.41 to 1.66) and Asian origin • benefit for patients with EGFR mutation positive tumors of maintenance therapy following CT (HR 0.39, 95% CI 0.15 to 0.98; p= 0.05) (N=1) **Progression-free survival:** • Gefitinib vs. placebo: 4 RCTs: no difference in 1st-line (HR 0.82; 95%CI 0.60 to 1.12), but benefit for 2nd-line treatment (HR 0.82; 95%CI 0.75 to 0.90) and maintenance therapy (HR 0.70; 95%CI 0.53 to 0.91), higher benefit of maintenance therapy in EGFR positives (1 RCT; HR 0.17; 95%CI 0.07 to 0.41) • Gefitinib vs. CT in 1st-line treatment: 2 RCTs, 275 patients: mean PFS between 1.9 to 2.7 vs. 2 to 2.9 months (HR 1.19; 95%-CI 0.86 to 1.65), benefit with EFGR mutation (0.47; 95% CI 0.36 to 0.61) and Asian origin (0.65; 95% CI 0.43 to 0.98) • Gefitinib vs. CT in 2nd-line treatment: 2 RCTs, 1607 patients: mean OS ranged from 2,2 to 3 vs. 2.7 to 3.4 months (HR 1.04; 95%-CI 0.92 to 1.17), benefit with EFGR	**GRADE** (erfolgte nur für Gefitinib vs. CT) **PFS and OS: moderate** Abwertung aufgrund von Indirektheit (Erstlinientherapie) und fehlender Präzision (Zweitlinientherapie) **toxicities: high**

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		other risk of bias: conflicts of interest, in particular pharmaceutical funding or significant affiliations			mutation (0.24; 95% CI 0.12 to 0.47) and Asian origin (0.71; 95% CI 0.57 to 0.88) • benefit for <u>maintenance gefitinib after 1st-line therapy</u> (HR 0.70; 95%-CI 0.53 to 0.91; p=0.007) • benefit for patients <u>with EGFR mutation positive tumors in 1st-line CT</u> (HR 0.47; 95% CI 0.36 to 0.61; p<0.00001) and 2nd--line CT (HR 0.24, 95% CI 0.12 to 0.47; p<0.0001) • benefit for patients with EGFR mutation positive tumours of maintenance therapy following CT (HR 0.17, 95% CI 0.07 to 0.41; p< 0.0001) (N=1) **Toxicities:** • <u>Gefitinib vs. placebo:</u> o Skin rash: 2 RCTs, increased with gefitinib after 2nd-line or maintenance therapy (RR 7.92; 95%CI 1.46 to 43.03) o Diarrrhoe: 3 RCTs, more frequent in 2nd-line and maintenance therapy (RR 2.48; 95%CI 1.15 to 5.35) o Increased ALT: 1 RCT; more frequent with gefitinib (RR 9.11; 95%CI 1.18 to 70.32) o No difference of pruritus (1 RCT), constipation (1 RCT), nausea (2 RCTs), vomiting (2 RCTs), anorexia (3 RCTs), fatique (2 RCTs), asthenia (1 RCT), respiratory tract infection (2 RCTs), dyspnoe (3 RCTs), anaemia (1 RCT), abdominal pain (1 RCT), increased AST (1 RCT), neutropenia (1 RCT), anaemia (1 RCT), thrombocytopenia (1 RCT) • <u>Gefitinib vs. CT in 1st-or 2nd-line treatment</u>: o Skin rash: 4 RCTs, 1858 patients: increases from 9 with CT to 21 (95%CI 9 to 46) per 1000 with gefitinib (RR 2.40; 95%-CI 1.08 to 5.31), GRADE: high) o Constipation: 3 RCTs, 1719 patients: decreases from 19 with CT to 8 (95%CI 3 to 18) per 1000 with	

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					gefitinib (RR 0.41; 95%-CI 0.17 to 0.97), GRADE: high) ○ Fatique: 2 RCTs, 275 patients: decreases from 65 to 10 (95% CI 2 to 57) per 1000 with gefitinib (RR 0.16; 95%-CI 0.03 to 0.88), GRADE: moderate) ○ Asthenia: 3 RCTs, 1773 patients: decreases from 79 to 40 (95% CI 28 to 60) per 1000 with gefitinib (RR 0.51; 95%-CI 0.35 to 0.75), GRADE: high) ○ Neurotoxicity: 2 RCTs, 1529 patients: decreases from 29 to 2 (95% CI 0 to 10) per 1000 with gefitinib (RR 0.07; 95%-CI 0.01 to 0.34), GRADE: high) ○ Neutropenia: 4 RCTs, 1857 patients: decreases from 505 to 20 (95% CI 10 to 30) per 1000 with gefitinib (RR 0.04; 95%-CI 0.02 to 0.06), GRADE: high) ○ Febrile neutropenia: 3 RCTs, 1768 patients: decreases from 92 to 11 (95% CI 6 to 21) per 1000 with gefitinib (RR 0.12; 95%-CI 0.06 to 0.23), GRADE: high) **Overall response rate:** • gefitinib vs. placebo: ○ higher response with gefitinib (2 RCTs, RR 10.12; 95%CI 1.32 to 77.33) ○ no difference in 1st-line therapy (1 RCT, 202 patients), higher with gefitinib in 2nd-line (1 RCT, 1399 patients; RR 6.42; 95%CI 2.82 to 14.64) and maintenance therapy (1 RCT, 173 patients; RR 10.12; 95%CI 1.32 to 77.33) • gefitinib vs. CT: ○ no difference in 2nd-line therapy (2 RCTs), higher benefit for EGFR positives (7 RCTs, RR 1.71; 95%CI 1.34 to 2.19)	

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					Disease control rate: • gefitinib vs. placebo: o no difference in 1st-line therapy (1 RCT, 202 patients)**,** higher with gefitinib in 2nd-line (1 RCT, 1399 patients; RR 1.24; 95%CI 1.06 to 1.44) and maintenance therapy (1 RCT, 173 patients; RR 1.21; 95%CI 1.00 to 1.46) • gefitinib vs. CT: o no difference in 1st-line (1 RCT) or 2nd-line therapy (1 RCT), no difference for EGFR positives (5 RCTs) **Time to treatment failure**: benefit for 2nd-line gefitinib (HR 0.82; 95%-CI 0.75 to 0.90; p<0.001) **Quality of life:** Gefitinib vs. CT (2 RCTs, 1656 patients): • benefit for patients with EGFR mutation positive tumours in Functional Assessment of Cancer Therapy-Lung (FACT-L) (SMD 10.50, 95% CI 9.55 to 11.45; p < 0.000001), • lung cancer subscale (SMD 3.63, 95% CI 3.08 to 4.19; p< 0.00001) • Trial Outcome Index (SMD 9.87, 95% CI 1.26 to 18.48; p< 0.00001) scores compared with chemotherapy • PSI QoL improvement rate (MD 5.60; 95%CI 3.55 to 7.65)	
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** " This systematic review shows that gefitinib, when compared with standard first- or second-line chemotherapy or maintenance therapy, probably has a **beneficial effect on progression-free survival and quality of life in selected patient populations**, particularly those with tumours bearing sensitising **EGFR mutations**. Patients with EGFR mutations lived longer when given maintenance gefitinib than those given placebo. One study conducted subgroup analysis and showed that gefitinib improved overall survival over placebo in the second-line setting in patients of **Asian ethnicity**. All other studies did not detect any benefit on overall survival. The data analysed in this review were very heterogenous. We were limited in the amount of data that could be pooled, largely due to variations in study design. The risk of bias in most studies was moderate, with some studies not adequately addressing potential selection, attrition and reporting bias. This heterogeneity may have an impact on the applicability of the results.						

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Combining gefitinib with chemotherapy appears to be superior in improving progression-free survival to either gefitinib or chemotherapy alone, however further data and phase III studies in these settings are required. Gefitinib has a favourable toxicity profile when compared with current chemotherapy regimens. Although there is no improvement in overall survival, gefitinib compares favourably with cytotoxic chemotherapy in patients with EGFR mutations with a prolongation of progression-free survival and a lesser side effect profile." **Schlussfolgerung der Begutachterin:** Systematische Übersicht, geringfügige Einschränkung der Qualität (keine Untersuchungen zum Publikationsbias, aber Suche in Registern laufender Studien und Konferenzbänden und Kontaktierung von Autoren), basiert auf 35 Studien unter Einschluss von 12 089 Patienten im Stadium IIIB-IV (daher Abwertung aufgrund vin Indirektheit) mit meist geringem Verzerrungspotential (teilweise fehlenden Informationen zur Randomisierung und hohem Risiko von Verzerrungsrisiko aufgrund unvollständiger Auswertung der Ergebnisse in 5 Studien und selektivem Berichten von Endpunkten in 1 Studie) und Evidenzbewertung nach GRADE (Bewertung der Evidenz der Ergebnisse zu OS und PFS mit moderat mit Abwertung aufgrund der fehlenden Präzision [Zweitlinientherapie mit Vergleich zur CT] oder fehlender Übertragbarkeit auf Patienten unter 70 Jahre [Erstlinientherapie mit Vergleich zu CT], Evidenz der Ergebnisse zur Toxizität wurde mit hoch bewertet)					
Vickers 2019 (17) CRD42014013780 Search until 09/2015	**Systematische Übersicht und Netzwerk-metaanalyse** Efficacy of second-line treatments in all subgroup combinations determined by histology, PD-L1 and EGFR	Inclusion criteria: all relevant publications of phase 2/3 randomized controlled trials that were conducted in adult patients with locally advanced or metastatic NSCLC (IIIB/IV) and whose disease had progressed after first-line chemotherapy N=30 including 17 interventions Most patients in stage IV Risk of bias: high proportion of open-label studies, treatment switching in 1 RCT, different boundaries for PD-L1 expression	regimes containing docetaxel (any dose), erlotinib (150mg), gefitinib (250mg), gemcitabine (any dose), nintedanib (200mg), nivolumab (3 mg/kg), pembrolizumab (any dose), pemetrexed (500 mg/m^2), ramucirumab (10 mg/kg), vinorelbine (any dose), S-1 (40mg/m^2),	**OS* (N=30)** **PFS* (N=22)** only significant improvements (all vs. docetaxel 75 mg/m^2) were extracted	Results are presented for all combinations of non-squamous vs. squamous carcinoma, PDL-expression < vs. ≥ 5%, EGFR positive vs. negative (8 subgroups): **Nonsquamous, PD-L1 expression < 5% and EGFR negative:** **OS:** improvements with docetaxel plus ramucirumab and docetaxel plus nintedanib with gains in mean survival of 2.3 and 2.6 months **PFS:** improvements with docetaxel plus ramucirumab with a gain of 1.2 months in mean survival **Squamous, PD-L1 expression < 5% and EGFR negative** **OS:** improvements with docetaxel plus ramucirumab and nivolumab with gains in mean survival of 2.0 and 5.5 months **PFS:** improvements with docetaxel plus ramucirumab with a gain of 1.2 months **Nonsquamous, PD-L1 expression ≥5% and EGFR negative:** **OS**: improvements with nivolumab, docetaxel plus ramucirumab and docetaxel plus nintedanib with gains in mean survival of 12.9, 2.3, and 2.6 months benefit for nivolumab vs. docetaxel plus ramucirumab and docetaxel plus nintedanib	**1a**

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			bevacizumab (15 mg/kg). and best supportive care vs. **docetaxel** (75 mg/m^2)		**PFS:** Improvements with nivolumab and docetaxel plus ramucirumab with gains in mean survival of 5.0 and 1.2 months, benefit for nivolumab vs. docetaxel plus ramucirumab and docetaxel plus nintedanib **Squamous, PD-L1 expression ≥5% and EGFR negative** **OS:** improvements with nivolumab and docetaxel plus ramucirumab with gains in mean survival of 8.0 and 2.0 months **PFS:** improvements with nivolumab and docetaxel plus ramucirumab with gains in mean survival of 5.7 and 1.2 months Benefit for nivolumab vs.docetaxel plus ramucirumab **Nonsquamous, PD-L1 expression < 5% and EGFR positive** **OS:** improvements with (gain in mean survival in months in parentheses): docetaxel plus erlotinib (13.4), erlotinib plus pemetrexed (8.0), erlotinib (7.4), gefitinib (4.4), docetaxel plus nintedanib (2.6), and docetaxel plus ramucirumab (2.3) Benefit for docetaxel plus erlotinib vs. gefitinib and non-TKI regimens **PFS:** improvements with docetaxel plus erlotinib (8.1), erlotinib plus pemetrexed (7.0), erlotinib (6.8), gefitinib (5.4), and docetaxel plus ramucirumab (1.2) Benefit for docetaxel plus erlotinib, erlotinib, and gefitinib vs. docetaxel plus ramucirumab **Squamous, PD-L1 expression < 5% and EGFR positive:** **OS:** improvements with (gain in mean survival in months in parentheses): docetaxel plus erlotinib (11.9), erlotinib (6.5), nivolumab (5.5), gefitinib (3.9), and docetaxel plus ramucirumab (2.0**)**	

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					Benefit for docetaxel plus erlotinib vs. gefitinib and docetaxel plus ramucirumab **PFS:** improvements with docetaxel plus erlotinib (8.1), erlotinib (6.8), gefitinib (5.4), and docetaxel plus ramucirumab (1.2) Benefit for docetaxel plus erlotinib vs. non-TKI regimens **Nonsquamous, PD-L1 expression ≥5% and EGFR positive:** **OS**: improvements with (difference in months for mean survival shown in parentheses): docetaxel plus erlotinib (13.4), nivolumab (12.9), erlotinib plus pemetrexed (8.0), erlotinib (7.4), gefitinib (4.4), docetaxel plus nintedanib (2.6), and docetaxel plus ramucirumab (2.3) benefit for docetaxel plus erlotinib and nivolumab vs.docetaxel plus ramucirumab **PFS:** improvements with docetaxel plus erlotinib (8.1), erlotinib plus pemetrexed (7.0), erlotinib (6.8), gefitinib (5.4), nivolumab (5.0), and docetaxel plus ramucirumab benefit for docetaxel plus erlotinib, erlotinib, gefitinib, and nivolumab vs. docetaxel plus ramucirumab **Squamous, PD-L1 expression ≥5% and EGFR positive** **OS:** improvements for: docetaxel plus erlotinib (11.9), nivolumab (8.0), erlotinib (6.5), gefitinib (3.9), and docetaxel plus ramucirumab (2.0) benefit for docetaxel plus erlotinib vs. docetaxel plus ramucirumab **PFS:** improvements for docetaxel plus erlotinib (8.1), erlotinib (6.8), nivolumab (5.7), gefitinib (5.4), and docetaxel plus ramucirumab (1.2) Benefit for docetaxel plus erlotinib, erlotinib, nivolumab, and gefitinib vs. non-TKI regimes and non-PD-1 immunotherapies	

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Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** „In conclusion, the overall trends across OS and PFS indicated that there was always at least one intervention that performed better than single-agent docetaxel. Docetaxel plus ramucirumab gave a consistent significant benefit across all NSCLC subtypes. Docetaxel plus nintedanib showed a similar efficacy to docetaxel plus ramucirumab in the nonsquamous population. Superiority was observed for regimens containing erlotinib or gefitinib compared to non-TKI regimens when used in patients whose tumors have EGFR mutations, which was expected given the evidence in the literature …. For patients whose tumors had a PD-L1 expression of ≥5%, superiority was observed in those patients who received nivolumab compared to non-PD-L1 immunotherapies. This was particularly evident for patients with nonsquamous NSCLC and PD-L1 expression ≥5%. It was not clear whether this was generally the case for patients whose tumor had high PD-L1 expression or whether nivolumab was effective across squamous tumor types, regardless of PD-L1 expression. There was insufficient evidence available to assess bevacizumab and S-1. “ **Schlussfolgerung der Begutachterin: :** Systematische Übersicht mit Netzwerkmetaanalyse aller Behandlungsoptionen in der Zweitlinientherapie der Stadien IIIB und IV mit ausführlichen Subgruppenanalysen, geringfügige Einschränkung der Qualität (keine Untersuchungen zum Publikationsbias, aber Suche in Registern laufender Studien und Konferenzbänden und Kontaktierung von Autoren und Qualitätsbewertung durch 1 Autor), basiert auf 30 Studien ohne doppelte Verblindung der Ärzte und Patienten mit sehr unterschiedlichen Nachbeobachtungszeiten und ohne Ergebnisse zur Toxizität. Es fehlen Angaben zum Cross-over und verblindeter Erhebung von PFS (daher Abwertung aufgrund von Studienlimitationen), die meisten Patienten waren im Stadien IV, es erfolgten eine konfounderadjustierte Analysen ohne Veränderung ddes Ergebnisses, insgesamt erfolgte keine Abwertung der Evidenz aufgrund der Netzwerkmetaanalyse (Aufwertung des Evidenzgrades)						
Walls 2018 (18) Search until 07/2017	**Systematische Übersicht** predictors of 3 three key clinical outcomes in treatment of NSCLC with RT: which patients are likely • to fail radical RT • to benefit from particular types pf (chemo)RT	Inclusion criteria: • RCTs, non-RCTs and systematic reviews on • predictive factors or risk prediction models linked to response rate, loco-regional control, metastatic relapse, or toxicity • patients with stage I-III NSCLC who underwent radical RT with or without sequential, concurrent or adjuvant CT • All types of radical RT (conventional 2-Gy	Predictive factors: those covariates that are routinely available at baseline before the start of treatment, such as patient demographics, co-morbidities, disease characteristics, tumor markers, or radiological finding*	**Local disease control** (DFS, disease progression, failure free survival, local failure, local PFS, local or disease recurrence, nodal failure, non-local relapse-free survival, primary tumor control, TTP, tumor growth) **Distant disease control**	**Prediction of RT toxicities (110 studies with 112 reports):** No consistent prognostic value to predict oesophageal or lung toxicity, CT was most commonly reported (20 % of 112 reports), age, gender, performance status, tumour stage, fractionation, RT technique and molecular markers were significant risk factors in ≤ % of reports reporting toxicity: Oesophagitis (N=37): significant predictors included patient factors (age in 5 %, gender in 3 %, performance status in 3 %, race in 5 %, molecular markers [SNP] in N=5 % of reports), tumor factors (stage in 3 % of reports) and treatment factors (CT in 24 %, fractionation in 3 %, RT technique in 8 % of reports), 65 % of reports identified no significant predictor Oesophageal structure (N=1) no significant predictor identified Composite oesophageal toxicity (N=18): significant predictors included patient factors (gender in 6 %, symptoms in 6 %, molecular markers [TGF-β] in 6 %, weight loss in 17 %	**2a-** Abwertung aufgrund von sehr schwerwiegenden Studien-limitationen und Indirektheit

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		fractions, hypo-fractionated, ablative stereotactic courses) Exclusion criteria: • Non-full text manuscripts, • a language other than English • small sample size (n<50) • other outcomes • predictive factors not available before beginning radical RT • studies including radiation and dosimetric parameters as predictive factors, except they were part of a final risk prediction model N=259 reports on 255 studies Single-/multi-center studies: 66 /22 % n=71 933 patients Tumour stage (I only / III only / mixed I-III / other combinations): 15/39/25 /21 % of studies Staging (PET /PET or CT/non-PET /NR): 19/8/23/51 % of studies		(metastatic DFS, distant metastases or distant failure) **Metastases free survival** **Treatment related toxicity**	of reports), tumor factors (stage in 11 % of reports) and treatment factors (CT in 28 % of reports), 61 % of reports identified no significant predictors Radiation pneumonitis (N=58): significant predictors included patient factors (age in 9 %, comorbidity in 3 %, gender in 2 %, lung function in 7 %, lung volume in 2 %, medications in 2 %, performance status in 7 %, smoking in 9 %, molecular markers [APEX1, AT1, Protein, SNP, TGF-β, TNF, VEGF, XRCC1, XRCC3] in 10 % of reports), tumor factors (PET data in 2 %, PTV in 5 %, stage in 5 %, tumor state in 3 % of reports) and treatment factors (CT in 10 %, RT technique in 3 % and fractionation in 2 % of reports)), 64 % of reports identified no significant predictors Lung fibrosis (N=2): no significant predictor identified Composite lung toxicities (N=27): significant predictors included patient factors (age in 15 %, comorbidity in 11 %, gender in 4 %, lung function in 4 %, performance status in 4 %,race in 4 % and weight loss in 7 % of reports), tumor factors (histology [large cell vs. adenocarcinoma] in 4 %, stage in 11 %, tumor state in 7 % of reports) and treatment factors (CT in 7 %, fractionation in 4 %, treatment center in 4 %, RT technique in 7 % of reports)), 70 % of reports identified no significant predictors Composite acute toxicities (N=1): significant predictors included tumor site Death due to RT toxicity (N=4): significant predictors included tumor site in 50 % of reports, 50 % of reports identified no significant predictors **Prediction of local control (N=181 reports):** Most commonly reported significant predictors were tumor stage, performance status and CT administration:	

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		Tumor histology (squamous cell CA/ non-squamous cell CA/mixed/NR): 1/3/81/16 % of studies Age (predominantly elderly >65 yrs/ non-elderly only/mixed /NR): 5 / 0 /90 /5 % od studies <u>Risk of bias:</u> RCTs: 8 % (of them 65 % with high risk of bias) Further comparative studies: 3 % 90 % con-comparative studies (all high risk of bias) 10 risk prediction models, 1 prognostic model was externally validated, no model was validated for response to therapy			significant predictors included patient factors (age in 6 %, blood marker in < 1 %, gender in 9 %, medication in < 1 %, molecular markers (e.g. AI, Bcl-2, COX2, EGFR, FasL, FGF-2, HER-2, MMP-2, p53, SPARC expression, Rb, trace elements, VEGF, etc] in 7 %, performance status in 17 %, smoking in 2 %, symptoms in 1 % and weight loss in 4 % of reports), tumor factors (date in <1 %, histology [SCC or lymphovascular invasion] in 7 %, imaging [texture] in 2 %, PET data in 8 %, PTV in < 1 %, stage in 34 %, tissue in < 1 %, tumor site in 3 % of reports) and treatment factors (booster field size in < 1 %, CT in 12 %, contouring in 2 %, field size in <1 %, fractionation in 3 %, RT technique in 5 % of reports)), 49 % of reports identified no significant predictors **Prediction of distant tumor control (N=72 reports):** Most commonly reported significant predictors were tumor stage, performance status and tumour histology: significant predictors included patient factors (age in 6 %, blood marker in 1 %, comorbidity in 4 %, gender in 8 %, medication in 1 %, molecular markers (e.g. SNP, apoptotic index, index based on CRP, albumin, etc] in 7 %, performance status in 15 %, and weight loss in 6 % of reports), tumor factors (histology [SCC, lymphovascular invasion, or tumor grade] in 11 %, PET data in 8 %, stage in 24 %, total tumor volume in 1 %, tumor site in 4 % of reports) and treatment factors (CT in 3 %, contouring in 1 %, fractionation in 4 %, RT technique in 1 % of reports)), 46 % of reports identified no significant predictors **Brain metastases (N=8):** significant predictors included patient factors (age in 25 %, molecular markers [neuron-specific enolase or CA125] in 25 %, performance status in 13 % of reports), tumor factors (histology [SCC or tumor grade] in 38 %, tumor marker in	

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
					13 % of reports) and treatment factors (CT in 13 % of reports)), 50 % of reports identified no significant predictors	
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** „The conclusion of the presented analysis is that there are no published, effective and validated predictive tools for estimation of risk of local/distant recurrence or toxicity after radical RT for NSCLC. The authors have identified an important space for future research in the field of lung cancer radiotherapy." **Schlussfolgerung der Begutachterin:** Systematische Übersicht von Kohortenstudien (größtenteils ohne Kontrollgruppe) zur prädiktiven Güte von Patienten- und Tumorcharakteristika und Behandlungsoptionen zur Prädiktion von Toxizität, Regionale Kontrolle und Metastasierung ohne berichtete Ergebnisse (abgesehen von Signifikanzen) mit moderater Einschränkung der Qualität (keine Registrierung des Protokolls, Extraktion erfolgte größtenteils durch 1 Reviewer, keine detaillierten Angaben zur Qualitätsbewertung ohne Poolen der Ergebnisse und Untersuchungen zu Publikationsbias oder Suche in Registern laufender Studien und Konferenzbänden), basiert auf 259 Veröffebtlichungen zu 255 Studien, von denen 8 % randomisiert durchgeführt wurden und weitere 3 % eine Vergleichsgruppe enthielten. Die Evidenz wurde aufgrund der Qualität der systematischen Übersicht, der fehlenden Vergleichsgruppen in den Originalstudien und des Fehlens von Effektschätzern und dem Einschluss von Patienten der Grade I-III ohne Subgruppenanalysen abgewertet.						
Wang 2017 (19) Search until 02/2017	**Systematische Übersicht** Evaluation of treatment benefit of ALK+ NSCLC patients in the treatment of surgery, chemotherapy, and/or EGFR-TKI.	Inclusion criteria: • patients with NSCLC • ALK rearrangement was detected by immunohistochemistry, fluorescent in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR) • containing ALK fusion positive (ALK+) and negative (ALK-) groups • at least one of the following outcomes was available: ORR to CT or EGFR-TKI, HRs with 95% CI for OS or RFS/PFS	Patients with ALK rearrangement (ALK+) vs. ALK-	Primary: Overall survival (OS) recurrence/ progression free survival (RFS/PFS) objective response rate (ORR).	**ALK rearrangement** • more prevalent in patients with adenocarcinoma vs. non-adenocarcinoma (N=5, n=1357): 11.8 % vs 1.9% (RR 4.31 (95 %CI 2.29 to 8.1) with moderate heterogeneity between studies (I^2=31 %) • more prevalent in patients with never/light smoking history (N=5, n=1355): 17.5% vs 1.9 % (RR 7.88 (95 %CI 4.63 to 13.4) with small heterogeneity between studies (I^2=0 %) **Overall survival** (N=7): • no difference between ALK+ and ALK- shown in all studies with substantial heterogeneity between results of different studies (I^2=96 %) • In non-smokers (N=2) with metastatic NCLC, patients with ALK+ had worse prognosis compared to ALK- (HR 1.65, 95% CI=1.28-2.12) with small heterogeneity between studies (I^2=0 %) • In studies with smokers and non-smokers (N=6), patients with ALK+ had better survival compared to ALK-(HR 0.81,	**1a-** Abwertung aufgrund von Indirektheit

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		• patients had not received any ALK-TKI therapy. N=15 (12 prospective, 3 retrospective) N=7 only recruited patients with lung adenocarcinoma N=3 only enrolled never smoking NSCLC patients			95% CI= 0.72-0.91) with small heterogeneity between studies (I^2=0 %) • Better prognosis of ALK+was stated in the subgroup of all prospective studies (N=4, RR 0.80; 95 %CI 0.71 to 0.91), as well as in resectable patients (N=2, RR 0.72; 95 %-CI 0.56 to 0.92) and advanced/metastatic (N=2; RR 0.83; 95 %-CI 0.72 to 0.96) • Better prognosis of ALK+was stated in both Asian subgroup (HR 0.78, 95% CI 0.67 to 0.92) and Majority Caucasian subgroup (HR 0.84, 95% CI 0.71 tp 0.98) **Recurrence/progression-free survival** (N=8): • no difference between ALK+ and ALK- shown in all studies with substantial heterogeneity between results of different studies (I^2=67 %) • In <u>non-smokers</u> (N=4) with metastatic NCLC, patients with ALK+ had worse prognosis compared to ALK- (HR 1.23, 95% CI=1.05 to 1.44) with small heterogeneity between studies (I^2=0 %) • In studies with <u>smokers and non-smokers</u> (N=5), patients with ALK+ had better prognosis compared to ALK- (HR 0.80, 95% CI= 0.70-0.90) with small heterogeneity between studies (I^2=11 %) • Result was stated in both Asian subgroup (HR 0.83, 95% CI 0.72 to 0.96) and Majority Caucasian subgroup (HR 0.74, 95% CI= 0.61-0.91) • result was stated in the subgroup of resectable patients (N=2, RR 0.86; 95 %-CI 0.71 to 1.03) and advanced/metastatic (N=3; RR 0.76; 95 %-CI 0.66 to 0.89) **Overall response rate (N=7):**	

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
					• Patients with ALK+ less frequently responded to platinum based CT: 16.1 vs. 31.1 % (N=3, RR 0.46; 95%-CI 0.25 to 0.85) with small heterogeneity between studies (I^2=0 %) • Patients with ALK+ more frequently responded to pemetrexed based CT: 33.7 vs. 15.1 % (N=3, RR 0.46; 95%-CI 0.25 to 0.85) with moderate heterogeneity between studies (I^2=48 %) • No patient with wild type EGFR and ALK+ responded to EGFR-TKI: 0 vs. 10.6 % (N=4, RR 0.36; 95%-CI 0.09 to 1.49) with small heterogeneity between studies (I^2=0 %)	

Zusammenfassende Beurteilung

Schlussfolgerungen der Autoren der Studie: „Smoking status had a profound influence on the ALK-related prognosis of NSCLC. ALK rearrangement predicted a better prognosis in the general population with NSCLC, but a poor survival in the non-smoking population. Therefore, stratification according to smoking status is strongly recommended for future studies exploring ALK-related prognosis "

Schlussfolgerung der Begutachterin: Systematische Übersicht von zumeist prospektiven Kohortenstudien zur prädiktiven Güte einer ALK-Mutation mit Subgruppenanalysen für Raucher und Nichtraucher, Race und Tumorstatus zur Prädiktion des Gesamt- und progressionsfreien Überlebens und des Tumoransprechens einer Chemotherapie bei Patienten mit NSCLC mit geringer Einschränkung der Qualität (keine Registrierung des Protokolls, fehlendes Berichten der Ausschlusskriterien), basiert auf 15 vergleichenden Studien, von denen 12 prospektiv durchgeführt wurden. Die Evidenz wurde aufgrund von Indirektheit abgewertet, da alle Patienten mit NSCLC eingeschlossen wurden und eine Differenzierung in Subgruppenanalysen ausschließlich zwischen resektierbaren und Patienten mit fortgeschrittenen oder metastasiertem NSCLC erfolgte.

AE: Adverse event; AI: Apoptic index; AT:Angiotensin receptor; CC: Consolidation chemotherapy; CG: Control group; CI: Confidence interval; CrI: Credible intervals; CRT: Chemo-radiotherapy; CT: Chemotherapy; CTCAE: Common Terminology Criteria for Adverse Events; DCR: Disease control rate; DFS: Disease-free survival; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; FACT-L: Functional Assessment of Cancer Therapy-Lung; FGF-2: Fibroblast growth factor-2; HER-2: Humon epidermal growth factor receptor-2; HR: Hazard ratio; IG: Intervention group; LCS: Lung Cancer Symptom Scale; MMP-2: Matrix metalloproteinase; N: Number of studies; n: Number of participants; NCI CTCAE: National Cancer Institute Common Toxicity Criteria; NNT: Number needed to treat; NNH: Number needed to harm; NR: not reached; NSCLC: Non-small cell lung cancer; OR: Odds Ratio; OS: overall survival; PD-L1: programmed death ligand 1; PFS: Progression-free survival; PSI: Pulmonary Symptom Index; PTV: Planning target volume, QoL: Quality of life; Rb: Retinoblastoma protein; RCT: Randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumors; RoB: Risk of bias; RR: Relative Risk; RT: Radiotherapy; SAE: Serious adverse event; SCC: Squamous cell carcinoma; SNP: Single-nucleotide polymorphism, TGF-β: Transforming growth factor beta, TKI: Tyrokinase inhibitors; TNF: Tumor nectosis factor, TOI: Trial outcome index; TTF: Time to treatment failure; VEGF: Vascular endothelial growth factor; wks: weeks; yrs: years

Fragestellung 2a: Welche adjuvante Chemotherapie ist bei Patienten mit NSCLC im Stadium III nach kompletter Resektion sinnvoll?

Studiencharakteristika

Die vorliegende systematische Übersicht (Burdett 2015) (21) bewertet die Wirksamkeit einer zusätzlichen adjuvanten Chemotherapie in Ergänzung zur Operation (oder zusätzlich zue Operation und Strahlentherapie) bei Patienten mit einem frühen Grad einer NSCLC in den Stadien I bis III. Sie basiert auf einer systematischen Suche bis Dezember 2013 und Ergebnissen aus 35 randomisierten Studien zum Vergleich einer Behandlung mit Operation und adjuvanter Chemotherapie mit einer alleinigen Operation und 15 randomisierten Studien zum Vergleich einer Behandlung mit Operation, Strahlentherape und adjuvanter Chemotherapie mit einer Operation und Strahlentherapie. Individuelle Patientendaten zum Vergleich zur Operation lagen für 26 Studien mit insgesamt 8447 Studienteilnehmern vor, bei denen 3323 Todesfälle auftraten und 34 Vergleiche möglich waren. Für den Vergleich zur Operation und Strahlentherapie lagen individuelle Patientendaten für 12 Studien mit insgesamt 2660 Studienteilnehmern vor, bei denen 1909 Todesfälle auftraten und 13 Vergleiche möglich waren. Die systematische Übersicht schließt Patienten aller Stadien ein, wobei sehr wenige Patienten in den Stadien IIIB und IV waren und berichtet Ergebnisse für Subgruppenanalysen bei Zusammenfassung der Patienten der Stadien III und IV.
Sechs weitere randomisierte randomisierte Studien wurden nach Erscheinen der systematischen Übersicht veröffentlicht (Barlesi 2015, Hata 2017, Iwamoto 2015, Kenmotsu 2017, Kreuter 2014, Okamoto 2018) (22-29). Vier dieser Studien wurden in Japan durchgeführt und 2 in Westeuropa. Die Studien schließen insgesamt 1493 Patienten der Stadien IB bis III nach vollständiger Resektion ein und vergleichen verschiedene Chemotherapien (Gemcitabine+Cisplatin vs. Docetaxel+Cisplatin, Cisplatin und Pemetrexed vs. Cisplatin und Vinorelbine sowie verschiedene Therepien auf der Grundlage von S-1 (23, 24, 29).

Bewertung der methodischen Qualität

Die methodische Qualität der systematischen Übersicht von Burdett 2015 wird in Tabelle 9 zusammenfassend dargestellt. Diese wurde als Cochrane Review durchgeführt und entspricht den Anforderungen des Cochrane Handbuches (30). Damit erfüllt die Arbeit alle methodischen Anforderungen, allein zum Publikationsbias wurden trotz der hohen Anzahl von Studien keine Untersuchungen berichtet. Damit weist diese Arbeit einen hohen Qualitätsstandard auf. Ihre Evidenz für den Einsatz einer adjuvanten Chemotherapie wurde mit 1a bewertet, auch wenn für einzelne Substanzen keine sichere Aussage zur Wirksamkeit getroffen werden kann (siehe Ergebnisse in Tabelle 10).
Der Evidenzgrad der randomisierten Studien wurde mit 1b (Kenmotsu 2017) und 2b bewertet. Die Abwertungen basieren auf Studienlimitationen, einer aufgrund der geringen Studiengröße (80 bis 200 Studienteilnehmer) eingeschränkten Präzision der Ergebnisse und Indirektheit, da die Studien Patienten der Stadien IB-III einschließen und 3 der 5 Studien ausschließlich in Japan durchgeführt wurden. Auf eine Abwertung der in Japan durchgeführten Studie von Kenmotsu 2017 wurde verzichtet, da die Aussage der der deutschen Studie von Kreuter 2014 entspricht. Diese Gründe werden in Tabelle 10 unter Schlussfolgerungen der Begutachterin detailliert erläutert.

Tabelle 9: Methodische Bewertung der systematischen Übersicht zur Wirksamkeit einer adjuvanten Chemotherapin bei Patienten mit NSCLC im Stadium III nach kompletter Resektion

Studie	Proto-koll	Suche	Doppelte Auswahl	Doppelte Extraktion	Ausge-schlossene Studien	Bewer-tung VZP	Meta-analysen	Einfluss VZP	Publik ations-bias
Burdett 2015	☺	☺	☺	☺	☺	☺	☺	☺	☹
☺: niedriges Verzerrungsrisiko, 😐: Bewertung ist teilweise unklar, ☹: hohes Verzerrungsrisiko VZP: Verzerrungspotential									

Wirksamkeit und Sicherheit

Die systematische Übersichtsarbeit von Burdett 2015 konnte einen deutlichen Vorteil einer adjuvanten Chemotherapie im Anschluss an die Operation auf das Gesamtüberleben nachweisen (HR 0,86; 95% KI 0,81-0,92; p< 0.0001). Eine adjuvante Chemotherapie konnte die Überlebenswahrscheinlichkeit der Studienteilnehmer nach 5 Jahren von 60 % bei alleiniger Operation auf 64 % erhöhen. Es wurde keine bedeutsame Heterogenität des Behandlungseffektes für verschiedene Patientengruppen in Abhängigkeit von Alter, Geschlecht, Histologie, Zustand (ECOG) und in Abhängigkeit vom Stadium der Erkrankung (Stadien I-III) nachgewiesen. Für die in diesem Bericht untersuchten Patienten mit NSCLC im Stadium III konnte die Überlebenswahrscheinlichkeit von 30 auf 35 % erhöht werden.
Es konnte ein deutlicher Vorteil einer adjuvanten Chemotherapie im Anschluss an die Operation und Strahlentherapie nachgewiesen werden (HR 0,88; 95% KI 0,81-0,97; p= 0.009). Eine adjuvante Chemotherapie konnte die Überlebenswahrscheinlichkeit der Studienteilnehmer nach 5 Jahren von 29 % bei Operation und Strahlentherapie auf 33 % erhöhen. Auch für diese Behandlungsoption wurde keine bedeutsame Heterogenität des relativen Behandlungseffektes für verschiedene Patientengruppen in Abhängigkeit von Alter, Geschlecht, Histologie, Zustand (ECOG) und in Abhängigkeit vom Stadium der Erkrankung (Stadien I-III) nachgewiesen.
Für beide Vergleiche wurden ähnliche Vorteile für die Rekurrenz der Erkrankung mit geringen Unterschieden zwischen den verschiedenen Chemotherapien nachgewiesen. Zusammenfassend Autoren gehen davon aus, dass zukünftige Studien die Gesamtaussage dieser Übersichtsarbeit nicht verändern werden.
Die randomisierten Studien untersuchten vorrangig die Machbarkeit und Sicherheit verschiedener Therapieoptionen. Die Ergebnisse werden unter Hauptergebnisse in Tabelle 10 detailliert beschrieben. Zwei Studien vergleichen die Wirksamkeit von Pemetrexed und Cisplatin mit der von Vinorelbin und Cisplatin Kenmotsu 2017, Kreuter 2014). Beide Studien zeigen keinen Unterschied in der Wirksamkeit, aber eine geringere Toxizität einer Kombinationstherapie von Pemetrexed und Cisplatin.

Tabelle 10: Evidenztabelle zur Wirksamkeit und Sicherheit adjuvanter Chemotherapien bei Patienten mit NSCLC im Stadium III nach kompletter Resektion

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Barlesi 2015 (22, 31) 08/2014 to 12/2017 Frankreich	**RCT** efficacy of gemcitabine plus cisplatin with docetaxel plus cisplatin in completelly resected NSCLC on quality of life	Inclusion Criteria: • 18–75 yrs patients with completely resected (R0) Stage IB–III NSCLC, ECOG 0 or 1 • adequate bone marrow reserve and organ function, including calculated creatinine clearance of 45 ml/min Exclusion Criteria: • postoperative complications (acute respiratory distress syndrome, bronchial fistula or severe pneumonia) • previous history of cancer within ≤ 5 years or clinically significant cardiac dysfunction, active infection or neurological/ psychiatric disorders n=136 74% males median age 57 (36-71) Stage IB/II/III: 32/34/34% bi(lobectomy): 85%	within 8 wks after surgery: **Cisplatin** (75 mg/m^2, d1) plus **gemcitabine** (1250 mg/m^2, d1 and d8) (n=67) vs. **Cisplatin** (75 mg/m^2, d1) **docetaxel** (75 mg/m^2 d1) (n=69) for three cycles (9 weeks)	Primary: Quality of life (EORTC QLQ-C30, QLQ-LC12: raw scores from each functional and symptom scale were translated onto an overall scale from 0 to 100,.higher functional scores are indicative of global health scores better QoL, whereas lower symptom and single item scores reflected fewer symptoms) Secondary: overall survival, safety and cost	**Quality of life:** • (GHS) slightly improved from 63.5 vs. 62.7 at baseline to 64.5 vs. 65.4 after 3 months with no differences between groups (p=0.8) • no significant differences for other functional scores between groups • Social function was not altered by the number of infusions (Days 1 and 8 for the GC arm) • no differences for symptom scores, except for alopecia, where the CG showed a significantly higher score compared to IG **Safety:** • satisfactory compliance (80.6 vs. 85.5 % completed all the 3 planned cycles of CT) • 32.8 vs. 21.7% experienced Grade 3/4 haematological toxicities with no significant difference between arms: – anaemia: 1.5 vs. 0% – neutropenia: 28.4 vs. 21.7 % – Thrombopenia: 9.0 vs. 1.4 % • 32.8 vs. 26.1 % experienced non-haemotological toxicities: – asthenia: 7.5 vs. 7.2 % – nausea/vomiting: 10.4 vs. 7.2 % – infection: 3.0 vs. 1.4 % – neuropathy: 0 vs. 1.4 % – alopecia: fewer with IG: 3.0 vs. 13.0 % (p=0.03) **Overall survival:** • no differences between groups: median follow-up: 20.2 months, 1-year survival: 100 vs. 96.8% 2-year survival: 92.9 vs. 89.8% • 15 (7 vs. 8) patients died in the course of study	**2b** Abwertung aufgrund von Studienlimitationen, geringer Präzision und Indirektheit

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		adenocarcinoma/Squamous cell carcinoma/others: 55/23/22% minor postoperative complications: 15%				
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie: „**In conclusion, DC or GC adjuvant chemotherapy for completely resected NSCLC might be an acceptable alternative to currently recommended combinations and might be compared with the VC regimen. This study did not demonstrate any significant negative QoL impact of DC and GC in resected lung cancer patients, and might be useful when discussing treatment options with such patients." **Schlussfolgerung der Begutachterin:** Multizentrische, in Frankreich durchgeführte Studie unter Einschluss von 136 NSCLC Patienten (Grad 1B-III, daher Abwertung aufgrund von Indirektheit) zur Bestimmung des optimalen Regimes einer CT nach vollständiger Resektion. Es fehlt eine nähere Beschreibung der Randomisation und Verblindung (z.B. in der Erfassung der Lebensqualität). Es existiert aber ein Protokoll in französischer Sprache (kein Zugriff auf Volltext). Die Studie wurde auf Empfehlung des Steering-Kommites vorzeitig aufgrund neuer ASCO-Empfehlungen für 4 (statt der hier untersuchten 3) Zyklen CT gestoppt (daher Abwertung aufgrund geringer Präzision). Ergebnisse zur Lebensqualität nach 93 Monaten liegen für 71% der Patienten vor, bei Gesamtüberleben werden in der Grafik viele Drop-outs sichtbar, welche nicht beschrieben werden (Abwertung aufgrund von schwerwiegenden Studienlimitationen), die Studie wurde von Lilly Oncology, Sanofi-Aventin, Amgen und mit öffentlichen Mitteln unterstützt.					
Burdett 2015 (21) Search from 1995 to 12/2013	**Systematic Review** Effects of CT following surgery, or following surgery plus RT in patients with histologically diagnosed early stage NSCLC on OS, time to locoregional recurrence, time to distant recurrence and recurrence-free survival	Inclusion Criteria: • RCTs that compared OS, time to locoregional recurrence, time to distant recurrence and recurrence-free survival of additional adjuvant CT in patients with histologically diagnosed early stage NSCLC • published and unpublished completed trials with proper randomised • patient had undergone a potentially curative resection and not received previous CT	**Surgery plus adjuvant CT**: ○ platinum plus – vinca alkaloid/ etoposide – or vinorelbine – or taxane o platinum plus vinca alkaloid + tegafur and uracil/tegafur other platinum regimens ○ tegafur and uracil/tegafur	Primary: OS Secondary: time to locoregional recurrence time to distant recurrence recurrence-free survival	**Overall survival:** Surgery+adjuvant CT vs. surgery (N=35, N= 26 with individual patient data; IPD, n=8447 with 3223 deaths): • benefit of adding CT after surgery (HR 0.86; 95% CI 0.81 to 0.92; p< 0.0001) with small heterogeneity between results of different studies (I^2=4%) • no influence of age group, sex, histology, PS and stage of the disease on the effect, for stage III survival was improved • with differences depending on CT category: – Platinum plus vinca alkaloid/ etoposide (N=9, n=2404): no difference: HR 0.94; 95%CI 0.84 to 1.05) – Platinum+vinorelbine (N=4, n=1304): benefit: HR 0.82; 95%CI 0.70 to 0.97) – Platinum+taxane (N=1, n=244): no difference: HR 0.77; 95%CI 0.57 to 1.05) – Other platinum regimes (N=4; n=699): no difference: HR 0.90; 95%CI 0.72 to 1.13)	**1a**

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
	Investigation of predefined patient subgroups benefit from cisplatin-based CT	Exclusion criteria: • trials using long-term alkylating agents for >1 year Surgery trials: mostly men with a median age of 61 (18-84) yrs tended to have good performance status and tumours of stage I-II adenocarcinomas or squamous cell carcinomas. Surgery+RT trials: mostly men, good performance status, median age of 59 yrs (range 27 to 81), stage III, squamous carcinomas stage IIIA, IIB and IV (combined as stage III) Risk of bias: inclusion of trials with adequate methods of randomization, no blinding, but OS is unlikely to be influenced, low reporting bias due to analysis of individual patient data	plus other agent ○ tegafur and uracil/tegafur vs. **Surgery** median follow-up: 5.5 yrs **Surgery (plus RT)** vs. **Surgery (plus RCT) plus adjuvant CT**: ○ platinum plus vinca alkaloid/ etoposide ○ platinum plus vinorelbine ○ other platinum regimens ○ antimetabolic agent only median follow-up: 6.4 yrs		– platinum plus vinca alkaloid + tegafur and uracil/tegafur (N=8, n=1375): benefit: HR 0.79; 95%CI 0.67 to 0.93) – Tegafur and uracil/tegafur+other agent (N=1, n=83): harm: HR 1.79; 95%CI 1.00 to 3.20) – Tegafur and uracil/tegafur (N=7; n=2390): benefit: HR 0.76; 95%CI 0.64 to 0.90 • absolute increase in survival of 4% (95%CI 3 to 6) at five years (5-yrs OS increased from 60 to 64%) • with no influence of subgroup analyses by age, sex, histological cell type, tumour stage, and performance status • for stage III, 5-year survival was improved by 5 % (95 % CI 3 to 8) from 30 to 25 % • Surgery plus RT+ adjuvant CT vs. surgery+RT (N=15, N= 12 with IPD, n=2660 with 1909 deaths): • benefit of adding CT after surgery+RT (HR 0.88; 95% CI 0.81 to 0.97; p= 0.0009) with small heterogeneity between results of different studies (I^2=0%) • no evidence of a differential effect by CT category, the extent of resection achieved or timing of CT in relation to RT • absolute increase in survival of 4% at five years (5-yrs OS increased from 29 to 33%) • no influence of subgroup analyses by age, sex, histological cell type, tumour stage, and performance status **Recurrence-free survival** Surgery+adjuvant CT vs. surgery (n=5379 with 2519 events): benefit of adding CT after surgery (HR 0.83; 95% CI 0.77 to 0.90; p< 0.0001)	

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
					Surgery+RT+adjuvant CT vs. surgery+RT (n=2247 with 1673 events): benefit of adding CT after surgery (HR 0.85; 95% CI 0.77 to 0.93; p=0.0006) **Time to locoregional recurrence** Surgery+adjuvant CT vs. surgery (n=5226 with 936 events): benefit of adding CT after surgery (HR 0.75; 95% CI 0.66 to 0.94; p< 0.0001) Surgery+RT+adjuvant CT vs. surgery+RT (n=2247 with 533 events): benefit of adding CT after surgery (HR 0.79; 95% CI 0.67 to 0.85; p= 0.0008) **Time to distant recurrence** Surgery vs. surgery+adjuvant CT (n=5224 with 1267 events): benefit of adding CT after surgery (HR 0.80; 95% CI 0.72 to 0.89; p= 0.0007) Surgery vs. surgery+adjuvant CT (n=2247 with 533 events): benefit of adding CT after surgery (HR 0.75; 95% CI 0.66 to 0.87; p< 0.0001)	

Zusammenfassende Beurteilung

Schlussfolgerungen der Autoren der Studie: "Results from 47 trial comparisons and 11,107 patients demonstrate the clear benefit of adjuvant chemotherapy for these patients, irrespective of whether chemotherapy was given in addition to surgery or surgery plus radiotherapy.

These systematic reviews and meta-analyses use individual participant data, which is considered the gold standard of this type of review. We included all eligible trials if possible, no matter what language they were published in or whether they were published or not. The first meta-analysis (surgery versus surgery plus adjuvant chemotherapy) included 92% of all patients in eligible trials and the second meta-analysis (surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy) included 86% of all patients in eligible trials.

We are confident that further research is unlikely to change the findings. The studies were well designed and conducted, address the review question, and the effects are consistent across trials. The impact of any data we have not been able to include in our analyses is small."

Schlussfolgerung der Begutachterin: Systematische Übersicht, geringfügige Einschränkung der Qualität (keine Untersuchungen zum Publikationsbias, aber Suche in Registern laufender Studien und Konferenzbänden und Kontaktierung von Autoren), basiert auf 47 Vergleichen in Studien unter Einschluss von 11 107 Patienten aller Stadien (geringe

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Anzahl im Stadium IIIB und IV) mit NSCLC mit einer Auswertung von individuellen Patientendaten und in der Regel geringem Verzerrungspotential (fehlende Verblindung beeinflusst den Hauptendpunkt Gesamtüberleben kaum). Es wird die Wirksamkeit von adjuvanten Chemotherapien zusätzlich zur Operation oder zu Operation und Strahlentherapie berichtet und es werden Ergebnisse aus Subgruppenanalysen (auch für Stadien) berichtet. Die Suche erfasste Studien mit einem Publikationsdatum bis Dezember 2013, die Autoren gehen davon aus, dass zukünftige Studien die Behandlungseffekte nicht beeinflussen werden.						
Hata 2017 (23) 04/2005 to 01/2012 Japan	**RCT** feasibility of the conventional treatment schedule of S-1 and the shorter treatment schedule of S-1 as adjuvant treatment of patients with completely resected NSCLC	Inclusion Criteria: • histologically confirmed primary lung adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and adenosquamous carcinoma; • R0 resection of the primary tumor; pathological stage IB to IIIA disease • patients aged 20-74 yrs; ECOG 0 or 1; • adequate organ function able to start within 9 weeks after surgery; • no prior therapy Exclusion criteria: • history of previous CT, RT or surgery for lung cancer; • pulmonary fibrosis; pleural effusion, ascites, or cardiac effusion that required drainage; concomitant	within 9 wks after surgery: conventional treatment schedule of S-1 (n=39): administered for 4 weeks followed by a 2-week rest vs. shorter treatment schedule of S-1 (n=41): administered for 2 weeks followed by a 1-week rest over 12 months unless there was any evidence of recurrence, other malignancies, or SAEs	Primary: rates of completing the planned administration schedule over 12 months Secondary: relative total administration dose of S-1 toxicity 3-year disease-free survival (DFS) Median follow-up: 64 (range 6-113) months	**Completion rates** (over 12 months): • higher in IG: 73.7% (95% CI 58.0%–85.0%) vs. 45.0% (95% CI: 30.7%–60.2%) (p=0.001) • 73.7% vs. 45.0% received S-1 administration according the planned schedule • S-1 administration was halted because of – AEs or refusal for 18% (n = 6 AEs, n= 1 refusal) vs. 38%) (n = 9 AEs, n= 6 refusal). – tumor recurrence or other non-S-1-related complications for 8% (n =1 tumor recurrence, n = 2 non-S-1-related complications) vs. 18% (n = 4 tumor recurrence, n =3 non-S1-related complications) • higher averages of the relative dose intensity over 12 months in IG: 77.2 % vs. 58.4% (p = 0.01) **Adverse events:** • primary adverse events were hematological, gastrointestinal, and cutaneous signs and symptoms • no difference in AEs: 38 (100%) (grade 1/2 in 89% and grade 3 in 11%) vs. 39 (98%) (grade 1/2 in 93% and grade 3 in 5%; p = 0.42) • no difference in SAEs grade 3: 4 (11%) (elevated bilirubin, neutropenia, and rash) vs. 2 (5%) (anorexia and nausea, p = 0.43) • Elevated bilirubin, AST, ALT, and alkaline phosphatase levels were more frequent in IG vs. CG (p = 0.01, <0.01, 0.01, <0.01, respectively). • Two patients, 1 in each died during drug administration period, although the causes death were unknown and were not considered to be related to S-1 administration	**2b** Abwertung aufgrund von Studienlimitationen, geringer Präzision und Indirektheit

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		malignancy; significant comorbidity; diarrhea; pregnancy; • desiring to have children; • drug allergy to S-1 or any of its components n=80 randomized, 78 analysed age: 63±8 yrs males: 65% ECOG 0/1: 94/6 % Adeno/squamous/large cell carcinoma: 64/29/5 % Stage IB/IIA/IIB/IIIA: 78/1/4/4 % Lobectomy: 96 %			**Disease-free survival and recurrance:** • No difference in 3-year DFS rates: 79.0% vs. 79.3% (p=0.94) • 9 (23.7%) vs. 8 (20.0%) relapsed within 3 years with predominant locoregional recurrence in both arms (6 vs. 5)	
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie: „**The superiority of feasibility of the shorter schedule was not recognized in the present study. The conventional schedule showed higher completion rates over 12 months (p = 0.01) and relative dose intensity of S-1 (p = 0.01). Toxicity showed no significant difference among the shorter schedule and the conventional schedule, except for grade 1–3 elevation of bilirubin." **Schlussfolgerung der Begutachterin**: Multizentrische, in Japan durchgeführte Machbarkeitsstudie unter Einschluss von 80 NSCLC Patienten (Grad 1B-IIIA, daher Abwertung aufgrund von Indirektheit und fehlender Präzision) zum Vergleich von 2 Regimes zur Verabreichung einer Chemotherapie auf der Grundlage von S-1 mit zentraler Randomisierung, aber ohne Beschreibung der Randomisierungsordnung, ohne Verblindung oder verblindete Endpunkterfassung und Registrierung des Protokolls (daher Abwertung aufgrund von schwerwiegenden Studienlimitationen). Die Studie wurde von JSPS KAKENHI unterstützt (kein Einfluss auf Datensammlung und –analyse, Interpretation der Ergebnisse und Schreiben der Veröffentlichung.						
Iwamoto 2015 (24) Japan 09/2007 to 12/2009 (Japan)	**RCT** Efficacy and safety of S-1 versus cisplatin +S-1 in patients with completely	Inclusion criteria: • adults (20-74 yrs) • completely resected NSCLC (stage II or IIIA, metastasis to a single mediastinal lymph node only)	within 8 weeks after surger: **Longterm S-1** (40 mg/m^2 twice per day) for 2 consecutive weeks repeated	Primary: relapse-free survival (RFS) at 2 years and identification of predictive	**Feasibility:** • 52.6 % received 15 cycles of adjuvant CT vs. 74.7% completed four cycles of adjuvant CT as planned • High median relative dose intensities (85.2 vs. 86.4 and 94.1% **Survival:**	**2b** Abwertung aufgrund von geringer Präzision und Indirektheit

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
	resected stage II and IIIA non–small cell lung cancer	• ECOG PS 0 or 1 • Adequate bone marrow and organ function <u>Exclusion criteria:</u> • drug allergies, interstitial pneumonia, concomitant malignancies • heart failure, uncontrolled diabetes mellitus, and active infections. • Pneumonectomy n=200 median age: 62 years males: 76% IIA/B/III: 23/34/43 % Adeno/Squamous/other carcinoma: 67/23/10% Lobectomy: 100% ND0-1 /ND2 lymph node dissection: 5/95 %	every 3 weeks for 1 year (n=100) vs. **Cisplatin/S-1** (60 mg/m^2) d1 plus S-1 (40 mg/m^2 twice per day) for 2 consecutive weeks repeated every 3 weeks for four cycles (n=100)	biomarkers* <u>Secondary:</u> OS rate of AEs (NCI-CTC 3.0) medical treatment completion rate relapse *Not extracted	• Comparable 2-year RFS rate: 65.6% (95% CI 55.3–74.0%) vs. 58.1% (95% CI 47.7–67.2); HR 0.90 (95%CI 0.59–1.37). • comparable 5-year OS rates: 72.6% (95% CI, 64.3–82.0) vs. 72.2% (95% CI, 63.8–81.7) **Safety:** • anemia or neutropenia (grade 3 or 4): lower in IG (anemia: 1.0% vs. 8.4% (p=0.018); neutropenia: 13.4% vs. 27.4% (p=0.02) • nonhematologic toxicities (grade 3 or 4): anorexia (anorexia: 2.1 vs. 9.5%; p=0.032) and nausea (0 vs. 6.3%; p=0.014) were lower in IG • but: more grade 1 or 2 skin rash with IG (26.8% vs.9.5; p=0.002) • 17 vs. 18 deaths (not treatment related)	

Zusammenfassende Beurteilung

Schlussfolgerungen der Autoren der Studie: „In conclusion, this study suggests that adjuvant long-term S-1 monotherapy or CDDP+S-1 for completely resected stage II–III NSCLC is a viable alternative to cisplatin doublet chemotherapy in terms of efficacy and toxicity. UMPS/OPRT expression may be a useful marker for identifying patients who would benefit most from adjuvant long-term S-1, although the fact that we did not adjust for multiple testing may limit the relevance of this finding. „

Schlussfolgerung der Begutachterin: Multizentrische, in Japan durchgeführte Phase II unter Einschluss von 200 Patienten mit NSCLC nach vollständiger Resektion (Grad IIA/B-IIIA) (daher Abwertung aufgrund von Indirektheit) mit adäquater Beschreibung der Randomisationgszuweisung, aber ohne verblindete Messpunkterhebung und ohne Zugriff auf das Protokoll (trotz Angabe der Registrierungsnummer) mit vollständiger Auswertung aller Patienten nach 2 Jahren zeigt Machbarkeit, Wirksamkeit und Sicherheit einer Langzeit-Monotherapie mit S-1 bei geringen Nebenwirkungen. Abwertung aufgrund von fehlender Präzision (geringe Fallzahl) und Indirektheit (43% der Patienten waren im Stadium III, Studie wurde vollständig in Japan durchgeführt). Die Studie wurde von der West Japan Oncology Group unterstützt, mehrere Autoren berichten Interessenkonflikte (Forschungsförderung und Honorare durch pharmaceutische Firmen).

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Kenmotsu 2017 (25) 03/2012-08/2016 Japan	**RCT** efficacy of pemetrexed plus cisplatin versus vinorelbine plus cisplatin as postoperative adjuvant chemotherapy in patients with pathologic stage II-IIIA nonsquamous NSCLC	Inclusion criteria: • patients who underwent complete surgical resections by lobectomy or pneumonectomy with resection of any involved N2 lymph nodes within 3-8 weeks before enrollment. • patients were age 20-75 years with histologically confirmed pathologic stage II or IIIA nonsquamous NSCLC, proven results of the EGFR gene mutation test, ECOG 0 or 1, and adequate hematologic and organ function. Exclusion criteria: • Severe postoperative complications, interstitial pneumonia on computed tomography of the chest, current pregnancy, and other severe comorbidity. • Patients who received neoadjuvant CT or had planned to receive EGFR tyrosine kinase inhibitors n=804, 784 treated	**vinorelbine** (25 mg/m^2, days 1 and 8) plus **cisplatin** (80 mg/m^2, day 1) (n=402, n=287 (71.4 %) completed treatment) vs. **pemetrexed** (500 mg/m^2, day 1) plus **cisplatin** (75 mg/m^2, day 1) (n=402 randomised, n=342 (85.0 %) completed treatment) every 3 wks for 4 cycles	Primary: overall survival (changed to recurrence-free survival in an protocol amendment) Secondary: recurrence-free survival rate of treatment completion toxicity (NCI-CTC) for up to 30 days beyond the last dose of any protocol treatment.	**recurrence-free survival** (RFS): Disease recurrence or death in 53% vs. 51% Median RFS: no difference: 37.3 months (95% CI 28.8 to 52.5) vs. 38.9 months (95% CI, 28.7 to 55.3 months), HR 0.98 (95% CI, 0.81 to 1.20), With no differences depending on pathologic stge (stage IIIA: 1.05 (95%CI 0.82 to 1.34) 2-year RFS: 60.7% (95% CI, 55.7% to 65.3%) vs. 58.3% (95% CI, 53.2% to 63.0%) 3-year RFS: 50.2% (95% CI, 45.0% to 55.2%) vs. 51.1% (95% CI, 45.8% to 56.0%) **Overall survival (OS):** 75 vs. 71 patients had died at time of analysis Median OD: not reached, HR 0.98 (95% CI, 0.71 to 1.35) 3-year OS: 83.5% (95% CI, 79.2% to 87.0%) vs. 87.2% (95% CI, 83.8% to 90.2%) **Adverse events:** any grade AE: 100 vs. 99.7 % grade 3-5 AE: 89.4% vs. 47.4% Grade 3-4 febrile neutropenia: 11.6% vs. 0.3% (p<0.01) Grade 3-4 WBC count decrease, neutrophil count decrease, and anemia: 51.0%, 81.1 % and 9.3 % vs. 5.9%, 22.7% and 2.8% (p<0.01) grade 4 WBC count decrease and neutrophil count decrease: 9.3% and 56.6% vs. 0.3% and 3.3% One treatment-related death in each arm by sudden death and pneumonitis	**1b-** Abwertung aufgrund von Indirektheit

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		males: 58.9 % ECOG 0: 76.7 IIA/IIB/IIIA: 33.9/13.8/52.3 % Adenocarcinoma/others: 95.9/4.1 % EGFR pos: 24.5 % Lobectomy: 98.5 %				
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie: "**In conclusion, although the JIPANG study failed to show the superiority of pemetrexed plus cisplatin in terms of recurrence-free survival, toxicity profiles favored this regimen. Therefore, this combination can be an option for postoperative adjuvant chemotherapy in patients with completely resected nonsquamous NSCLC. The results of the JIPANG study indicate that the optimal platinum-based chemotherapy is still unclear in the adjuvant chemotherapy setting for resected nonsquamous NSCLC." **Schlussfolgerung der Begutachterin:** Multizentrische, in Japan durchgeführte Phase III unter Einschluss von 904 Patienten mit NSCLC (Grad II-IIA, >50 % im Grad IIIA) nach vollständiger Resektion mit Ergebnissen zum Grad IIIA für das krankheitsfreie Überleben mit adäquater Beschreibung der Randomisationsgszuweisung, aber ohne verblindete Messpunkterhebung und ohne Zugriff auf das Protokoll mit vollständiger Auswertung aller behandelten Patienten (98%) zeigt keinen Unterschied in der Wirksamkeit, aber eine geringere Toxizität in der Gruppe mit Pemetrexed und Cisplatin, keine Abwertung der Evidenz aufgrund von Indirektheit (Studie wurde vollständig in Japan durchgeführt, Ergebnisse entsprechen denen der deutschen Studie). Die Studie wurde von der West Japan Oncology Group, Pharma-Valley Center und der Japan Agency for Medical Research and Development unterstützt, mehrere Autoren berichten Interessenkonflikte (Forschungsförderung und Honorare durch pharmaceutische Firmen).						
Kreuter 2014 (26-28) (TREAT study) NCT00349089 10/2006 to 12/2009 Deutschland, Belgien und Luxemburg	**RCT** feasibility of a protocol with reduced toxicity might improve feasibility of postoperative delivery of adjuvant chemotherapy drugs in NSCLC, to improve	Inclusion criteria: • adults (≥18, < 75 yrs) • histo-pathologically confirmed NSCLC (stage IB, IIA, IIB or T3N1) without need for further radiotherapy and R0 resection and removal of mediastinal lymph nodes > 1,5 cm on the preoperative CT sca • full recovery after surgery	4-6 weeks postoperative: **Cisplatin(**75 mg/m^2 d1; q d22) **and Pemetrexed (**500 mg/m^2 d1) with vitamin-supplemen-tation (folic acid, vitamin B 12) and	Primary: feasibility of 4 cycles of adjuvant CT (no death due to cancer, toxicity, or comorbidity; no non-acceptance by the patient leading to premature withdrawal; and no DLT Secondary: drug delivery, time to treatment	**Feasibility:** 90 % vs. 66 % of the planned doses were given **Tumor relapse and relapse-free survival (RFS):** • Relapse in 31 % vs. 36 % • RFS: medians not reached, very similar 3-year RFS rates (59 vs. 60%), no difference in RFS: HR 0.831 (95% CI: 0.317–2.177); p=0.707) • More patients with local relapses in IG (18% vs. 5%), with most being mediastinal lymph node metastases in IG • no differences in rates of distant relapse (20.9% versus 18.5%). • More frequent brain metastases in IG (75% vs. 21%) • no difference in local RFS and distant metastasis–free survival	**2b** Abwertung aufgrund von Studienlimitationen, geringer Präzision und Indirektheit

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
	compliance and survival	• Karnovsky performance ≥ 80%, ECOG 1 Exclusion criteria: • Presence of a Pancoast tumor • Involvement of N2/N3 lymph nodes • Distant metastases n=132 age: 59 (38-74) years 26% females 29% smoker 66% ex-smoker 83% lobectomy, 14% pneumenectomy, 3% complex resections Stage IB/IIA/IIB/T3N1: 38/10/47/5 % COPD (I/II/III): 23/13/2% under therapy with bronchodilators: 28%	dexamethasone (4 mg of oral or equivalent, twice daily the day before, the day of and the day after each dose of pemetrexed for rash prophylaxis, unless medically contraindicated) (n=67) vs. **Cisplatin (**50 mg/m^2 d1, 8; q d29) **and Vinorelbine (**25 mg/m^2 d1, 8, 15, 22; q d29) (n=65) for 4 cycles	failure, distant metastases free survival, local RFS, OS, localization of relapse, dose delivery, RFS safety: NCICTC version 3.0	**Deaths and Overall survival:** 27% vs. 26% of patients died with comparable between groups, 17% due to tumor relapse (18% vs. 15%), 5% unrelated to therapy or tumor (5% in each arm), and 5% unknown. no differences in death by resection type: 83% of the patients received a lobectomy, with death rates of 22% in both arms, and 14% of patients received a pneumonectomy, with a death rate of 4% (5 vs. 3%) no differences on OS, medians not reached vs 59 months; (HR 0.594; 95% CI 0.165–2.131, p=0.424); **Toxicities:** generally mild, no grade 3/4 toxicity most frequent pulmonary toxicities: grade 1/2 cough (13.4% vs. 7.7%) and dyspnoe (9% vs. 4.6%) Pneumonia noted in 1 vs. 0 patients, bronchitis in 1 patient in each arm, no COPD exacerbations reported.	

Zusammenfassende Beurteilung

Schlussfolgerungen der Autoren der Studie: "In conclusion, the present study provides evidence that adjuvant chemotherapy does not have a negative effect on pulmonary function. However, a non-significant difference between D LCO decline in different therapy arms warrants further study."(28)

"Although adjuvant chemotherapy with CPx is safe and characterized by less toxicity and better dose delivery than CVb, overall survival was not influenced by treatment arm in the context of this phase II trial."(26)

Schlussfolgerung der Begutachterin: Multizentrische, in Deutschland, Belgien und Luxemburg durchgeführte Phase II unter Einschluss von 132 Patienten mit NSCLC nach vollständiger Resektion (Grad IB-T2N1) ohne adäquater Beschreibung der Randomisation (trotz veröffentlichtem Protokoll) und ohne Verblindung (daher Abwertung aufgrund von Studienlimitationen) zeigt Machbarkeit und Sicherheit einer Therapie mit Cisplatin und Pemetrexed bei geringen Nebenwirkungen. Trotz vollständigerer Therapie konnten keine Unterschiede hinsichtlich des Überleben und Anzahl der Rückfälle zwischen den Interventionsgruppen gezeigt werden.Abwertung aufgrund von fehlender Präzision (geringe Fallzahl) und Indirektheit (5% der Patienten waren im Stadium T3N1, 38% im Stadium IB und 57% im Stadium II).

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Okamoto 2018 (29) 2009-2013 Japan	**RCT** efficacy and safety of S-1 versus cisplatin + S-1, followed by S-1 in patients with completely resected stage IB-III NSCLC	Inclusion criteria: • adults (20-75 yrs) • completely resected NSCLC (stage IB, II or III) • ECOG PS 0 or 1 • No previous CT or RT • Adequate bone marrow and organ function Exclusion criteria: • drug allergies, cardiac infarction • uncontrolled diabetes mellitus, problematic infections. Interstitial pneumonia, concomitant malignancies n=141 mean age: 62.7±7.8 years males: 76% PS 0/1: 76/24% Smoking history: 81% IIA/B/IIIA: 31/26/42 % Adeno/Squamous/large/other carcinoma: 63/28/3/6 % Lobectomy: 92% Pneumonectomy: 8%	within 8 weeks after surger: **Longterm S-1** (80 mg/m^2 oral) for 2 consecutive weeks repeated every 3 weeks for 1 year (n=100) vs. **S-1** (80 mg/m^2 oral) for 3 consecutive weeks + **Cisplatin** (60 mg/m^2) d8 repeated every 5 weeks for four cycles, followed by **Longterm S-1** (80 mg/m^2 oral) for 2 consecutive weeks repeated every 3 weeks for 1 year (n=100)	Primary: disease-free survival (DFS) at 2 years Secondary: OS Safety feasibility	**Survival:** • Comparable 2-year DFS rate: 52 % (95% CI 40-63) vs. 61% (95% CI 48-70); HR 1.37 (95% CI 0.88–2.13). • comparable OS: HR 0.94 (95% CI 0.48-1.85) **Safety:** • no significant differences in occurance of grade 3-4 AEs • main grade 3-4 AEs: appetite loss: 4.3 vs. 11.6 %, decreased neutrophil count (5.7 vs. 10.1% and anemia (0vs. 5.8 %) • no treatment related deaths **Feasibility:** • no differences in treatment completion: 45.7 % (95% CI 41.9-66.3) vs. 43.5 % (95%CI 44-69.4)	**2b** Abwertung aufgrund von geringer Präzision und Indirektheit
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** „In conclusion, long-term adjuvant chemotherapy with S-1 was a feasible and promising treatment for patients with completely resected NSCLC, regardless of whether cisplatin was added. We recommend that S-1 monotherapy should be investigated further owing to its low toxicity and practical convenience.“						

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Schlussfolgerung der Begutachterin: Multizentrische, in Japan durchgeführte Phase II unter Einschluss von 141 Patienten mit NSCLC nach vollständiger Resektion (Grad IIA/B-IIIA) (daher Abwertung aufgrund von Indirektheit) mit adäquater Beschreibung der Randomisationsgszuweisung, aber ohne verblindete Messpunkterhebung und Hinweise auf ein veröffentlichtes Protokoll mit vollständiger Auswertung aller Patienten zeigt Machbarkeit, Wirksamkeit und Sicherheit einer Langzeit-Monotherapie mit S-1 bei geringen Nebenwirkungen. Abwertung aufgrund von fehlender Präzision (geringe Fallzahl) und Indirektheit (42 % der Patienten waren im Stadium III, Studie wurde vollständig in Japan durchgeführt). Die Studie wurde mit öffentlichen Fördergeldern unterstützt, 2 Autoren einer großen Gruppe berichten Interessenkonflikte (Forschungsförderung und Honorare durch pharmaceutische Firmen).						
AE: Adverse event; CG: Control group; CI: Confidence interval; CRT: Chemo-radiotherapy; CT: Chemotherapy; CTCAE: Common Terminology Criteria for Adverse Events; d: Tag; DCR: Disease control rate; DFS: Disease-free survival; DLT: dose-limiting toxicity; ECOG: Eastern Cooperative Oncology Group; FACT-L: Functional Assessment of Cancer Therapy-Lung; GHS: Global health scores; HR: Hazard ratio; IG: Intervention group; LCS: Lung Cancer Symptom Scale; N: Number of studies; n: Number of participants; NCI CTCAE: National Cancer Institute Common Toxicity Criteria; NR: not reached; NSCLC: Non-small cell lung cancer; OR: Odds Ratio; OS: overall survival; PFS: Progression-free survival; PSI: Pulmonary Symptom Index; QoL: Quality of life; RECIST: Response Evaluation Criteria in Solid Tumors; RCT: Randomized controlled trial; RFS: Relapse-free survival; RoB: Risk of bias; RR: Relative Risk; RT: Radiotherapy; SAE: Serious adverse event;TTF: Time to treatment failure; wks: weeks; yrs: years						

Fragestellung 2b: Welche neoadjuvante Chemotherapie ist im Stadium III vor einer geplanten Resektion sinnvoll?

Studiencharakteristika

Es konnten drei systematische Übersichten (Luo 2017, NSCLC 2014, Zhang 2019) (32-34) identifiziert werden, welche vergleichende Studien zur Behandlung mit Induktionstherapie und gleichzeitiger Chemostrahlentherapie (Luo 2017) oder randomisierte Studien zu neoadjuvanter Chemotherapie und anschließender Operation mit einer Behandlung ohne Induktionstherapie bzw. neoadjuvanten Chemotherapie vergleichen. Dabei wurden alle bis 2015 (Luo 2017) buw. bis 2013 veröffentlichten Studien (NSCLC 2014, Zhang 2017) eingeschlossen.
In die systematische Übersichtsarbeit Luo 2017 wurden 7 Studien mit insgesamt 1143 Patienten eingeschlossen, wobei zwei Studien Patienten der Stadien IIA bzw. IIB einschließen. Alle anderen Studien schließen ausschließlich Patienten der Stadien IIIA und IIIB ein, so dass nicht alle Patienten im resektablen Stadium waren. In die Arbeit der NSCLC-Arbeitsgruppe (NSCLC 2014) gingen individuelle Patientendaten aus 15 Studien von insgesamt 2358 potentiell resektablen Patienten ein, von denen 23 % in Stadium IIIA und weniger als 1 % im Stadium IIIB behandelt wurden. Daher waren Subgruppenanalysen zum Einfluss verschiedener Chemotherapieregime, dem Einsatz einer postoperativen radiotherapie und verschiedener Patientencharakteristika möglich. Es werden Ergebnisse zum Gesamt- und rekurrenzfreiem Überleben, der Resektionsrate und der Zeit bis zum Auftreter von Rekurrenzen berichtet.
Eine dritte systematische Übersichtsarbeit (Zhang 2017) berichtet Ergebnisse auf der Grundlage veröffentlichter Ergebnisse aus 11 Studien mit insgesamt 3226 NSCLC-Patienten ohne Metastasen, wobei 3 Studien ausschließlich Patienten im Stadium III und 5 Studien Patienten im Stadium I einschließen. Es werden Ergebnisse zum Gesamt- und krankheitsfreien Überleben, der Mortalität, dem Auftreten von Rekurrenzen und Nebenwirkungen der Therapien berichtet.
Es konnten zwei randomisierten Studien identifiziert werden, welche nach Abschluss der Suche in den systematischen Übersichten veröffentlicht wurden (Eberhardt 2015, Ma 2015) (35, 36). Ziel einer multizentrischen in Deutschland durchgeführten Studien (Eberhardt 2015, ESPATÜ) war der Vergleich der Wirksamkeit einer besonders hoch dosierten Chemo- und Strahlentherapie ohne Folgeoperation mit einer Chemo-Strahlentherapie mit Anschlussoperation. Dazu wurden 246 Patienten im Stadium IIIA (N2) oder IIIB rekrutiert, von denen nach einer Induktions- und anschließenden neiadjuvanten Chemo-Strahlentherapie 161 den 2 alternativen Behandlungsmöglichkeiten zugeordnet wurden. Eine monozentrischen in China durchgeführteStudie (Ma 2015) untersuchte die Wirksamkeit einer neoadjuvanten Chemotherapie auf der Grundlage von Docetaxel und Cisplatin und randomisierte 82 Patienten im Stadium IIIA in eine Gruppe mit und ohne neoadjuvante Chemoherapie bei snschließender Operation.
Zusätzlich wurden 2 Auswertungen von Patientendaten der US-amerikanischen National Cancer Data Base eingeschlossen, in welcher nach einem Propensity-Score–Matching Patienten, welche eine Induktionstherapie erhalten hatten mit den Patienten vergleichen wurden, welche zuerst operativ behandelt wurden (Anderson 2017, Speicher 2016) (37, 38). Die Propensity-Score-Analyse stellt die Vergleichbarkeit beider Therapiegruppen in Hinsicht auf bekannte prognostische Größen sicher (39). Es wurden die Daten von Patienten mit NSCLC im Stadium cT1-T3, N1 M0 (Speicher 2016) und T3 N0M0 (Anderson 2017) ausgewertet, wobei Speicher 2016 auch Ergebnisse zum Überleben für Patienten im Stadium T3 präsentiert.

Bewertung der methodischen Qualität

Die methodische Qualität der systematischen Übersichten (Luo 2017, NSCLC 2014, Zhang 2017) (32-34) wird in Tabelle 11 zusammenfassend dargestellt. In allen systematischen Übersichten traten methodische Probleme auf. Die Evidenz der sytematischen Übersichten wurde mit dem Evidenzgrad 1a- (NSCLC 2014) und 2a- (Luo 2017, Zhang 2017) bewertet. Die Abwertung der Evidenz erfolgte in allen Übersichten aufgrund von Studienlimitationen der eingeschlossenen Originalstudien und

zusätzlich aufgrund der geringen Präzision (Luo 2017) und der Indirektheit der Ergebnisse der Einzelstudien ohne Subgruppenanalysen für das resektable Stadium IIIA (Luo 2017, Zhang 2017).
Die methodische Qualität der multizentrischen deutschen Studie (Eberhardt 2015) wurde insgesamt mit gut bewertet. Dabei können Verzerrungen der Ergebnisse aufgrund der fehlenden Verblindung der Endpunkterhebung subjektiver Endpunkte (Toxizitäten, progressionsfreisn Überleben), der fehlenden Registrierung eines Protokolls sowie der vorzeitigen Beendigung aufgrund der langsamen Rekrutierung können nicht ausgeschlossen werden. Auch für die zweite Studie (Ma 2019) liegt kein Protokoll vor, es fehlt eine Beschreibung der verblindeten Zuweisung der Intervention und der Endpukterhebung der erhobenen Endpunkte. Die Qualität der Evidenz wurde für Eberhardt 2015 mit 1b- und für Ma 2019 mit 2b bewertet. Diese Bewertung basiert auf der aus der geringen Anzahl von Probanden folgenden Abwertung der Evidenz aufgrund der geringen Präzision der Ergebnisse in beiden Studien. Für Ma 2019 erfolgte eine weitere Abwertung der Evidenz aufgrund einer möglicherweise eingeschränkten Übertragbarkeit der Ergebnisse dieser monozentrischen, in China durchgeführten Studie.
In den Kohortenstudien (Anderson 2017, Speicher 2016) wurde durch die Propensity-Score-Analyse eine Vergleichbarkeit der Gruppen hinsichtlich der in den Krankenakten verfügbaren prognostisch relevanten Variablen hergestellt. Unbekannte oder nicht erfasste Störgrößen konnten nicht berücksichtigt werden, so dass der Evidenzgrad mit 2b bewertet wurde.

Tabelle 11: Methodische Bewertung der systematischen Übersichten zur Wirksamkeit neoadjuvanter Chemotherapien bei Patienten mit NSCLC im Stadium III

Studie	Proto-koll	Suche	Doppelte Auswahl	Doppelte Extraktion	Ausge-schlossene Studien	Bewer-tung VZP	Meta-analysen	Einfluss VZP	Publik ations-bias
Luo 2017	☹	☺	😐	☺	☹[b]	☹	☺	☹	☹
NSCLC 2014	☺[a]	☺	😐	😐	☹[b]	😐	☺	☺	☺
Zhang 2017	☹	☹[d]	😐	☺	😐[c]	☺	☺	☹	☺

☺: niedriges Verzerrungsrisiko, 😐: Bewertung ist teilweise unklar, ☹: hohes Verzerrungsrisiko
*: Netzwerkmetaanalysen
a: protocol available on request
b: keine Beschreibung der Auswahl der Studien in einem Flussdiagramm
c: Darstellung der Gründe im Flowchart, aber fehlende Liste der ausgeschlossenen Studien mit Zuordnung zum Ausschlussgrund
d: missing time period of the systematic search
VZP: Verzerrungspotential

Wirksamkeit und Sicherheit

Für die Induktionstherapie konnten Luo et al. 2017 im Vergleich zur alleinigen Chemo-Strahlentherapie ein Überlebensvorteil nach 5 Jahren nachgeweisen, auch wenn für die Zeiträume nach 1-4 Jahren eine hohe Heterogenität der Ergebnisse der 2 retrospektiven Studien und kein Überlebensvorteil beobachtet wurde. Im Vergleich zu Chemo-Strahlen- und Konsolierungstherapie traten in der Gruppe mit Induktionschemotherapie bei vergleichbarer Wirksamkeit weniger schwerwiegende Nebenwirkungen auf. Ergebnisse zum Resktionserfolg werden nicht berichtet.

Die systematische Übersichtsarbeit der NSCLC-Metaanalysen Gruppe (NSCLC 2014) berichtet einen deutlichen Überlebensvorteil (HR 0,87; 95 %-KI 0,78–0,96), welcher für Patienten im Stadium III das 5-Jahresüberleben von 20 auf 25 % erhöhen konnte. Dieser Überlebensvorteil ist mit einer Verlängerung des rekurrenzfreien Überlebens und der Zeit bis zum Auftreten von Rekurrenzen assoziiert. Der relative Effekt wurde weder vom Chemotherapieregime noch durch Patientencharakteristika beeinflusst. Im Unterschied zu diesen Ergebnissen konnte Zhang 2017 weder für das 3- noch das 5-Jahresüberleben

nachweisen, berichtet jedoch eine um 13,4 (95 %-KI 7-20) Monate verlängerte mediane gepoolte Überlebenszeit. Diese ist auch hier mit selteneren Operationen und besseren Operationsergebnissen (höhere R0-Resektion), einem verlängerten rekurrenzfreien Überleben, selteneren Rekurrenzen und einer verringerten Gesamtsterblichkeit assoziiert.

Die randomisierte Studie von Ma 2019 bestätigt eine geringere Operationsdauer, eine höhere Resektionsrate und den Überlebensvorteil einer neoadjuvanten Chemotherapie mit Docetaxel und Cisplatin im Vergleich zur alleinigen Operation bei Patienten mit NSCLC im Stadium IIIa.

In der ESPATÜ-Studie (Eberhardt 2015) konnte für beide Behandlungsoptionen eine hohe Wirksamkeit mit einem 5-Jahresüberleben von 40 % ohne Unterschiede zwischen den Gruppen bei akzeptabler Toxizität nachgewisen werden.

Beide Studien zur Induktionsterapie konnten im Gegensatz zu Luo 2017 auf der Basis einer methodisch sehr guten konfounderadjustierten Auswertung für Patienten im Stadium III keine Verlängerung des Kurz- oder Langzeitüberlebens nachweisen, auch wenn Anderson 2017 höhere R0-Resektionsraten nach Induktionstherapie im Vergleich zur Gruppe ohne Induktionschemotherapie zeigen konnte.

Tabelle 12: Evidenztabelle zur Wirksamkeit und Sicherheit neoadjuvanter Chemotherapien bei resektablen Patienten mit NSCLC im Stadium III

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Anderson 2017 (37) USA (National Cancer Database) 2006-2011	**Retrospective cohort study with Propensity score adjustment** Impact of induction therapy prior to an operation in patients with cT3 NSCLC on survival and subsequent surgical resection	Inclusion criteria: • Adult patients with a single, primary cancer diagnosis of NSCLC who underwent surgical resection • tumour sizes > 7 cm (cT3), no clinically positive lymph nodes (cN0) and no signs of distant metastases (cM0) (7^{th} edition AJCC) • cT2, tumour size >7cm (6^{th} edition AJCC) Exclusion criteria: patients with T4 (invasion into surrounding structures) tumours, N1, N2 or N3 nodal disease status or with distant metastases n=3819, 1749 matched and analysed age: 61 (IQR 53-68) males: 56.9 % white: 89.3 % Charlson-Deyo score (0/1/2): 65.1 / 25.2 /9.8 % Tumor size: 63 (38 -80) cT stage (2/3): 11.2/88.8 %	**Induction CT** and. surgical resection (lobectomy or pneumonectomy) (n=583) vs. **surgical resection alone** (n=3236, 1166 matched)	Primary: Overall survival Secondary: 30- and 90-day mortality rates 30-day readmission rates surgical margin status number of lymph nodes removed hospital length of stay Confounder adjustment (propensity score matching) for age, gender, race, Charlson-Deyo Comorbidity Index score, treatment facility type, education quartile, income quartile, insurance status, tumour size, AJCC pathological T and N stages and use of adjuvant CRT	**predictors of induction cCT:** • older patients (OR 0.67; 95%CI 0.61 to 0.75), with a higher Charlson-Deyo score (1 vs. 0: OR 0.61; 95%CI 0.50 to 0.76, ≥ 2 vs. 0: OR 0.70; 95 % CI 0.52 to 0.95) and Medicare/Medicaid insurance (OR 0.8; 95 % CI 0.65 to 1.0) were less likely to receive induction therapy prior to operative resection • with confounder adjustment: patients who underwent induction CT were more likely to have a lower pathological T stage and less likely to have a lower pathological N stage (both p-values < 0.001). **Treatment (**with confounder adjustment)**:** Patients who underwent induction CT • had a longer time to surgery (121 (IQR 99-147) vs. 30 (IQR 15-51) days • were less likely to receive adjuvant radiation (6.9% vs 16.7%) chemotherapy (13.6% vs 55.5%, both p-values < 0.001). • were more likely to undergo an open operative approach (87.3% vs 77.8%, p= 0.005) **Surgical results (**with confounder adjustment)**:** • Patients with induction therapy were less likely to have positive surgical margins (386 events): 6.7% vs 10.0%, p = 0.04), • R0: 90.3 vs. 90 %, R1: 2.7 vs. 5.2 % • no differences in removed nodes (9 (IQR 4-17) vs. 10 (IQR 6-17) **Hospital Length of stay:** no difference (6 vs. 6 days	**2b**

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		pT stage (0/1/2/3/4/X): 3.6/5.2/20.5/58/2.3/7.8 % pN stage (0/1/2/3/X): 75.1/13.1/4.5/0/7.2 % days to definitive surgery: 49 (IQR 23-108) adjuvant RT: 13.4 % adjuvant CT: 41.5 % lobectomy: 81.5 % surgery (VATS/ Converted/Open): 14.3/6.3/79.4 %			**Mortality** and **readmission** (with confounder adjustment): • Similar short-term outcomes of 30-day mortality (2.6 vs. 1.5%, p = 0.15) and 30-day readmission rates (4.5% vs 4.5%, p = 0.99) • Higher 90-day mortality (6.6 vs. 3.4 %, P = 0.003) with induction • similar overall 5-year survival: 49.3 vs. 52.5% (p = 0.116) .	
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** „Despite yielding increased rates of R0 resection, induction chemotherapy for cT3N0M0 NSCLC is not associated with improved survival and should not be considered routinely. Further studies are warranted to elucidate cohorts that may benefit from induction therapy." **Schlussfolgerung der Begutachterin:** Retrospektive Auswertung der in der US-amerikanischen National Cancer Datenbank gespeicherten Daten aller in den Jahren 2006 bis 2011 behandelten Patienten mit NSCLC im Stadium cT3. Es erfolgte ein Propensity-Score Matching mit dem Ziel der Vergleichbarkeit der Gruppe mit und ohne Induktionstherapie für alle vorliegenden und prognostisch als relevant erachteten Variablen (age, gender, race, Charlson-Deyo Comorbidity Index score, treatment facility type, education quartile, income quartile, insurance status, tumour size, AJCC pathological T and N stages and use of adjuvant CRT) und anschließende Auswertung von Daten von 1749 Patienten, von denen 583 mit Induktionschemotherapie behandelt wurden. Die Datenerhebung basiert auf vorliegenden Krankenakten. Auch nach dem Matching wurde ein geringeres pT-Stadium und ein höheres N-Stadium häufiger bei Patienten mit Induktionstherapie festgestellt. Auch wenn Patienten nach Induktionstherapie seltener positive Operationsränder aufwiesen, konnte kein langfristig besseres Überleben nachgewiesen werden. Zu beachten ist, dass das Überleben mit dem Zeitpunkt der Diagnose beginnt und Patienten in der Gruppe mit Induktionstherapie später operiert wurden, so dass die Therapie insgesamt länger dauerte.						
Eberhardt 2015 (ESPATUE) (35) 01/2004 to 01/2013, mainly in Germany	**RCT** Efficacy of a definitive concurrent CRT boost in patients after a complex induction protocol	<u>Inclusion criteria:</u> • pathologically proven NSCLC stage IIIA (N2) or selected IIIB disease with medical/functional operability • ECOG 0 or 1, < 10 % weight loss in the 6 months before	**Induction CT** (3 cycles cisplatin 50 mg/m^2 d 1, 8 + paclitaxel 175 mg/m^2 d1 every 21 days)+ **neoadjuvant CRT** (to 45 Gy given as 1.5 Gy	<u>Primary:</u> OS <u>Secondary:</u> PFS over a median follow-up of 78 months	**Treatment compliance:** N=246 recruited, 237 induction CT as planned, and 227 CRT according to the protocol, 161 (65.4%) were randomized, 66/80 (82.5 %) received the assigned, planned boost CRT and 70/81 (86.4 %)received surgery with R0 resection in 66/3 and 1 patients **Surgical results** (only reported for IG): 70 patients (86.4 %) received surgery,	**1b-** Abwertung aufgrund geringer Präzision

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		• Diagnosis, adequate renal, hepatic, and hematologic functions n=246 72% males ≥ 60 yrs: 47 % ECOG 0/1/2: 69/30.5/0.5 % Histology (adeno, squamous cell, large cell/mixed or other carcinoma): 43.5/38.5/9/9 % Tumour node (T4, N0 or N1/ T1-3, N2/T1-4; N3 or T4, N2): 32.4 / 30.5 / 37 %) Stage IIIA/IIIB: 30.5/69.5 %	twice daily, concurrent cisplatin 50 mg/m^2 d 2, 9 + concurrent vinorelbine 20 mg/m^2 d 2, 9) Patients whose tumors were reevaluated and deemed resectable in the last week of RT: **CRT boost** (n=80) (risk adapted between 65 and 71 Gy) vs. **surgery** (n=81)		R0: 94.3 % R1/R2: 4.3/0.01 % **Overall survival:** • 47 vs. 43 deaths with no differences between groups (p=0.34) • 5-year-OS: 40% (95% CI, 29% to 52%) vs. 44% (95% CI, 32% to 56%) **Progression-free survival:** • 47 vs. 43 deaths and 6 vs. 12 progressions without death vwith no differences between groups (p=0.75) 5-year-PFS: 35% (95% CI, 25% to 46%) vs. 32% (95% CI, 22% to 43%) **Toxicities:** • All toxicities (grade 3/4) were not unexpected and could be considered acceptable, most common (all grade 3/4): – Leukopenia: 44/16 vs. 49/11 % – Anemia: 9/0 vs. 12/0 % – Thromocytopenia: 8/3 vs. 10/1 % – Nausea/vomiting: 9/0 vs. 12/0 % – Neuropathy: 6/0 vs. 6/0 % – Esophagitis: 26/0 vs. 14/0 % – Fatique: 10/0 vs. 6/0 % – Pain: 20/0 vs. 23/0 % • Deaths ((probably therapy-related reasons): – 2 patients before random assignment – 7 patients after random assignment: – 2 in IG (1 from pneumonia after neutropenia, 1 after pneumonia and multiorgan failure) vs. – 5 in CG (3 as a result of lung bleeds, 2 after pneumonia and empyema, all > 30 days after thoracotomy)	

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** „In conclusion, both trimodality treatment that includes surgery and bimodality treatment without surgery but with a definitive chemoradiotherapy boost lead to excellent long-term OS and PFS. In our patients,who included those with resectable stage IIIA(N2) or selected stage IIIB NSCLC, we observed 5-year OS rates greater than 40%, an acceptable toxicity profile, and moderate treatment-induced events when performed in high-level multimodality treatment centers." **Schlussfolgerung der Begutachterin:** Methodisch gute multizentrische deutsche RCT unter Einschluss von 246 potentiell resektabler NSCLC, Stage III-Patienten, von denen 161 randomisiert einer zusätzlichen CRT-Boosttherapie vs. Placebotherapie zugeordnet wurden. Es existiert keine Beschreibung einer verblindeten Endpunkterhebung und der öffentlichen Registrierung eines Studienprotokolls. Die Studie wurde aufgrund der langsamen Rekrutierung vorzeitig beendet (geplant war die Randomisierung von 300 Patienten, daher Abwertung aufgrund geringer Präzision) ohne nachgewiesene Unterschiede für OS und PFS, Finanzierung der Studie durch die Deutsche Krebshilfe, Interessenkonflikte der Autoren können nicht ausgeschlossen werden.						
Luo 2017 (32) Search from 01/1994 to 12/2015	**Systematic Review** Effect of induction CT on survival outcomes of patients with NSCLC	Inclusion criteria: publications that studied survival outcomes in NSCLC patients treated with induction chemotherapy and concurrent CRT Exclusion criteria: noninduction CT, articles with no control group, a lack of data sufficient for OR determination, and non-English language studies Search in 4 databases N=7 with n=1143 patients: 5 RCTs and 2 retrospeczove cohort studies Stages: N=2 with IIA/IIB-IIIB and N=5 with IIIA/IIIB patients	**Induction chemotherapy and concurrent CRT** (N=7) vs. **concurrent CRT alone** (N=2) or **concurrent CRT followed by consolidation CT** (N=5) N=4 trials investigated cisplatin-based CT (taxane, etoposide, gemcitabine, vinorelbine, and docetaxel) N=2 trials investigated carboplatin	Survival	**Induction CT followed by concurrent CRT versus concurrent CRT alone** **Overall survival** (N=2, n=596): • No differences shown for 1-year OS (OR 2.07; 95 %CI 0.64 to 6.69), 2-year OS (OR 1.42; 95 %CI 0.85 to 2.35), 3-year OS (OR 1.42; 95 %CI 0.98 to 2.08), 4-year OS (OR 1.97; 95 %CI 0.91 to 4.26) with substantial heterogeneity between studies for 1 and 4.year OD (I^2= 89 % and 67 %) • Longer OS with induction CT at 5-year OS (OR 1.98; 95 %CI 1.24 to 3.17) with small heterogeneity between studies (I^2=0 %) **Induction chemotherapy followed by concurrent CRT versus concurrent CRT followed by consolidation CT**: **Overall survival** (N=5, n=547): • No differences shown for 1-year OS (OR 1.09; 95 %CI 0.77 to 1.54), 2-year OS (OR 1.05; 95 %CI 0.74 to 1.49) and 3-year OS (OR 0.99; 95 %CI 0.67 to 1.46) with small heterogeneity between studies (I^2= 26 %, 0 % and 23 %) • No differences shown for 4-year OS (OR 1.12; 95 %CI 0.52 to 2.42) and 5--year OS (OR 0.84; 95 %CI 0.33 to 2.18) with moderate heterogeneity between studies (I^2= 48 and 59 %) **Overall response rate** (N=5, n=547):	**2a-** Abwertung aufgrund von Studien-limitationen, geringer Präzision und Indirektheit

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
			combined with paclitaxel CT, N=1 trial on gemcitabine with docetaxel Median follow-up : 3.3 years		No differences shown (OR 1.25; 95%CI 0.86 to 1.83) with no heterogeneity (I^2=0 %) between studies **Adverse effects (grade III/IV)** : • No differences shown for esophagitis: 16 vs. 21 % (OR 0.71; 95 %CI 0.46 to 1.11), thrombocytopenia: 6.4 vs. 9.4 (OR 0.66; 95 %CI 0.33 to 1.30) and radiation pneumonitis : 4 vs. 7.7 % (OR 0.49; 95 % CI 0.23 to 1.06) • Less leucopenia: 26 vs. 44 %; OR 0.43; 95 %CI 0.30 to 0.62), all with low heterogeneity between studies • No significant difference in the number of treatment-related severe pulmonary, neurological, infection, cardiovascular, liver, and renal toxicity was observed between the 2 modalities.	
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie**: „In conclusion, published evidence is limited but does support the inclusion of induction chemotherapy for locally advanced NSCLC to achieve long-term survival. Both induction chemotherapy and consolidation chemotherapy are efficient for patients of locally advanced NSCLC who treated by concurrent CRT, given the potential toxicities of adding consolidation chemotherapy to concurrent CRT, clinicians should consider using this treatment strategy only in the context of a clinical trial to allow better assessment of its effectiveness." **Schlussfolgerung der Begutachterin:** Systematische Übersicht, moderate Einschränkung der Qualität (kein Protokoll, keine Informationen zum doppelten Screenen, keine Bewertung des Verzerrungspotentials, keine Subgruppenanalysen), basiert auf 7 Studien (5 randomisierten Studien und 2 retrospektiven Studien) mit Daten von 1143 Patientendaten von 2358 Patienten mit resektablen NSCLC (5 Studien schlossen nur Stadium III ein, andere ab Stadium IIA bzw. IIB, alle Studien schließen bis Stadium IIIB ein, so dass Resktabilität nicht klar ist, daher Abwertung aufgrund von Indirektheit), Verzerrungspotential basiert vorrangig auf retrospektivem Design in 2 Studien mit Vergleichsgruppen ohne Konsolidierungstherapie und Einschränkungen der systematischen Übersicht (daher Abwertung aufgrund von Studienlimitationen) und fehlender Präzision der Ergebnisse, aufgrund derer (nahezu) keine Unterschiede zwischen den Gruppen gezeigt werden konnten.						
NSCLC 2014 (33) Search until 05/2013	**Systematic Review** Effect of preoperative chemotherapy for patients with resectable NSCLC	Inclusion criteria: • RCTs comparing CT with subsequent surgery versus surgery alone • started 12/1964 including CT-naive NSCLC patients, suitable for surgery,	**CT and subsequent surgery** (with or without postoperative RT and CT) vs. **Surgery**	Primary: Overall survival Secondary: recurrence-free survival time to locoregional and distant recurrence	**Overall survival** (N=15, 2385 patients, 1427 deaths): • benefit of preoperative chemotherapy (HR 0.87, 95% CI 0.78–0.96; p=0.007) with an improvement in 5-year survival at 5 years (from 40% to 45%), for stage III from 20 to 25% • Only small heterogeneity between results (I^2=25%) despite a variety of CT regimens, exclusive use of preoperative CT,	**1a-** Abwertung aufgrund von Studien-limitationen

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		without any previous malignancy • Trials that planned to use postoperative RT in both arms or postoperative CT in the preoperative arm • Published and unpublished trials with no language restrictions N=19 RCTs, individual patient data were eligible for 15 RCTs with n=2358 patients with low risk of bias 80% males median age: 62 (IQR 55-68) yrs 88% with PS 0 or 1 IB-IIB: 70% IIIA: 23% IIIB: <1% IV: <1% Predominatelly squamous carcinoma: 50% or adenocarcinoma (29%) Risk of bias: Early stop in 12 RCTs, small trials with extreme positive and negative estimates seem to strongly aff ect this result	(with the same postoperative RT and CT) N=10 with only pre-operative CT, 5 RCTs with post-operative CR usually to responders N=7 with cisplatin, N=4 with carboplatin, N=3 with cisplatin or carboplatin, N=1 with docetaxel N=8 with postoperative RT	(from 6 months after randomization) cause-specific survival complete and overall resection rates postoperative mortality	use of postoperative RT in both arms, and inclusion of all stages or only a specific stage of patient • No evidence for significant different effects , but – Slightly larger effects for younger patients, – patients with better oerformance status, – lower clinical stage – for males – patients with adenocarcinoma • slightly larger relative effect if postoperative CT is given to responders (HR 0·78, 95% CI 0·64–0·95) vs. preoperative chemotherapy alone (HR 0·94, 95% CI 0·75–1·18) • 30-day / 6 months-mortality (9/15 RCTs, 1611/2381 patients, 52/254 deaths) after surgery: no difference between groups **Resection** (N=11, n=1778): • 4 RCTs with 100% resection in both arms • No reliable analysis possible for the remaining trials • No influence of preoperative CT on complete resection shown **Recurrence-free survival (14 RCTs, 2326 patients, 1524 events):** • benefit of preoperative CT (HR 0·85, 95% CI 0·76–0·94, =0·002) with no substantial heterogeneity • absolute improvement in RFS of 6% at 5 years (from 30% to 36%). • greater relative benefit on time to recurrence in trials with postoperative CT (HR 0·53, 95% CI 0·39–0·73, p<0·001) vs. only preoperative CT (HR 0·78, 95% CI 0·63–0·96, p=0·02). **Time to locoregional and distant recurrence** (13 RCTs, 1913 patients, 426 and 526 events): • benefit of preoperative CT on time to distant recurrence (HR 0·69, 95% CI 0·58–0·82) with no substantial	

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
					heterogeneity between studies and resulting absolute improvement of 10% at 5 years (from 60% to 70%). • no influence stated on time to locoregional recurrence (HR 0·88, 95% CI 0·73–1·07; p=0·20	
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** „Findings, which are based on 92% of all patients who were randomised, and mainly stage IB–IIIA, show preoperative chemotherapy signifi cantly improves overall survival, time to distant recurrence, and recurrencefree survival in resectable NSCLC. The fi ndings suggest this is a valid treatment option for most of these patients. Toxic eff ects could not be assessed." **Schlussfolgerung der Begutachterin:** Systematische Übersicht, geringe Einschränkung der Qualität (fehlendes Flussdiagramm), basiert auf 15 randomisierten Studien mit verfügbaren ondividuellen Patientendaten von 2358 Patienten mit resektablen NSCLC (ca. 23% im Stadium III), Verzerrungspotential basiert vorrangig auf ungeplantem Studienabbruch in 12 Studien, es konnte ein Einfluss von extrem kleinen Studien mit extrem positiven und negativen Ergebnissen gezeigt werden (daher Abwertung aufgrund von Studienlimitationen). Es wird die Wirksamkeit von neoadjuvanten Chemotherapien vor der Operation auf das Überleben und die Rekurrenz gezeigt, es fehlen jedoch Ergebnisse zur Sicherheit (Auftreten von Nebenwirkungen der Therapie).						
Ma 2019 (36) 05/2013-05/2017 China	**RCT** effect of docetaxel plus cisplatin preoperative neoadjuvant CT in stage III NSCLC	Inclusion criteria: • confirmed stage IIIA NSCLC • age < 70 years and karnofsky performance status score ≥ 70 • no distant metastasis Exclusion criteria: • patients with severe heart, liver, and kidney disease • those who had undergone CRT n=82 57 % males Age: 42-69 (57.04 ±2.63) yrs Weight: 45-68 (61.57 ±1.86) kg	**neoadjuvant chemotherapy** (n=41) (docetaxel iv, 75 mg/m2 d1 +cisplatin, 25 mg/m2 d2,5 over 3 weeks with a total of 2 courses+ surgery (3 weeks after the end of CT) vs. **surgery** (n=41) after preoperative examination.	Surgical resection rate operative time intraoperative blood loss 1-yr OS	**surgical resection rate:** higher with IG: 97.6 vs. 80.5 % (p=0.013) **Operation time:** shorter with IG: 109.4 ±17.4 vs. 148.2± 23.5 min (p<0.001) **intraoperative blood loss:** lower with IG: 498.2±31.6 vs. 602.8±51.6 ml (p<0.001) **Overall survival:** Higher 1-year survival with IG: 95.1 vs. 78 % (p=0.023) **Toxicities:** • No treatment-related death in both groups • No allergic reaction and peripheral neurotoxicity during the treatment • Main adverse reactions: radiation esophagitis, radiation pneumonia and leukopenia (all grade I-II) • no grade III-IV adverse reactions occurred	**2b** Abwertung aufgrund geringer Präzision und Indirektheit

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		63.4% squamous cell carcinoma, 29.3 % adenocarcinoma, 7.3 % of adenosquamous carcinoma				
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** „In conclusion, presurgical treatment with docetaxel and cisplatin can play a synergistic role, and it is feasible to treat stage III NSCLC." **Schlussfolgerung der Begutachterin:** Monozentrische chinesische RCT (daher Abwertung aufgrund eingeschänkter Übertragbarkeit) unter Einschluss und Randomisierung von 82 NSCLC-Patienten im Stadium III (aufgrund der Anzahl Abwertung wegen fehlender Präzision). Es existiert keine Beschreibung der verblindeten Zuweisung der Behandlung, verblindeten Endpunkterhebung oder Registrierung eines Protokolls mit Nachweis von relevanten Unterschieden in Operationszeit, Resektionsrate, Blutverlust und Gesamtüberleben, ohne exakte Angaben zu Toxizitäten und Finanzierung der Studie, es werden keine Interessenkonflikte der Autoren berichtet						
Speicher 2016 (38) USA (National Cancer Database) 2006-2011 2 publication	**Retrospective cohort study with Propensity score adjustment** Impact of induction therapy in patients with cT1-T3 N1 M0	<u>Inclusion criteria:</u> • Patients diagnosed with clinical T1-3 N1 M0 NSCLC • treated with lobectomy or pneumonectomy • Patients treated with postoperative CT were included regardless of	**Induction CT** and surgical resection (n=565) vs. **surgical first** (n=4799, 1130 matched)	<u>Survival</u> Confounder adjustment (propensity score matching) for patient age, sex, race, Charlson/Deyo Comorbidity Score, clinical T stage,	**predictors of induction CT:** • younger patients (OR 0.77; 95%CI 0.69 to 0.85), with a lower comorbidity burden (Charlson-Deyo score: 1 vs. 0: OR 0.63; 95%CI 0.51 to 0.78, ≥ 2 vs. 0: OR 0.61; 95 % CI 0.44 to 0.85), a private insurance and higher education • patients with T2 tumors (vs. T1: OR 1.78; 95 %CI 1.40 to 2.27) and T3 tumors **Treatment (**with confounder adjustment)**:** Patients who underwent induction CT • had a longer time to resection (125 (105 to 153) vs. 32 (16 to 50) (38),	**2b**

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
s with slightly differing numbers, but similar results	NSCLC on survival	whether postoperative RT was used Exclusion criteria: • Sublobar resections • patients with a previous cancer diagnosis or missing information regarding use of CT or clinical nodal status • Patients who received preoperative RT without preoperative CT n=5364, 1695 matched and analysed, predictors of IT are listed under results		extent of resection required (pneumonectomy vs lobectomy), and treatment facility type (academic or community hospital)	• were less likely to receive adjuvant RT (13.5 vs. 16.6 %), CT (16.1 vs 59.7 %) **Surgical results (**with confounder adjustment)**:** no differences in • extent of resection: Locectomy: 76.6 vs. 74.5 % and pneumonectomy: 23.5 vs. 25.5 %, • surgical approach: VATS: 14.2 vs. 14.3 %, Converted: 7.1 vs. 6.3 %, Open: 78.7 vs. 79.5 %, • removed nodes: 11 (6-20) vs. 12 (7 to 19) • positive margins: 9.4 vs. 9.5 % • Surgical margins: R0: 90.6 vs. 90.5 % • R1/R2: 4.7 / 0.4 vs. 4.9/0.4 % • Positive not otherwise specified: 4.3 vs. 4.1 % **Hospital Length of stay:** 6 (4 to 8) days with no differences between groups **Mortality** and **readmission** (with confounder adjustment): • Similar short-term outcomes of 30-day mortality (3.2 vs. 2.5%, p = 0.47) and 30-day readmission rates (5.5 vs 3.7 %, p = 0.11) and 90-day mortality (6.6 vs. 4.0 %, p = 0.19) similar overall survival (p=0.525): 1-year survival: 86.5 vs. 84.9 % 5.year survival: 45.6 vs. 49.0 % Median survival: 47.4 vs. 56.1 months patients with tumors >4 cm (with confounder adjustment): no differences in survival (p=0.892) 1-year survival: 84.6 vs. 82.3 % 5.year survival: 42.1 vs. 46.1 Median survival: 46.9 vs. 50.9 months Patients with T3 tumors (with confounder adjustment):	

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
					no differences in survival (p=0.323) 1-year survival: 83.1 vs. 80.3 % 5.year survival: 45.0 vs. 43.4 % (p=0.32) Median survival: 48.2 vs. 51.7 %	
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** „Induction chemotherapy for cN1 NSCLC is not associated with improved survival. This finding supports the currently recommended treatment paradigm of surgery first for cN1 NSCLC." **Schlussfolgerung der Begutachterin:** Retrospektive Auswertung der in der US-amerikanischen National Cancer Datenbank gespeicherten Daten aller in den Jahren 2006 bis 2011 behandelten Patienten mit NSCLC im Stadium cT1-T3 N1. Es erfolgte ein Propensity-Score Matching mit dem Ziel der Vergleichbarkeit der Gruppe mit und ohne Induktionstherapie für alle vorliegenden und prognostisch als relevant erachteten Variablen (patient age, sex, race, Charlson/Deyo Comorbidity Score, clinical T stage, extent of resection required and treatment facility type) und eine anschließende Auswertung von Daten von 1695 Patienten, von denen 565 mit einer Induktions-Chemotherapie behandelt wurden. Die Datenerhebung basiert auf vorliegenden Krankenakten. Es konnte weder für die Operationsergebnisse noch für das Überleben ein Vorteil für Patienten nach Induktionstherapie nachgewiesen werden. Dieses Ergebnis gilt sowohl für alle eingeschlossenen Patienten als auch für die in Subgruppen untersuchten Patienten mit großen Tumoren bei Diagnose (>4 cm) und Patienten mit T3 Tumoren.						
Zhang 2017 (34) Search period not named (last included study from 2013)	**Systematic Review** Comparision of neoadjuvant CT by surgery with upfront surgery in efficacy and safety among nonmetastatic NSCLC patients	Inclusion criteria: • RCTs on pathologically diagnosed non-metastatic NSCLC patients (NCCN) • comparison of neoadjuvant CT and surgery and surgery alone or • RCTs comparing neoadjuvant CT with upfront surgery • Patients with no age, sex and racial limitations, naive for CT and CRT in good condition to receive surgery, regardless of the chemotherapeutic	**Neoadjuvant CT and surgery** (n=1624) **vs.** **surgery alone** (n=1639) median follow-up: 55 months	Primary: 3- and 5-year survival rates overall survival disease-free survival total and perioperative mortalities recurrence Scondary: overall and R0 resection postoperative complications CT-related response and toxicity	**Overall survival:** • 3-year OS (10 RCTs, 2854 patients): no difference: 54.7% vs. 50.0%, RR: 1.08, 95% CI: 0.93–1.27 with substantil differences between studies (I^2=75%) • 5-year OS (all RCTs): benefit with IG: 35.6% vs. 27.9%, RR: 1.35, 95% CI: 0.98–1.85,p = 0.07) with substantil differences between studies (I^2=87%) • Longer pooled OS duration (4 RCTs, 1022 patients): 53.7 vs. 33.7 months, WMD: 13.43, 95% CI: 6.89–19.97 with no heterogeneity between studies (I^2=0%) **Disease-free survival:** • 3-year DFS rate: benefit with IG IG (8 RCTs, 2072 patients): 40.4% vs. 35.0%, RR: 1.16, 95% CI: 1.04–1.29, p = 0.01 with moderate heterogeneity between studies (I^2=44 %) • 5-year rate (7 RCTs, 1717 patients): benefit with IG: 23.0% vs.19.4%, RR: 1.19, 95% CI: 1.00–1.41, p = 0.06) with moderate heterogeneity between studies (I^2=37 %) • Median DFS (4 RCTs, 1022 patients): benefit with IG: 29.9 vs. 18.2 months, WMD: 9.53, 95% CI: 4.93–14.12, p <	**2a-** Abwertung aufgrund von Studien-limitationen, Inkonsistenz und Indirektheit

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		regimen and dose, surgical procedure and tumor stage Exclusion criteria: • RCTs with only 1 arm receiving postoperative therapy • RCTs on patients with other pulmonary diseases (e.g., pneumonia and tuberculosis) unless separate results were reported • earlier report of data updated in a subsequent publication N=11 with 3263 patients Males: 81 % ECOG 0-1: 91 % Squamous cell /adenocarcinoma: 48/30 % N=3 mit ausschließlichem Einschluss im Stadium III, N=5 nur Stadium I Risk of bias: All RCTs had adequate sequence generation, but no blinding of observers and patients,6 RCTs trials did not report allocation concealment, 7 did not		Response (tumour downstaging)	0.0001; with no heterogeneity between studies (I^2=0 %) and HR 0.87 (95% CI: 0.76–1.00, p = 0.04) **Total and perioperative mortality:** • Lower mortality in IG (11 RCTs, 3263 patients): 64.6 vs. 70.7% RR: 0.91, 95% CI: 0.83–0.99, p = 0.03 with substantil differences between studies (I^2=82%) • No difference in perioperative mortality (10 RCTs, 3052 patients): 3.8% vs. 3.7%, RR: 1.03, 95% CI: 0.72–1.48 with no differences between studies (I^2=0%) **Recurrance and metastasis:** • Lower overall postsurgical recurrence (6 RCTs, 1601 patients): 46.5% vs. 52.0%, RR: 0.89, 95% CI: 0.80–1.00, p = 0.04 with small differences between studies (I^2=10%) • No differences in local recurrance rates (6 RCTs, 1601 patients): 17.7% vs. 18.2%, RR: 0.96, 95% CI: 0.79–1.18, p = 0.71 with no differences between studies (I^2=0%) • lower incidence of distant metastasis (4 RCTs, 1271 patients): 21.6% vs. 27.5%, RR: 0.78, 95% CI: 0.65–0.95, p = 0.01 with no differences between studies (I^2=0%) **Surgery and resection:** • lower surgery in IG: 91.5% *vs.* 96.5%, RR: 0.96, 95% CI: 0.93–0.99, p=0003 and resection rates: 89.5% vs. 93.1%, RR: 0.97, 95% CI: 0.93–1.00, p = 0.04 • higher R0 resection rate in IG: 89.9% vs. 86.5%, RR: 1.04, 95% CI: 1.00–1.08, p = 0.05 **Postoperative adverse events:** • no difference: 17.3% vs. 16.3%, RR: 1.06, 95% CI: 0.88–1.28, p = 0.54 **Safety analysis of neoadjuvant CT (only in IG):** • most common NAC-related adverse effects: • leucopenia (20.8%) and nausea/vomiting (10.6%) (reported in 8 RCTs) • serious alopecia in 7.3% of patients (reported in 3 RCTs)	

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		address loss of follow-up, and 4 did not report sample size calculation				

Zusammenfassende Beurteilung

Schlussfolgerungen der Autoren der Studie: „NAC (neoadjucant CT) may provide better survival, reduced recurrence, and improved R0 resection rates among NSCLC patients who had surgery, especially in occident patients. Further studies are needed to clarify the ethnic differences“

Schlussfolgerung der Begutachterin: Systematische Übersicht, moderate Einschränkung der Qualität (kein Protokoll, Datum der Suche fehlt, missverständliche Beschreibung des Verzerrungspotentials und keine Untersuchung zum Einfluss des Verzerrungspotentials auf die Ergebnisse), basiert auf 11 randomisierten Studien von 3263 Patienten der Stadien I-III (deshalb Abwertung der Evidenz aufgrund von Indirektheit), Verzerrungspotential basiert vorrangig auf fehlender verblindeter Endpunkterfassung, sowie einer fehlenden Beschreibung der verblindeten Zuteilung und Nachbeobachtung (daher Abwertung aufgrund von Studienlimitationen). Es wird die Wirksamkeit von neoadjuvanten Chemotherapien vor der Operation auf das Überleben, die Rekurrenz gezeigt, wobei die Ergebnisse häufig eine substantielle Heterogenität aufweisen (z.B. bedingt durch verschiedene CT Regimes, daher Abwertung aufgrund von Inkonsistenz)

AJCC: American Joint Committee on Cancer; AE: Adverse event; CG: Control group; CI: Confidence interval; CRT: Chemo-radiotherapy; CT: Chemotherapy; CTCAE: Common Terminology Criteria for Adverse Events; d: Tag; DCR: Disease control rate; DFS: Disease-free survival; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IG: Intervention group; N: Number of studies; n: Number of participants; NCI CTCAE: National Cancer Institute Common Toxicity Criteria; NSCLC: Non-small cell lung cancer; OR: Odds Ratio; OS: overall survival; PFS: Progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors; RCT: Randomized controlled trial; RFS: Relapse-free survival; RoB: Risk of bias; RR: Relative Risk; RT: Radiotherapy; SAE: Serious adverse event;TTF: Time to treatment failure; wks: weeks; yrs: years

Fragestellung 3: Sind VATS oder RATS im resektablen Stadium III der Thoraktomie gleichwertig?

Studiencharakteristika

Die systematische Übersichtsarbeit einer internationalen Autorengruppe um Ng 2019 (9) schließt alle in den Jahren 2000 bis Januar 2018 veröffentlichten randomisierten und Beobachtungsstudien bei Patienten mit NSCLC der Stadien I bis III ein, welche eine Behandlung mit VATS (multi-port VATS, robotic VATS und uni-port minimal invasiver video-assistierter thrakoraler Operation (VATS)) mit einer konventionellen offenen Thoraktomie vergleichen. Insgesamt konnten 142 geeignete Studien identifiziert werden, bei denen in 7 Studien eine randomisierte Zuweisung existierte und bei 13 Studien eine Propensity-Score basiertes Matching der Interventions- und Kontrollgruppen erfolgte. Informationen zur Stadienverteilung wurden von den Autoren nicht extrahiert, auch wenn zahlreiche der eingeschlossenen Studien Patienten im Stadium I einschließen (siehe Eingeschlossene Studien: Fragestellung 3). Die meisten Studien wurden in Asien durchgeführt, aber es wurden auch europäische Studien identifiziert. Auf Grundlage dieser Evidenz erfolgten konsenbasierte Leitlinienempfehlungen welche in Tabelle 14 zusammenfassend dargestellt sind.
Zusätzlich wurden zwei nach Abschluss der Suche veröffentlichte konfounderadjustierte Studien (Batihan 2020 , Huang 2019) (40, 41) identifiziert, in welchen eine Mindestanzahl von 40 Patienten im Stadium III in den Interventionsgruppen behandelt wurden.
Dies betrifft eine retrospektive Studie (Batihan 2020), in welche Daten von 60 Patienten mit NSCLC und Tumoren mit einem Durchmesser über 5 Zentimetern eingeschlossen wurden, welche entweder mit VATS oder Thoraktomie behandelt wurden. Es liegen Ergebnisse einer konfounderadjustierter Auswertung der Endpunkte Gesamtüberleben und krankheitsfreies Überleben. Diese basieren auf Charakteristika des Patienten (Alter, Geschlecht, FEV1, Komorbiditäten), der Tumorerkrankung (Tumorgröße, Stadium, pathologischer Subtyp, die Länge des krankheitsfreien Intervalls, Nodalstatus) und der Behandlung (VATs vs. Thoraktomie, Zeit zwischen der Operation und der adjuvanten Therapie, Anzahl der sezierten Lymphknoten).
Eine weitere randomisierte Studie (Huang 2019) schloss 113 Patienten mit NSCLC im Stadium c-N2 ein und berichtet ausschließlich kurzfristige ergebnisse während des Aufenthaltes im Krankenhauses von mit RATS und konventioneller Lobektomie behandelten Patienten.

Bewertung der methodischen Qualität

Die methodische Qualität der systematischen Übersichtsarbeit von Ng 2019 (9) ist in Tabelle 13 dargestellt. Es existieren moderate Einschränkungen der Qualität wie ein fehlendes Protokoll, keine Informationen zur Suche in Registern und Referenzlisten eingeschlossener Studien und fehlende Heterogenitätsuntersuchungen. Die Evidenz wurde aufgrund eingeschränkter Übertragbarkeit abgestuft, da die systematische Übersichtsarbeit Studien mit Patienten der Stadien von I-III einschliet, welche häufig in asiatischen Ländern durchgeführt wurden. Zusätzlich wurden die beschriebenen Studienlimitationen festgestellt und vergleichende Kohorten- und Fall-Kontrollstudien eingeschlossen. Limitationen der eingeschlossenen Primärstudien, welche nur sehr schwer zu vermeiden sind, betreffen den Durchführungs- und Beobachtungsbias aufgrund fehlender Verblindung. Zusätzlich existiert eine substantielle Heterogenität der Ergebnisse der Einzelstudien, wobei diese die Gesamtaussage der Arbeit nur geringfügig beeinflusst. Insgesamt wurde die Evidenz mit 2a- bewertet. Die Evidenz der zwei Studien wurde mit 2b (Huang 2019) und 2b- (Batihan 2020) bewertet. Die Abwertung der Evidez basiert auf der geringen Präzision der Ergebnisse der konfounderadjustierten retrospektiven Kohortenstudie und der zusätzlichen eingeschränkten Übertragbarkeit der Ergebnisse der randomisierten Studien.

Tabelle 13: Methodische Bewertung der systematischen Übersichten zur Wirksamkeit und Sicherheit VATS oder RATS im resektablen Stadium III bei Patienten mit NSCLC

Studie	Proto-koll	Suche	Doppelte Auswahl	Doppelte Extraktion	Ausge-schlossene Studien	Bewer-tung VZP	Meta-analysen	Einfluss VZP	Publik ations-bias
Ng 2019	☹	😐[a]	😐	☺	☺[b]	☺	☺	☹	☺

☺: niedriges Verzerrungsrisiko, 😐: Bewertung ist teilweise unklar, ☹: hohes Verzerrungsrisiko
a: no search in trial registries reported
b: Verweis auf online-Appendix 2 (konnte nicht geöffnet warden)
VZP: Verzerrungspotential

Wirksamkeit, Sicherheit und Empfehlungen

Auf Grundlage der in der systematischen Übersicht von Ng 2019 zusammengefassten Evidenz wurden von der International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) in einer Konsensuskonferenz 15 Empfehlungen formuliert. Diese betreffen die optimale Methode einer Lobektomie (mVATS, rVATS, uVATS oder offene Lobektomie) bei Patienten mit NSCLC hinsichtlich der Endpunkte Gesamtüberleben, krankheitsfreies Überleben, Auftreten von Rekurrenzen, Nodal Upstaging, vollständige Durchführung der adjuvanten Chemotherapie, Nebenwirkungen, Lebensqualität, postoperative Schmerzen, Länge des Krankenhausaufenthaltes nach der Operation und Kosten.
Die Qualität der Evidenz und die Empfehlungsgrade basieren auf dem Klassifizierungssystem der ACC/AHA (42) (Tabelle 14).
Die Evidenzgrade liegen zwischen

- B-R (randomized- Evidenz basiert auf mindestens einer randomisierten Studie moderater Qualität oder einer Metaanalyse dieser RCTs) für eine Empfehlung (Nr.10),
- B-NR (non-randomized - Evidenz basiert auf mindestens einer nicht-randomisierten, Beobachtungs-Studie oer Studie auf Grundlage von Refisterdaten guter Qualität oder einer Metaanalyse dieser Studien) für 3 Empfehlungen (Nr. 6,14 und 15),
- C-LD (limited data - Evidenz basiert den oben genannten Studien mit Einschränkungen im Design oder Ausführung oder einer Metaanalyse dieser Studien) für 10 Empfehlungen (1-3,5,7—9, 11-13)
- C-EO (Expertenkonsens) für 1 Empfehlung (Nr. 4).

Auf Grundlage dieser Evidenz basieren

- 5 moderate (II-A) Empfehlungen, da die Teilnehmer der Konsensuskonferenz davon ausgehen, dass der Nutzen das Risiko der Interventionen deutlich übersteigt (Nr. 5,8,10, 14 und 15) und
- 11 schwache Empfehlungen, da die Teilnehmer der Konsensuskonferenz davon ausgehen, dass der Nutzen das Risiko der Interventionen übersteigt oder beide gleich sind.

Tabelle 14: Konsensbasierte Empfehlungen der Gesellschaft für International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS)

Nr.	Empfehlungen	Evidenz-grad	Empfehlungs-grad
1	mVATS lobectomy may be associated with improved overall survival compared to open lobectomy.	C-LD	II-B
2	mVATS may have similar disease-free survival when compared to open lobectomy.	C-LD	II-B
3	mVATS may be associated with a lower recurrence rate, primarily related to distant recurrence when compared to open lobectomy.	C-LD	II-B
4	rVATS has no difference in overall survival and recurrence when compared to mVATS lobectomy.	C-EO	II-B

Nr.	Empfehlungen	Evidenz-grad	Empfehlungs-grad
5	**Open lobectomy results in an increase in nodal upstaging when compared to mVATS.**	**C-LD**	**II-A**
6	mVATS, uVATS, and rVATS may be equivalent in terms of number of lymph nodes harvested and nodal upstaging.	B-NR	II-B
7	mVATS may facilitate the completion of adjuvant chemotherapy when compared to open lobectomy.	C-LD	II-B
8	**mVATS lobectomy for the treatment of NSCLC is associated with a decreased risk of adverse events when compared to open lobectomy.**	**C-LD**	**II-A**
9	mVATS, uVATS, and rVATS may be associated with similar rates of adverse events.	C-LD	II-B
10	**mVATS can improve postoperative pain (Class IIA, Level B-R),** and may be associated with improved quality of life (Class IIB, Level B-R), and overall function (Class IIB, Level C-EO) when compared to open lobectomy.	B-R und C-EO	II-A und B
11	uVATS lobectomy may reduce early postoperative pain and analgesic requirements compared with mVATS.	C-LD	II-B
12	mVATS and rVATS may be associated with a decreased length of stay when compared to open lobectomy.	C-LD	II-B
13	There is no significant difference in length of stay between mVATS, uVATS, and rVATS.	C-LD	II-B
14	**mVATS is associated with reduced costs when compared to open lobectomy.**	**B-NR**	**II-A**
15	**rVATS is associated with higher costs when compared to mVATS lobectomy.**	**B-NR**	**II-A**

mVATS: multiport video-assisted thoracic surgery; rVATS: robotic video-assisted thoracic surgery; uVATS: uniportal video-assisted thoracic surgery

Evidenzgrade:

B-R: randomized (moderate-quality evidence from 1 or more RCTs or meta-analyses of moderate-quality RCTs)

B-NR: nonrandomized (moderate-qaulity evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies or meta-analyses of such studies)

C-LD: limited data (randomized or nonrandomized observational or registry studies with limitations of design or execution, meta-analyses of such studies or physiological or mechanistic studies in human subjects)

C-EO: expert opinion (consensus of expert opinion based on clinical experience

Empfehlngsgrade:

IIa: moderate Empfehlung (benefit>>risk)

IIb: schwache Empfehlung (benefit≥risk)

Die Ergebnisse von Batihan 2020 zeigen eine kürzere Zeit mit Drainage im Krankenhaus und eine geringe Zeit im Krankenhaus mit VATS sowie ein verbessertes rekurrenzfreies Überleben. Unterschiede im Gesamtüberleben konnten nicht gezeigt werden. Die Ergebnisse zum rekurrenzfreien- und Gesamtüberleben basieren auf einer konfounderadjustierten Auswertung und weisen aufgrund der geringen Fallzahl sehr breite Konfidenzintervalle auf.

Huang 2019 konnte für Patienten mit RATS im Stadium c-N2 einen Vorteil in einigen peri- und postoperativen Endpunkten, nicht aber hinsichtlich der Aufenthaltsdauer im Krankenhaus zeigen.

Tabelle 15: Evidenztabelle zur Wirksamkeit und Sicherheit VATS oder RATS im resektablen Stadium III bei Patienten mit NSCLC

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Batihan Ergebn2020 (40) 01/2014-12/2018	**Retrospective study with confounder adjustment** Comparision of intraoperative and post-operative results of VATS and thoracotomy in patients NSCLC with tumors > 5 cm (≥T3)	Inclusion criteria: • patients who underwent anatomic lung resection for lung cancer with tumors > 5 cm (≥ T3) • Tumor size was defined according to the maximum diameter in the pathological specimens Exclusion criteria: • Patients who underwent neoadjuvant CT/RT, chest wall resection, tracheobronchoplasty, and angioplasty n=849 screened, n=60 included characteristics (VATs vs. Thoracotomy): 62.2±1.6 vs. 63.2±2.1 yrs Males: 91.7 vs. 97.2 % Co-morbidities: none: 62.5 vs. 52.5 % Heart disease: 42. Vs. 11.1 % Hypertension: 8.3 vs. 8.3 % Diabetes: 8.3 vs. 11.1 %	Thorax computed tomography (CT), PET-CT, and bronchoscopy if mediastinal lymph node enlargement or high FDG uptake first mediastinal lymph node sampling via endobronchial ultrasound with real-time guided transbronchial needle aspiration (EBUS-TBNA) or mediastinoscopy was performed **VATS** (n=24) vs. **Thoracotomy** (n=36)	postoperative complication (any complication occurring ≤30 days after surgery) prolonged air leakage (air leak > 7 days after surgery) recurrence-free survival postoperative mortality (≤30 days after surgery)	**Perioperative data:** no differences shown • Operation durations:228.7±91.9 vs. 260.2±102.8 min) • Intraoperative complications: 1 vs. 2 • Drainage time: shorter with VATS (5.0±3.4 vs. 8.1±5.0 days) • Lengths of stay: shorter with VATS (5.4±2.3 vs. 9.1±5.3 days) **Postoperative complications** (%): Total: 8 (33.3) vs. 14 (38.9) • Prolonged air leakage: 4(16.7) vs. 9 (25) • Hemorrhage: 1 (4.1) vs. 1(2.8) • Pneumonia: 3 (12.5) vs. 2 (5.6) • Empyema: 0 vs. 1 • Bronchopleural fistula: 0 vs. 1 **Recurrence-free survival:** better with VATS: • Median: 53.3 vs. 37.6 months (p=0.031) • 1-year recurrence: 81.2 vs. 78.8 % • 3-year recurrence: 81.2 vs. 50.2 % HR_a: 7.211 (95%CI 1.309-40.83) (p=0.023)* **Overall survival:** no difference shown • Median: 52.3 vs. 38.5 months • 1-year OS: 77.6 vs. 82.9 % (p=0.056) • 3-year OS: 77.6 vs. 57.2 % HR_a: 1.609 (95%CI 0.978-3.812) (p=0.064)* *Adjustierung erfolgte für Charakteristika des Patienten (Alter, Geschlecht, FEV1, Komorbiditäten), der	**2b-** Abwertung aufgrund geringer Präzision

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		COPD: 16.7 vs. 16.7 % Pathology: adeno: 58.3 vs. 63.9 % squamous cell: 29.2 vs. 30.6 % large cell: 12.5 vs. 5.6 % <u>Operation:</u> Lobectomy: 91.6 vs. 72.2 % Bilobectomy: 4.2 vs. 27.8 % Postoperative p staging: Stage II: 37.5 vs. 38.9 % Stage III: 62.5 vs. 61.1 %			Tumorerkrankung (Tumorgröße, Stadium, pathologischer Subtyp, die Länge des krankheitsfreien Intervalls, Nodalstatus) und der Behandlung (VATs vs. Thoraktomie, Zeit zwischen der Operation und der adjuvanten Therapie, Anzahl der sezierten Lymphknoten).	
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** „In conclusion, this current study demonstrates significant differences in drainage time, length of hospital stays, overall and recurrence-free survival in favor of VATS. Therefore, according to these results, we emphasize that VATS is a feasible surgical procedure for tumors larger than 5 cm. Difficulties may be experienced in the retraction of the lung and providing adequate exposure for safe dissection but this kind of issue can be overcome with the proper placement of ports, the use of appropriate surgical instruments, and teamwork." **Schlussfolgerung der Begutachterin:** Monozentrische türkische retrospektive Studie unter konsekutivem Einschluss aller 60 NSCLC-Patienten mit einem Tumordurchmesser über 5 cm (62 % im Stadium III), bei denen von eine pulmonare Resektion in den Jahren 2014-2018 durchgeführt wurde. Die Durchführung von VATS nahm bei diesen Patienten mit zunehmender Erfahrung der Operateure zu. Die Datenerhebung basiert auf vorliegenden Krankenakten. Es wurden geringe Unterschiede in den Charakteristika der Patienten festgestellt. Die Ergebnisse zum Einflus der Operationstechnik auf das Gesamt- und progressionsfreie Überleben basieren auf konfounderadjustierten Analysen. In der Gruppe mit VATS waren die Zeiten mit Drainage und im Krankenhaus kürzer. Unterschiede im Auftreten von peri- und postoperativen Komplikationen wurden nicht nachgewiesen. In konfounderadjustierten Analysen konnte ein verlängertes krankheitsfreies Überleben nachgewiesen werden. Unterschiede im Gesamtüberleben konnten, evtl. auf Grundlage der geringen Fallzahlen nicht nachgewiesen werden (daher Abwertung aufgrund geringer Präzision).						
Huang 2019 (41) ChiCTR-INR-17012777	**RCT** Non-inferiority of RATS for cN2 stage NSCLC on short-term outcomes	<u>Inclusion criteria:</u> • patients 18 to 75 yrs with clinically diagnosed c-N2 NSCLC • exhibited as a suspicious pulmonary	radical lobectomy combined with mediastinal lymph node dissection (hilar	Short-term perioperative outcomes (not specified)	RATS surgery was converted to thoracotomy in 5 subjects due to extensive pleural adhesion (2 cases) and equipment issues (3 cases), thus 53 RATS (91.4 %) cases were analysed **perioperative outcomes:** <u>no difference shown</u> in:	**2b** Abwertung aufgrund eingeschränkter Übertrag-barkeit und

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
01/2016-12/2018 Shanghai		lesion with enlarged mediastinal lymph nodes (diameter > 1 cm on CT scan) • adequate organ function to tolerate pulmonary resection <u>Exclusion criteria:</u> • invasion into neighboring organs, extensive pleural adhesion, • earlier thoracotomy, high dose radiation on the chest, • history of other malignancies in the past 5 years (except for nonmelanoma skin cancer, cervix cancer in situ, or early-stage prostate cancer) • predicted postoperative FEV1 or diffusing capacity of lung for carbon monoxide value < 40 % • pregnant or lactating female patients, inability to obtain consent • intraoperative pleural adhesion or technical	and mediastinal lymph nodes were routinely dissected, and ≥ 3 mediastinal lymph nodes (N2) stations was harvested) **RAT**S using the da Vinci Surgical System followed the strict definition of the Cancer and Leukemia Group B 39802, (anatomic lobectomy, visualization only by thoracoscope and non-ribspreading technique) (n=58) vs. **conventional lobectomy** with a rib-spreading thoracotomy of 15 to 20 cm (n=55)		distribution of different pulmonary resections)Lobectomy, bilobectomy, sleeve lobectomy) Operative time: 108±39 vs. 103±30 minutes POD1 drainage: 300 (95-840) vs. 320 (50-979) ml In all cases, the mediastinal lymph node was completely dissected. R0 resection: 98.2 vs. 94.3 % <u>Benefit of RATS in:</u> Intraoperative blood loss: less with RATS (86.3±41.1 vs. 165.7±46.4 ml; p<0.001) Chest tube duration: less with RATS (4 [2-63] vs. 5 [3-66]; p<0.01) Total drainage: less with RATS (820 [220-2460] vs. 960[320-4630]; p=0.05) Lower VAS on postoperative days 1-5 (no further explanations, all with p<0.001) **Costs:** Higher with RATS (100 367±19 251 vs. 82 002POD1-520 434 ¥ **Length of hospital stay:** No difference shown (10 [7-31] vs. 11 [6-44] days; p=0.07) **Complications:** Mortality: 1 (1.7 %) vs. 0 Any complications: no differences shown (27.6 vs. 38.2 %	fehlender Präzision, es liegen bisher ausschließlich Ergebnisse bis zur Entlassung aus dem Krankenhaus vor

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		challenge to achieve hemostasis needed conversion from RATS to thoracotomy • occult pleural metastasis • major protocol violation; clinician decides the patient should not continue the trail according to individual condition; patients withdraw from the trial • histologic finding is not NSCLC n=113 males: 71 % age: 61.2±8.2 yrs smoking history: 51.3 % no comorbidities: 65 % adeno/aquamous /large cell carcinoma: 66/23/3.5 % Tumour size: 3.45±1.4 cm Pathologic stage IIIA/B: 29/11.5 % IV: 3.5 %	Within the first 2 years patients were reviewed in outpatient clinic in 3-month intervals. Then, the surveillance was scheduled on a 6-month basis for the next 3 years			
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie: "**In conclusion, RATS is safe and effective to treat patients with cN2 NSCLC owing to its similar shortterm outcomes of thorough dissection of lymph node and occurrence of postoperative complications compared to axillary thoracotomy and may be superior due to its lesser intraoperative blood loss. However, long-term follow-up is warranted to verify the superior or equivalent oncologic outcome of RATS lobectomy. The report could be expected by the end of 2020."						

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Schlussfolgerung der Begutachterin: Multizentrische chinesische Nicht-unterlegenheits-RCT unter Einschluss und Randomisierung von 113 NSCLC-Patienten (c-N2, davon 40.1 % im Stadium III), (daher Abwertung aufgrund von eingeschränkter Übertragbarkeit der Ergebnisse) von denen 108 (91.4 % ohne Konversation zur konventionellen Lobectomy ausgewertet wurden (aufgrund der Fallzahl Abwertung augrund geringer Präzision). Für den Vergleich zwischen RATS und konventioneller Lobektomie werden ausschließlich Ergebnisse bis zum Zeitpunkt der Entlassung aus dem Krankenhaus berichtet, langfristige Ergebnisse sollen Ende 2020 veröffentlicht werden (nicht gefunden). Randomisierung und Zuweisung wird adäquat beschrieben, keine verblindete Endpunkterhebung oder Beschreibung des primären Endpunktes, Protokoll existiert in chinesischer Sprache.						

Ng 2019 (9) Search from 2000-01/2018	**Systematic review** optimal surgical approach for lobectomy (multiport video-assisted thoracic surgery (mVATS), uniportal video-assisted thoracic surgery (uVATS), robotic video-assisted thoracic surgery (rVATS)) compared to conventional open lobectomy to improve clinical and resource outcomes	Inclusion criteria: • RCTs and non-randomized observational studies (prospective or retrospective cohort and case–control studies) • Adult patients undergoing upfront lobectomy for stages I–III NSCLC • Studies comparing VATS (mVATS, rVATS, or uVATS) to conventional open thoracotomy, as well as studies that compared mVATS to rVATS or uVATS • any VATS lobectomy using more than one port was considered to be multiport VATS • studies reporting mixed lung resection procedures, whe data extraction and analysis of outcomes for lobectomy for NSCLC patients could be segregated out. Exclusion criteria: • Studies that assessed other types of surgery (segmentectomy, bilobectomy, sleeve	**minimally invasive surgical (MIS) approaches** (multiport video-assisted thoracic surgery (**mVATS**), uniportal video-assisted thoracic surgery (**uVATS**), and robotic video-assisted thoracic surgery (**rVATS**)) vs. **conventional open lobectomy** mVATS vs. open lobectomy (N=115) mVATS vs. rVATS (N=9) mVATS vs. uVATS (N=13) rVATS vs. open lobectomy (N=1) mVATS to rVATS vs. open lobectomy (N=4) combined mVATS / rVATS vs. open	Primary: Overall survival. Secondary: Recurrence-free survival local or distant tumor recurrence lymph node evaluation, pathological upstaging adverse events length of stay postoperative pain scores quality of life ability to return to normal activities respiratory function* cost-effectiveness* *not extracted	**mVATS vs. open lobectomy:** **Survival and recurrence:** • 5-year-survival (N=30, n=16200): higher with mVATS (72 % vs. 67 %; OR 1.35; 95%CI 1.17 to 1.56) with substantial heterogeneity between studies (I^2=60 %) • 5-year DFS (N=14, n=4108): no difference shown (no recurrence in 65 vs. 61%; OR 1.15; 95%CI 0.94 to 1.40) with moderate heterogeneity between studies (I^2=48 %) • Overall disease recurrence (N=22, n=6176): lower with mVATS (15 vs. 19 %; OR 0.73; 95%CI 0.61 to 0.87) with small heterogeneity between studies (I^2=24 %) • Local recurrences (N=14, n=3691): no differences shown (5 vs. 6 %; OR 0.77; 95%CI 0.58 to 1.03) with small heterogeneity between studies (I^2=0 %) • Distant recurrences (N=14, n=3691): lower with mVATS (6 vs. 10 %; OR 0.67; 95%CI 0.52 to 0.85) with small heterogeneity between studies (I^2=0 %) **Lymph node evaluation and pathological upstaging:** No difference in lymph nodes (N=28; n=29341) and lymph node stations (N=15; n=6714) dissected • Reduced odds of nodal upstaging with mVATS (11 vs. 14%; OR 0.71; 95%CI 0.58 to 0.97) with moderate heterogeneity between studies (I^2=57 %) **Complications and adverse events:** All less frequent with mVATS: • Complications (N=53, n=88 460): (36 vs. 42 %; OR 0.64; 0.59 to 0.71) with substantial heterogeneity between studies (I^2=64 %) • Cardiopulmonary (N=17, n=143 390): (OR 0.60; 0.48 to 0.75) with substantial heterogeneity between studies (I^2=74 %) • Atrial fibrillation (N=23, n=12 246): (OR 0.62; 0.45 to 0.84) with moderate heterogeneity between studies (I^2=46 %) • Prologed air leak (N=33, n=18 762): (OR 0.78; 0.67 to 0.90) with small heterogeneity between studies (I^2=12 %)	**2a-** Abwertung aufgrund von Indirektheit und Studienlimitationen, Aufwertung aufgrund hoher Präzision

		lobectomy, pneumonectomy, and wedge resection) • studies where patients received neoadjuvant chemotherapy or radiation • studies that included patients with advanced lung cancer • studies that included patients with benign neoplasm or infectious disease N=145 studies, n=369793 N=7 RCTs with n=1276 N=138 n-RCTs (cohort and case-control studies) with n=368517 142 studies published in English N=13 with propensity score matching Most studies were conducted in the United States, China, Japan, and South Korea, but also in several European countries and one South American country <u>Risk of bias:</u> All RCTs were rated as high risk of bias for blinding.	lobectomy (N=2)		• Wound infection (N=13, n=52 234): (OR 0.50; 0.36 to 0.68) with small heterogeneity between studies (I^2=0 %) • <u>30-day mortality</u> (N=15, n=23 629): (OR 0.77; 0.62 to 0.95) with small heterogeneity between studies (I^2=0 %) • No differences shown for 90-day mortality (N=6, n=12 479): (OR 0.78; 0.56 to 1.07) with small heterogeneity between studies (I^2=13 %) **Pain and quality of life:** Less postoperative <u>pain</u> (measured with VAS) with mVATS on days 1,7,14,30 and 90 Higher quality of life (1 RCT, n=201, EQ5D) at week 2, 8, 12, 26 and 52 and higher <u>quality of life</u> (N=3, n=332, Global QoL tool) at 1 year and better activities of daily lifing (N=1, n=103) **Length of hospital stay (N=35, n=36 776):** • shorter with mVATS (MD -1.95; 95%CI -3.1 to 0.73) with substantial heterogeneity between studies (I^2=97 %) **mVATs vs. rVATS:** **Survival and recurrence:** • 5-year-survival (N=1, n=313): no difference shown (OR 0.79; 95%CI 0.47 to 1.33) • 5-year DFS (N=1, n=313): no difference shown (OR 0.71; 95%CI 0.44 to 1.14) • Similar results after 2 years **Lymph node evaluation and pathological upstaging:** No difference in lymph nodes detection (N=5; n=7814), lymph node stations detection (N=2; n=179) and nodal upstaging (N=6; n=18 216) with substantial and small heterogeneity between studies (I^2=74, 69 and 18 %) **Complications and adverse events:** No differences shown for complications (N=1-6, n=999 to 24 513), atrial fibrillation, prologed air leak, pneumonia and 30-day mortality **Length of hospital stay:** No difference shown (N=6; n=7752)	

		N=138 nRCTs were rated with Newcastle-Ottawa scale (range 0-9, 9 indicats high methodological quality). Most studies have reasonably good quality, all studies were at risk for performance or detection bias because it was not possible to blind physicians, patients and personnel to the intervention, many of the outcomes are objective in nature, no clear evidence of publication bias, but inadequate power for some clinical outcomes			**mVATs vs. uVATS:** **Survival and recurrence:** • 3-year-survival (N=1, n=160): no difference shown (OR 0.57; 95%CI 0.20 to 1.64) **Lymph node evaluation and pathological upstaging:** No difference in lymph nodes detection (N=10; n=1789) and nodal upstaging (N=1; n=106) with substantial heterogeneity between studies (I^2=67 %) **Complications and adverse events:** No differences shown for complications (N=1 to 5, n=106 to 930, prologed air leak, pneumonia, perioperative and 30-day mortality **Pain and quality of life:** Less postoperative pain analgetics per months with uVATS (MD 4.2;95%CI 3.8 to 4.6) with small heterogeneity between studies (I^2=0 %) less pain (measured with VAS) with uVATS on days 1,3, 7 and 30 **Length of hospital stay:** No difference shown (N=7; n=1269)	

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (IG vs. CG); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** "In conclusion, we have performed an extensive systemic review and meta-analysis comparing mVATS to open lobectomy, and the most popular MIS approaches to each other. mVATS has been reported for over 25 years and a large number of studies with several thousand patients have been included in comparisons between mVATS and open lobectomy. However, only 7 of the 145 included studies were randomized trials. In addition to the general limitations of meta-analysis, it is hard to control for surgeon specific biases (e.g., treating smaller and peripheral tumors with an MIS approach), and institutional biases where some surgeons will use an open and others an MIS approach. With these limitations in mind, our analysis suggests that the mVATS approach is superior to thoracotomy, particularly with respect to adverse events, pain control and perhaps improved survival. With respect to the optimal MIS approach, fewer studies are available to make definitive statements. Robotic VATS may be more expensive than mVATS, but otherwise does not demonstrate superiority or inferiority compared to mVATS. There is a suggestion that uVATS may be associated with lower adverse events and pain. It is our goal that the extensive analysis provided in the manuscript and appendix will assist future investigators in planning new trials to explore differences between these techniques." **Schlussfolgerung der Begutachterin:** Systematische Übersicht zum Vergleich minimal invasiver Operationstechniken (mVATS, uVATS, rVATS) mit einer offenen Thorektomie unter Einschluss von RCTs und vergleichenden Beobachtungsstudien (Kohorten- und Fall-Kontrollstudien) mit einer Suche bis Januar 2018. Einschluss von 145 Studien mit 369 793 Studienteilnehmern mit NSCLC der Grade I-III (davon 7 randomisierte Studien und 13 Studien mit Propensity-Score-Matching), von denen die meisten in Asien durchgeführt wurden und viele Patienten in einem frühen Erkrankungsstadium einschließen (deshalb und wegen Einbezug der Grade I-III Abwertung aufgrund von eingeschränkter Übertragbarkeit). Die systematische Übersichtsarbeit weist eine moderate Einschränkung der Qualität auf (fehlendes Protokoll, Informationen zur Suche in Registern und zum Screenen der Referenzen, keine Heterogenitätsbetrachtungen), die Studien sind nicht verblindet (Durchführungs- und Beobachtungsbias kann nicht ausgeschlossen werden (daher Abwertung aufgrund von Studienlimitationen). Es wird die Wirksamkeit einer minimal invasiven Operation auf das Überleben (substantielle Heterogenität, aber 25/30 Studien zeigen Vorteil von mVATS) und krankheitsfreie Überleben sowie das Auftreten von Rekurrenzen, ein Upstaging aufgrund der Lymphknotenuntersuchung, dem Auftreten postoperativer Komplikationen (auch hier substantielle Heterogenität, aber in 51/53 Studien weniger Komplikationen mit mVATS im Vergleich zur Thorektomie), das Auftreten von Schmerzen, die Lebensqualität und die Länge des Krankenhausaufenthaltes gezeigt. Insgesamt wird die Qualität der Evidenz aufgrund der aus der hohen Anzahl von Studien und Teilnehmern und der aussagekräftigen Ergebnisse zu Überleben und Komplikationen um einen Grad von 2a (Systematische Übersicht auf Grundlage von Kohortenstudien) auf 2a- abgewertet.						
CG: Control group; CI: Confidence interval; d: Tag; DCR: Disease control rate; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IG: Intervention group; MIS: minimally invasive surgery; mVATS: multiport video-assisted thoracic surgery; N: Number of studies; n: Number of participants;RATS: robot-assisted thoracoscopic surgery; rVATS: robotic video-assisted thoracic surgery; uVATS: uniportal video-assisted thoracic surgery; VAS: Visual analogue scale; wks: weeks; yrs: years						

Fragestellung 4: Ist eine Konsolidierungstherapie nach definitiver Therapie im Stadium III (bimodal oder trimodal) von Vorteil?

Es konnten insgesamt drei RCTs zur Wirksamkeit einer Konsolidierungs-Chemotherapie (43-46), ein RCT zur Wirksamkeit einer zielgerichteten Therapie mit Icotinib (47) und ein RCT zur Wirksamkeit einer Konsolidierungs-Immuntherapie (48-50) eingeschlossen werden (siehe Eingeschlossene Studien: Fragestellung 4).

Studiencharakteristika

Die drei RCTs zur Wirksamkeit einer Konsolidierungschemotherapie (Hanna 2008 (45, 46), Ahn 2015 (43) und Flentje 2016 (44)) randomisierten insgesamt 826, vorrangig männliche Patienten mit nichtoperablem nicht-kleinzelligem Lungenkarzinom im Stadium III zu einer Konsolidierungschemotherapie oder einer Kontrollgruppe ohne experimentelle Therapie. Die Patienten erhielten bei Vorliegen einer stabiler Erkrankung ohne lokale Progression oder Fernmetastasen nach Abschluss der Chemo-Radiotherapie innerhalb eines Zeitraumes von 4-8 Wochen eine Konsolidierungstherapie auf der Basis von Docetaxel in Hanna 2008, Docetaxel und Cisplatin in Ahn 2015 und Vinorelbin und Cisplatin in Flentje 2016 (siehe Tabelle 16).
Die Studie zur zielgerichteten Therapie von Feng 2015 (47) randomisierte 41 Patienten mit EGFR-positivem NSCLC in den Stadien IB bis IIIA nach Resektion und platinhaltiger Chemotherapie in Gruppen mit und ohne zusätzliche Konsolidierungstherapie mit Icotinib.
Die Studie zur Immuntherapie Antonia 2017 (PACIFIC) (48-50) randomisierte 713 vorrangig männliche Patienten mit nichtoperablem nicht-kleinzelligem Lungenkarzinom im Stadium III zu einer Konsolidierungsimmuntherapie oder Plazebo. Patienten ohne Progression nach Chemo-Radiotherapie wurden mit Durvalumab behandelt.

Bewertung der methodischen Qualität

Die Evidenz der randomisierten, in Asien (Korea, China und Taiwan) durchgeführten, methodisch sehr guten großen Studie (Ahn 2015) wurde mit 1b bewertet, wobei die Übertragbarkeit der Ergebnisse dieser Studie von der Gruppe zu beurteilen ist. Die beiden anderen Studien (Flentje 2016, Hanna 2008) wurden mit dem Evidenzlevel 1b- und 2b (Feng 2015) bewertet. Die Abwertung der Evidenz erfolgte aufgrund schwerwiegender Studienlimitationen wie der fehlenden berichteten Informationen zur Randomisierung und der fehlenden öffentlichen Registrierung eines Studienprotokolls. Alle Studien wurden vorzeitig abgebrochen und rekrutiertenweniger Patienten als geplant. Gründe umfassen die langsame Rekrutierung (Flentje 2016) ohne Planung im Studienprotokoll, der fehlende Wirksamkeitsnachweis (Hanna 2008) und die Veröffentlichung von Zwischenergebnisse (Feng 2015). Alle 3 Studien wurden ohne Verblindung durchgeführt.
Die Evidenz der randomisierten internationalen randomisierten Studie zur Wirksamkeit der Immuntherapie wurde mit 1b bewertet. Diese Studie wurde mit doppelter Verblindung durchgeführt und nach Vorliegen der Ergebnisse der ersten geplanten Zwischenanalyse aufgrund der hohen Wirksamkeit vorzeitig abgebrochen (siehe Tabelle 16).

Wirksamkeit und Sicherheit

Konsolidierungs-Chemotherapie

In keiner der drei Studien konnte eine Verlängerung des Gesamt- oder progressionsfreien Überlebens nachgewiesen werden, während zum Teil schwerwiegende Nebenwirkungen (Grad 3-5) auftraten.
So berichtet die Studien von Hanna 2008 (45, 46) ein medianes Gesamtüberleben von 24,2 Monaten in der Gruppe mit Chemo-Radiotherapie und anschließender Konsolidierungstherapie und von 26,1 Monaten in der Gruppe mit ausschließlicher Chemo-Radiotherapie. In der Gruppe mit Konsolidierungstherapie mit Docetaxel wurden häufig schwerwiegende hämatologische (z.B. Neutropenie bei 24,7 % und febrile Neutropenie bei 10.9% der Patienten) und nicht-hämatologische Nebenwirkungen (z.B. Infektionen bei 11.0 % und Lungenentzündungen bei 9.6 % der Patienten)

beobachtet. Insgesamt 4 (5,5%) der mit Docetaxel behandelten Patienten verstarben aufgrund der Therapie (46). Während die Überlebenszeiten jüngerer und älterer Studienteilnehmer sich nicht unterschieden, traten bei Studienteilnehmern über 70 Jahren mehr Nebenwirkungen der Grade 3-4 auf und waren mehr Krankenhauseinweisungen notwendig (45).

Auch die Studie von Ahn 2016 (43) berichtet ein vergleichbares Gesamtüberleben in beiden Behandlungsgruppen über 21,8 und 20,6 Monate und ein Hazard-Ratio von HR 0,91 (95% KI 0,72-1,25) bei deutlich geringerer Toxizität der Konsolidierungstherapie mit Docetaxel und Cisplatin (43) (siehe Abbildung 2 und Abbildung 3).

Die Ergebnisse zum Gesamtüberleben wurden in der Studie Flentje 2015 zum Einsatz einer Konsolidierungstherapie mit Vinorelbin und Cisplatin mit einem medianen Gesamtüberleben von 20,8 und 18,5 Monaten. In dieser Studie werden häufige schwerwiegende (Grad 3-4) Nebenwirkungen (Leukopenie bei 26,7 % und Neutropenie bei 22,1 % der mit Vinorelbin und Cisplatin behandelten Patienten) beobachtet (44) (siehe Abbildung 3).

Zielgerichtete Konsolidierungstherapie

Die Studie von Feng 2015 (47) berichtet ein nicht-signfikant verbessertes krankheitsfreies Überleben nach 12, 18 und 24 Monaten bei geringer Toxizität der Konsolidierungstherapie mit Icotinib (siehe Tabelle 16)..

Konsolidierungs-Immuntherapie

Im Gegensatz zu diesen Ergebnissen konnte die Wirksamkeit einer Konsolidierungstherapie mit Durvulumab nachgewiesen werden (HR 0,68 (99.73 % KI 0,47-0,997. Die 1-Jahres-Überlebensraten konnten von 75.3% auf 83.1% und die 2-Jahres-Überlebensraten von 55,6 auf 66,3 % in der Interventionsgruppe mit Durvulumab als Konsolidierungstherapie erhöht werden. Dieses verbesserte Gesamtüberleben basiert auf einem besseren Tumoransprechen und einem verlängerten progressionsfreien Überleben. Die Anzahl von Nebenwirkungen der Grade 3 und 4 und schwerwiegender Nebenwirkungen war in der Gruppe mit Durvulumab im Vergleich zur Kontrollgruppe mit Plazebo leicht erhöht (30,5% vs. 26,1% und 29,1% vs. 23,1 %) (siehe Tabelle 16 und Abbildung 2 und Abbildung 3).

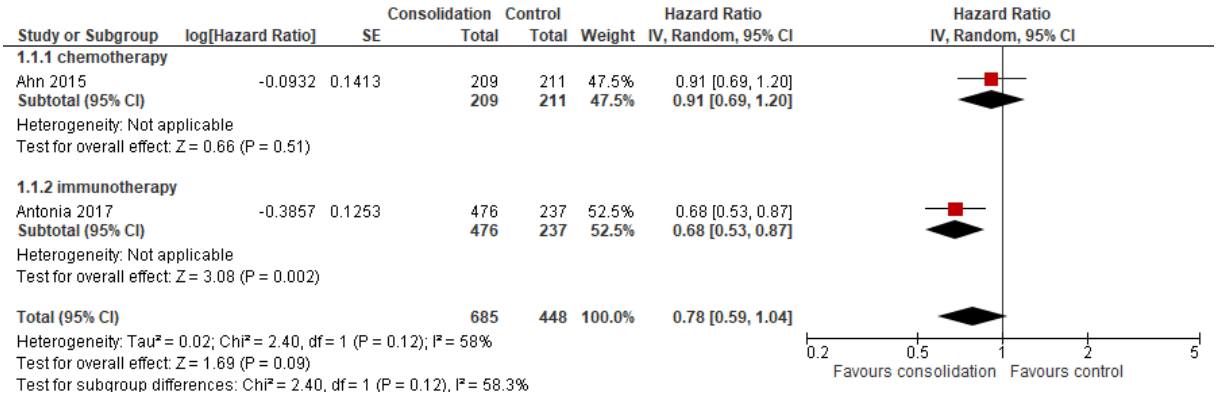

Abbildung 2: Behandlungseffekte einer Konsolidierungstherapie auf das Gesamtüberleben

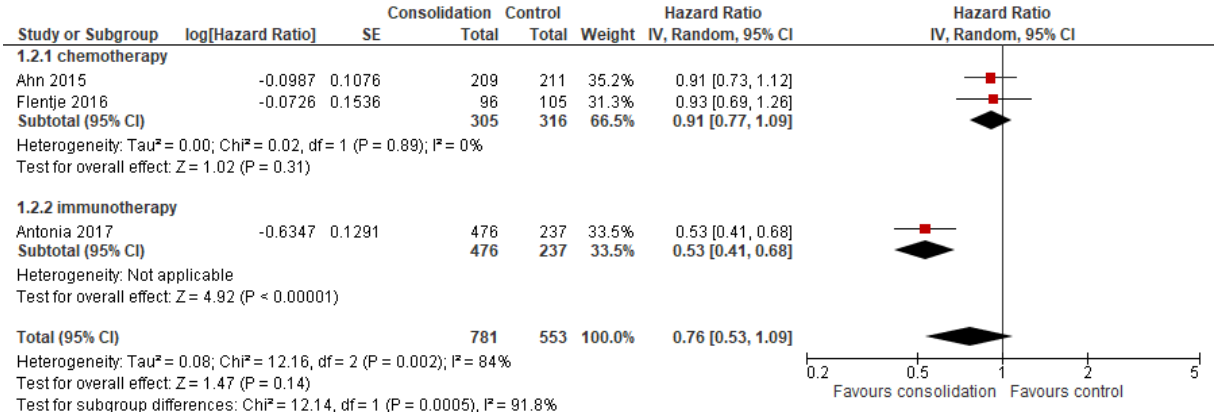

Abbildung 3: Behandlungseffekte einer Konsolidierungstherapie auf das progressionsfreie Überleben

Tabelle 16: Evidenztabelle zur Wirksamkeit und Sicherheit von Konsolidierungstherapien nach definitiver Therapie bei Patienten mit NSCLC im Stadium III

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (Index vs. Referenztest); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Ahn 2015 (43) KCSG-LU05-04 NCT00326378	**RCT** Efficacy of consolidation CT with docetaxel and cisplatin after concurrent CRT with the same agents in locally advanced NSCLC 10/2005-04/2011 in 31 centers in Korea, China, Taiwan	Inclusion Criteria: • histologically documented NSCLC with inoperable stage IIIA/IIIB disease (proven by computed tomography (CT), magnetic resonance imaging, and/or positron emission tomography (PET)) • N2 or N3 disease must have been confirmed by pathology or PET • ≥ 18 yrs, ECOG 0-1, • measurable disease (RECIST); no prior CT, RT to the chest, immunotherapy, or biologic therapy; FEV1≥0.8 L (spirometry) • adequate bone marrow, renal, and hepatic function • no local progression or distant metastases, adequate organ function before the start of CC Exclusion criteria: • pregnancy or lactating women, women without a pregnancy test ≤ 14 days before the first	**CRT for all patients:** docetaxel (20 mg/m^2 iv) + cisplatin (20 mg/m^2 iv. on days 1, 8, 15, 22, 29, and 36 + thoracic RT 5 days/week (once-daily fractions, 2.0 Gy per fraction, total 66 Gy in 33 fractions) 4-8 wks after CRT: **consolidation CT** (n=209): docetaxel (35 mg/m^2 iv. for 1 hour)+ cisplatin (35 mg/m^2 for 1 hour) on days 1,8, repeated every 3 weeks vs. **best supportive care** (n=211)	Primary: PFS Secondary: OS Overall response rate Patterns of failure Toxicity (AEs graded with CTCAE 3.0)	**Progression-free survival:** no difference (p=0.36) median: 9.1 months (95% CI 7.9-10.9) vs. 8.1 months (95% CI 7.6-8.9); HR 0.91 (95% CI 0.73-1.12) p=0.36 **Overall survival:** no difference (p=0.44) median: 21.8 (95% CI 17.7-24.7) vs. 20.6 months (95% CI 17.6-26.3); HR 0.91 (95% CI 0.72-1.25) **Overall response:** no difference (p=0.33) 43.1% (with 2.9% complete response) vs. 38.4% (with 4.3% complete response) **Disease control rate:** approximately 58% in both arms **Safety** (during consolidation therapy): slightly more febrile neutropenia (grade 3/4): 1.2/0.6 % neutropenia (grade 3/4): 4.6 / 2.3 % infection (grade 3/4): 2.3% vs. 2.9% radiation pneumonitis (grade 3/4): 1.2% vs. 1.2% treatment-related mortality (grade 3/4): 3.6% during CRT, 2.3% during CC.	**1b**

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (Index vs. Referenztest); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		administration, childbearing potential without the use of adequate contraception n=459 randomized, 420 analysed median age: 61 yrs (31-79) males: 82.6% ECOG (0/1/2): 23.6/68.6/7.6 Pathology (Adeno/squamous/other): 51.7/32.1/12.9 Stage (IIIA/IIIB): 22.1/77.9	for up to 3 cycles until unacceptable toxicity or evidence of disease progression 42.1% received planned 3 cycles, 54.1% finished ≥ 2 cycles, 31.6% did not receive any CC reasons for no CC: early death (n=22), consent withdrawal or patient refusal (n=14), AEs (n=12), disease progression (n=10) median follow-up: 50.7 months			
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** "In summary, this study confirms that the current strategy of consolidation treatment with cytotoxic chemotherapy after CCRT does not improve survival in patients with locally advanced (LA)-NSCLC. In future trials, CCRT without CC should remain the reference arm. Given that distant failure is the most common pattern of failure after CCRT in LA-NSCLC and the treatment outcome remains poor, we strongly believe that the concept ofconsolidation therapy needs to be further explored using less toxic, better tolerated agents."						

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (Index vs. Referenztest); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Schlussfolgerung der Begutachterin: Multizentrische asiatische RCT ohne Verblindung mit adäquat beschriebener Randomisierung und Studienregistrierung und modifizierter ITT-Analyse nach Ausschluss von 17 (3.9%) Patienten, welche randomisierte Studienphase nicht begonnen (kein Unterschied zwischen Gruppen) mit adäquater Studiengröße und Nachbeobachtungszeit, aber ohne Wirksamkeitsnachweis, Interessenkonflikte der Autoren können nicht ausgeschlossen werden.						
Antonia 2017 PACIFIC NCT02125461 (48-50)	**RCT** Efficacy and safety of durvalumab as consolidation therapy in patients with stage III, locally advanced, unresectable NSCLC that had not progressed after platinum-based CRT 04/2014-04/2016 in 26 countries	Inclusion Criteria: • histologically or cytologically documented stage III, locally advanced, unresectable NSCLC who received • no disease progression after this treatment, ≥ 18 yrs, WHO performance status 0-1, an estimated life expectancy ≥ 12 wks, completion of the last radiation dose within 1-14 days before randomization (after a protocol amendment, this criterion was changed to 1 to 42 days before randomization) Exclusion criteria: • previous exposure to anti–PD-1 or PD-L1 antibodies, • receipt of immunotherapy or an investigational drug within 4 wks before the first dose (6 weeks for monoclonal antibodies),	**CRT for all patients:** ≥ 2 cycles of platinum-based CT (etoposide, vinblastine, vinorelbine, a taxane [paclitaxel or docetaxel], or pemetrexed) concurrently with definitive RT (54 to 66 Gy), mean dose to the lung < 20 Gy (volume of lung parenchyma that ≥ 20 Gy) was < 35%, or both 1-42 days after CRT: **consolidation therapy** (n=476): durvalumab (10	Primary: PFS (RECIST) OS Secondary: 12 /8 months DFS objective response rate duration of response time to death or distant metastasis 24 months OS Health-related QoL (time to deterioration of cough, dyspnoea, chest pain, haemoptysis (all QLQ-LC13), and global health status or QoL) Safety: (CTCAE, version side-effect 4.03) AEs, SAEs	**Progression free survival** (49): • median: 16.8 (95% CI 13.0-18.1) vs. 5.6 months (95% CI 4.6-7.8); HR 0.52 (95% CI 0.42-0.65;p<0.001) • 12-month PFR rate: 55.9% (95% CI 51.0-60.4) vs. 35.3% (95% CI 29.0-41.7) • 18-month PFS rate: 44.2% (95% CI 37.7-50.5) vs.27.0% (95% CI 19.9-34.5) • consistent across all pre-specified sensitivity and subgroup analyses • no differences between males and females, NSCLC disease stage and depending on best response, higher benefit for ○ younger age: < 65 vs. ≥ 65 yrs: HR 0.43 (95%CI 0.32-0.57) vs. 0.74 (95%CI 0.54-1.01) ○ nonsmoker vs. smoker: HR 0.29 (95%CI 0.15-0.57) vs. 0.59 (95%CI 0.47-0.73) ○ nonsquamous vs. squamous types: HR 0.45 (95%CI 0.33-0.59) vs. 0.68 (95%CI 0.50-0.92) ○ PD-L1 ≥25 vs. <25%: HR 0.41 (95%CI 0.26-0.65) vs. 0.59 (95%CI 0.43-0.82) ○ EGFR mutation: negative vs. positive: HR 0.47 (95%CI 0.36-0.60) vs. 0.76 (95%CI 0.35-1.64) **Overall survival** (48): • median: NR (95% CI 34.7-NR) vs. 28.7 months (95% CI 22.9-NR); HR 0.68 (99.73 % CI 0.47-0.997; p=0.0025) • 12-month rate: 83.1% (95% CI 79.4-86.2) vs. 75.3% (95% CI 69.2-80.4) • 24-month rate: 66.3% (95% CI 61.7-70.4) vs. 55.6% (95% CI 48.9-61.8) (p = 0.005)	**1b**

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (Index vs. Referenztest); Effekt (95% KI)	**Evidenzgrad** (OCEBM)

		• active or previous autoimmune disease (within ≤ 2 yrs) or a history of primary immunodeficiency,
		• evidence of uncontrolled, concurrent illness or ongoing or active infections;
		• unresolved toxic effects ≥ grade 2 (CTCAE) and
		• ≥ grade 2 pneumonitis from previous CRT
		n=713
		age: 64 (23-90) yrs
		70.1% males
		disease stage (IIIA/IIIB/other): 52.9/44.7/2.4 %
		WHO (0/1): 48.8/50.8 %
		Tumour histologic type: (squamous, nonsquamous): 45.7/ 54.3 %
		Smoking (current/former/never): 16.4/76.4/9.0 %
		previous RT (<54 Gy/ ≥54 to ≤66 Gy/>66 to ≤74 Gy): 0.4/92.4/6.9 %
		previous CT (induction /concurrent with RT): 26.8 /99.7 %
			mg/kg of body weight iv)
			vs.
			Placebo (n=237) every 2 wks
			
			for up to 12 months until disease progression, could receive the drug again if disease control had been achieved
			
			<u>Median number of infusions:</u> 20 (1-27) vs. 14 (1-26)
			<u>median relative dose intensity:</u> 100% (29-100) vs. 100% (50-100)
			
			<u>Median follow-up:</u> up to 25.2 months (IQR 14.1-29.5) months
				vital signs, physical and laboratory examinations
				AEs of special interest and immune-mediated AEs (AEs of special interest that led to the use of systemic glucocorticoids, endocrine therapy, or other immune-suppressants, that were consistent with an immune-mediated mechanism, and that had no clear alternative cause)
					Time to death or distant metastases (48):
					median: 28.3 (95% CI 24.0-34.9) vs. 16.2 months (95% CI 12.5-21.1), HR 0.53 (95% CI 0.41-0.68)
					Frequency of new lesions (48):
					22.5% vs. 33.8% with a lower incidence of new brain metastases (6.3% vs. 11.8%)
					Time to second progression or death (48):
					median: 28.3 (95% CI 25.1-34.7) vs. 17.1 months (95% CI 14.5-20.7); HR 0.58 (95% CI 0.46-0.73)
					Overall response rate (48):
					30.0% (95% CI 25.8-34.5) vs. 17.8% (95% CI 13.0-23.6) (p<0.001) with ongoing response at 18 months in 73.5 vs. 18 months
					Safety (48) (during consolidation therapy):
					• 3 or 4 AEs: 30.5% vs. 26.1%
					• Discontinuation of trial regimen due to AEs: 15.4% vs. 9.8%
					  ○ Most frequent AEs leading to the discontinuation:
					  ○ pneumonitis (4.8% vs. 2.6% of patients),
					  ○ radiation pneumonitis (1.3% vs. 1.3%)
					  ○ pneumonia (1.1% vs. 1.3%)
					• SAEs: 29.1% vs. 23.1%
					• Death due to AEs: 4.4% vs.6.4%
					• AEs of special interest (any grade or cause): 66.7% vs. 49.1% with 56.8% and 43.6% of patients, reporting grade 1 or 2 events.
					Changes **in health-related quality of life** over 12 months (50):
					• Cough, dyspnoe, chest pain, fatique, appetite loss, physical functioning and global health status of QoL remained stable for both groups
					• No clinically important differences in:	

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (Index vs. Referenztest); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		Best response to previous CT (complete/partial response/ stable disease): 2.2/48.1/47.1 %			○ time to deterioration for most symptoms, functioning terms, or global health status or QoL ○ proportion of patients with clinically relevant improvements in most symptoms ○ proportion of patients whose scores improved for global health status or QoL or most functioning terms • time to deterioration of other pain (ie, any pain other than in the chest, arms, or shoulders) longer in durvalumab (HR 0.70; 05%CI 0.57-0.87) • emotional functioning favoured durvalumab	
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** " In conclusion, in the PACIFIC study, one of the coprimary end points was met at this planned interim analysis, and this study showed a significant increase in progression-free survival and no new safety signals with durvalumab in patients with stage III, unresectable NSCLC who had received chemoradiotherapy. These positive findings in an unselected patient population, irrespective of baseline expression of PD-L1 on tumor cells, suggest that durvalumab may be an effective adjuvant therapy in patients with stage III disease after standard treatment. Uncertainty about the potential mechanisms driving the interaction between immunotherapy and chemoradiotherapy warrants further investigation." (49) In conclusion, this trial showed a survival advantage with durvalumab therapy after concurrent chemoradiation therapy in patients with stage III, unresectable NSCLC (48). **Schlussfolgerung der Begutachterin:** Methodisch gute multizentrische internationale RCT mit doppelter Verblindung (Patienten, behandelnde Ärzte und Erfasser von PFS und Response) und guter Beschreibung der Erzeugung und verblindeten Zuweisung der Randomisierungsfolge, alle geplanten Endpunkte werden für alle randomisierten Endpunkte berichtet, ausreichende Power und Nachbeobachtungszeit zum Nachweis von Unterschieden für PFS und OS (daher hohe Präzision der Ergebnisse), Studie wurde wie im Protokoll geplant nach Nachweis der Wirksamkeit in der 1. Zwischenanalyse (nach 299 statt 491 beobachteten Todesfällen) abgebrochen, Finanzierung der Studie und Publikation durch Astra Zeneca, Interessenkonflikte der Autoren können nicht ausgeschlossen werden.					
Feng 2015 (47) NCT02430974	**RCT** efficacy and safety of CT with icotinib in patients undergoing resection of stage IB to IIIA EGFR-	Inclusion Criteria: • histologically confirmed activating EGFR-mutated NSCLC between stage IB (with high risk factors) and stage IIIA, received an operation to remove the lung lesion completely	**CT for all patients:** 4 cycles of platinum-based doublet CT (150 mg/m^2 paclitaxel + 80 mg/m^2 nedaplatin or 30 mg/m^2	Primary: DFS Secondary: toxicity (WHO toxicity grading scale for determining the severity of AEs)	**Disease free survival:** no difference (p=0.066) 12 months: 21/21 (100%) vs. 16/18 (88.9%); p=0.122 18 months: 20/21 (95.2%) vs. 15/18 (83.3%); p = 0. 225 24 months: 19/21 (90.5%) vs. 12/18 (66.7%); p = 0. 066 **Toxicity:** 4 patients in each group had ≥ 1 CT-related AE (19 vs. 22 %) gastrointestinal reactions (grade 1/2): 3/0 vs. 3/1 marrow suppression: 4/0 vs. 3/0 neurotoxicity: 4/0vs. 3/1	**2b** Abwertung aufgrund von schwer-wiegenden Studien-limitationen und geringer Präzision

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (Index vs. Referenztest); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
	mutated NSCLC 02/2011-12/2012 in 1 center in China	• high-risk stage IB NSCLC were defined as poorly differentiated tumors, vascular invasion, wedge resection, tumor size > 4 cm, visceral pleural involvement or incomplete lymph node sampling, • activating EGFR-mutation-positive disease: ≥ 1 of 4 mutations (exon 19 deletion, or 18 G719X, 21 L858R, or 21 L861Q mutations) • 18 years, ECOG 0 or 1, adequate hematological, biochemical and organ function <u>Exclusion Criteria:</u> • single mutation ofexon 20 T790M, 20 insertions or 19 D761Y (resistant to EGFR-TKI) • systemic anticancer therapy prior to surgery, other malignancies before or during the study, any unstable illness, pregnancy or lactation n=41 age: 56.6±10.3 yrs 69% males	lobaplatin on day 1 of a 3 wk cycle) 2 wks after CT: **consolidation therapy** (n=21): oral icotinib (125 mg, 3x daily) for 4 to 8 months or until occurrence of disease relapse, metastasis or unacceptable icotinib or CT toxicity vs. **Best supportive care** (n=20, 18 analyzed)	follow-up for up to 24 months	liver and kidney damage: 4/0 vs. 2/1 allergic reactions: 3/0 vs. 2/1	

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (Index vs. Referenztest); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		95% adenocarcinoma 51% present or former smoker lymph node status (N0/1/2): 59/10/31 % stage (IB/II/IIIA): 44/26/31 % EGFR mutations (19 delete, 21 L858R): 41/56%				
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** „The results suggest that chemotherapy plus orally icotinib displayed better DFS compared with chemotherapy only, yet the difference in DFS was not significant. We would think the preliminary result here was promising, and further trials with larger sample sizes might confirm the efficiency of adjuvant TKI in selected patients." **Schlussfolgerung der Begutachterin:** Monozentrische RCT aus China ohne Verblindung und Beschreibung der Zuweisung der Behandlung, abweichend vom Protokoll wurden 41 statt 58 rekrutiert, 2 (10 %) Patienten aus der Kontrollgruppe erhielten keine Chemotherapie und wurden aus der Analyse ausgeschlossen (daher Abwertung aufgrund von schwerwiegenden Studienlimitationen), Finanzierung der Studie durch ein „major drug discovery project"in China, es werden keine Interessenkonflikte der Autoren berichtet, Abwertung der Evidenz erfolgt aufgrund von Studienlimitationen und der geringen Präzision der Ergebnisse aufgrund der geringen Fallzahl und Nachbeobachtungszeit von bis zu 24 Monaten						
Flentje 2016 (GILT) (44)	**RCT** Benefit on PSF of adding 2 cycles of CT to best supportive care in patients with at least stable disease control following CRT	Inclusion Criteria: • histologically confirmed stage IIIA/ IIIB (TNM6) inoperable NSCLC • no malignant pleural effusion, weight loss < 10%, Karnofsky index ≥ 80, forced expiratory volume in 1 second (FEV1) < 1.5 L, no previous treatment • Staging based on bronchoscopy,	**CRT for all patients:** two cycles of oral vinorelbine (50 mg/m^2 days 1, 8 and 15) + cisplatin (20 mg/m^2 days 1–4) q4w) + concomitant RC (66 Gy)	Primary: PFS Secondary : OS objective response rate (RECIST 1.0) Disease control rate toxicity (CTCAE 3.0) Quality of life (LCSS)	**PFS**: no differences (p = 0.63) median: 6.4 (5.0–8.7) vs. 5.5 (3.8–7.4) months; HR: 0.93 (95% CI 0.69–1.26) better PFS for higher age >60 yrs: HR 0.72 (95%CI 0.53-0.97) **OS:** no differences (p = 0.51) median: 20.8 (13.5–25.3) vs. 18.5 (13.6–24.7) 4-year OS rate: 25.2 and 21.4 % **Response:** no differences (p=0.12) Complete response: 3.1 vs. 1.0 % partial response: 26.0 vs. 23.8 % stable disease: 37.5 vs. 31.4 % progressive disease: 12.5 vs. 30.5 % not evaluable: 20.8 vs. 13.3 %	**1b-** Abwertung aufgrund von schwer-wiegenden Studien-limitationen

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (Index vs. Referenztest); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
	05/2005-05/2009 in 34 German centres	thoracoabdominal CT, bone scintigraphy and brain CT or MRI • Patients received at least stable disease after CRT n=279 received CRT, n=201 randomized median age: 60.1 vs. 59.2 yrs (33.9-75.7), 50 %≥ 60 yrs 72% males Karnovsky Index (80/90/100 %): 15.4/41.8/42.8% Comorbidties (0/1/2/≥3): 19.9/37.3/35.3/7.5 % <5% weight loss: 7.9% Histology (squamous/adeno/large cell): 53.2/36.3/7.5% Stage (IIIA/IIIB): 15.4/84.6%	4-6 wks after CRT: **consolidation therapy** (n=96): 2 cycles oral vinorelbine (60–80 mg/m^2 days 1 and 8) + cisplatin (80 mg/m^2 day 1) q3w + best supportive care vs. **Best supportive care** (n=105) alone until time of restaging (around 12 wks after randomization) <u>median relative dose intensity:</u> 89.6 % received both cycles with a median dose intensity of 96.5 % for cisplatin and 93.3 % for vinorelbine	Follow-up every 3 months	ORR: 29.1 % (95% CI 20.4-39.4) vs. 24.8 % (95% CI 16.8-34.2) **Disease control rate:** no differences (p=0.127) 66.7 % (95% CI 56.0-76.0) vs. 56.2 % (95% CI 46.0-66.0) **Progression during follow-up:** 80.2 % vs. 90.5 % **Death from malignancy:** benefit for IG (p=0.049) 74.2 vs. 86.8/74.2 % **Cancer-specific survival**: no differences (p=0.333) 25.5 vs. 22.7 months **Safety** (during consolidation therapy): • Predominant side effects (grades 3 / 4): leukopenia (26.7 % vs. 0%) and neutropenia (22.1 vs. 0%) • febrile neutropenia occurred in < 2 % (1.0 vs. 0 %) • Non-haematological toxicities (only grade 3): nausea/vomiting (2.3/3.5 % vs. 0%) and fatique (3.5% vs. 0%) • 5 deaths (2 vs.3)	

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (Index vs. Referenztest); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
			Subsequent treatment: CT: 45.8 vs. 58.1 % Symptomatic RT: 47.9 vs. 41.9 %			
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** "Taking together the results from the GILT study and available evidence from controlled trials, CC after definitive concurrent CRT does not improve outcome in unselected patients. Further analyses should investigate the possible benefit in subpopulations." **Schlussfolgerung der Begutachterin:** Multizentrische RCT aus Deutschland ohne Verblindung, berichteten Informationen zur Randomisierung und Studienregistrierung, welche aufgrund der langsamen Rekrutierung vorzeitig abgebrochen wurde (geplant war die Randomisierung von 282 Patienten, rekrutiert wurden in 4 Jahren und 26 Kliniken nur 201 Patienten, die mediane Nachbeobachtungszeit wird nicht berichtet (daher Abwertung aufgrund von schwerwiegenden Studienlimitationen), Finanzierung der Studie und Publikation durch das Institute de Recherche Pierre Fabre, Interessenkonflikte der Autoren können nicht ausgeschlossen werden.						
Hanna 2008 (45, 46)	**RCT** efficacy of consolidation docetaxel in patients with inoperable stage III NSCLC patients Multicenter study, USA 03/2002-08/2006	Inclusion Criteria: • histologic or cytologic confirmation of unresectable NSCLC, stage IIIA or IIIB • measurable or assessable disease • FEV1 ≥1 L by spirometry within 42 days of study treatment • ECOG 0 to 1, unintended weight loss < 5% in the 3 months preceding study treatment • adequate bone marrow, renal and hepatetic function	**CRT for all patients:** cisplatin (50 mg/m^2 i.v. days 1, 8, 29, 36) + etoposide (50 mg/m^2 i.v. days 1–5, 29–33) + RT (1.8 Gy daily at 5 days/ wk for a total of 25 fractions (45 Gy) to the primary tumor and mediastinum + boost to the primary and involved nodes	Primary: OS Secondary: PFS toxicity	**Overall survival (OS)** (45): no differences depending on consolidation therapy or age group (p=0.75) • median from registration: 24.2 (95% CI 18.6 -34.8) vs. 26.1 months (95% CI 18.6-32.0) • 3-year rate: 32.4 % (95%CI 21.1-44.1) vs. 36.7 % (95% CI 25.3-48.9) • 5-year rate: 16.4 % (95%CI 7.4-28.7) vs. 23.8 % (95% CI 13.0-36.5) **Progression-free survival (OS)** (45): no differences median from registration: 10.8 (95% CI 8.6 -13.3) vs. 10.3 months (95% CI 8.2-15.2) **Toxicity:** (46) • high hematologic toxicities (grade 3/4) with docetaxel: neutropenia (24.7 %), febrile neutropenia (10.9%), anemia (1.3%)	**1b-** Abwertung aufgrund von Studien-limitationen

Referenz Zeitraum	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (Index vs. Referenztest); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
		• eligibility for consolidation therapy required completion of initial CRT within 4 to 8 weeks of random assignment without local progression or distant metastases, ECOG PS 0-2 at random assignment, adequate bone marrow and hepatic function, absence of symptomatic peripheral neuropathy <u>Exclusion criteria:</u> • disease extending into the cervical region • prior CT or RT • symptomatic peripheral neuropathy, malignant effusions, superior sulcus (Pancoast) tumors, or significant cardiac disease n=166 (45) age (<70 /≥70 yrs): 75.8/24.2% males: 69% ECOG 0: 61% stage IIIB: 63% FEV1 >2: 51% PET scan: 68% Current smoker: 45%	to 1.8-Gy daily in 8 fractions (14.40 Gy), total dose of 59.40 Gy in 33 fractions) 4-8 wks after CRT: **consolidation therapy** (n=82): docetaxel (75 mg/m^2 every 3 weeks for 3 cycles) vs. **observation** (n=84) Prophylactic granulocyte colony-stimulating factor support during consolidative chemotherapy permitted		• non-hematologic toxicities (grade 3-5): higher with docetaxel: infections (11.0 vs. 0%), pneumonitis (9.6 vs. 1.4%), treatment-related deaths (5.5 vs. 0%)	

Referenz Zeitraum	**Studientyp** **Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention** vs. **Kontrolle**	**Zielgröße(n)**	**Hauptergebnisse** (Index vs. Referenztest); Effekt (95% KI)	**Evidenzgrad** (OCEBM)
Zusammenfassende Beurteilung **Schlussfolgerungen der Autoren der Studie:** "Consolidation docetaxel after PE/XRT results in increased toxicities but does not further improve survival compared with PE/XRT alone in patients with stage III inoperable NSCLC."(46) "Consolidation docetaxel after EP/XRT does not improve survival in LA-NSCLC. Fit older adults with LANSCLC benefit from concurrent chemoradiation similarly as younger patients but experience higher rates of hospitalization and toxicity." (45) **Schlussfolgerung der Begutachterin:** Multizentrische RCT aus USA ohne Verblindung, berichteten Informationen zur Randomisierung und öffentliche Studienregistrierung (daher Abwertung aufgrund schwerwiegender Studienlimitationen). Fallzahl wurde zuerst aufgrund der langsamen Rekrutierung und hohen Drop-out-Rate nach der Chemo-Radiotherapie (243 rekrutiert, von denen 166 hinsichtlich der Konsolidierungstherapie randomisiert wurden) erhöht, anschließend wurde die Studie aufgrund der in einer geplanten Zwischenanalyse festgestellten fehlenden Wirksamkeit vorzeitig abgebrochen wurde (geplant war die Rekrutierung von 180 in der Konsolidierungsphase zu rekrutierenden Patienten, Zwischenanalyse erfolgte auf Grundlage von Daten von 147 Patienten, die mediane Nachbeobachtungszeit wird nicht berichtet, Finanzierung der Studie und Publikation durch Sanofi-Aventis, wenige kompensierte Interessenkonflikte der Autoren						
AE: Adverse event; CC: Consolidation chemotherapy; CG: Control group; CI: Confidence interval; CRT: Chemo-radiotherapy; CT: Chemotherapy; CTCAE: Common Terminology Criteria for Adverse Events; DFS: Disease-free survival; ECOG: Eastern Cooperative Oncology Group; FEV1: Forced expiratory volume in 1 second; HR: Hazard ratio; IG: Intervention group; LCSS: Lung Cancer Symptom Scale; N: Number of studies; n: Number of participants; NR: not reached; NSCLC: Non-small cell lung cancer; OR: Odds Ratio; OS: overall survival; PFS: Progression-free survival; QoL: Quality of life; RECIST: Response Evaluation Criteria in Solid Tumors; RCT: Randomized controlled trial; RoB: Risk of bias; RR: Relative Risk; RT: Radiotherapy; SAE: Serious adverse event; wks: weeks; yrs: years						

Referenzen

Anhang

Anhang 1: Suchstrategien für elektronische Datenbanken

Fragestellung 1

Tabelle 17: Suche in CENTRAL nach systematischen Übersichten, Fragestellung 1

Nr.	Suchbegriffe (21.9.2020) - CENTRAL	Treffer
#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	
#2	NSCLC	
#3	non-small cell lung cancer	
#4	**#1 or #2 or #3**	**13 557**
#5	MeSH descriptor: [Carcinoma, Squamous Cell] explode all trees	
#6	MeSH descriptor: [Adenocarcinoma of Lung] explode all trees	
#7	MeSH descriptor: [Carcinoma, Large Cell] explode all trees	
#8	MeSH descriptor: [Molecular Targeted Therapy] explode all trees	
#9	EGFR near/3 mutat*	
#10	ALK near3/translocat*	
#11	ROS1 near3/mutat*	
#12	#5 or #6 or #7 or #8 or #9 or #10 or #11	9589
#14	#4 and #12	2711
	45 Cochrane Reviews exportiert, 0 other reviews identifiziert	**45**

Tabelle 18: Suche in Medline, Fragestellung 1 zur Therapieauswahl auf Grundlage einer EGFR Mutation (ab 2015)

Nr.	Suchbegriffe (21.9.2020)	Treffer
1	exp Carcinoma, Non-Small-Cell Lung/	
2	(non-small adj3 cell adj3 (lung$ adj3 canc$)).ti,ab.	
3	(non-small adj3 cell adj3 lung$ adj3 carcinoma$).ti,ab.	
4	(non-small adj3 cell adj3 lung$ adj3 tumo?r$).ti,ab.	
5	(non-small adj3 cell adj3 lung$ adj3 neoplasm$).ti,ab.	
6	NSCLC.ti,ab.	
7	**OR/1-6**	**57588**
8	(EGFR adj3 mutation).ti	

Nr.	Suchbegriffe (21.9.2020)	Treffer
9	Exp molecular targeted therapy/	
10	8 or 9	29808
11	“randomi*ed controlled trial".pt	
12	controlled clinical trial.pt	
13	randomi*ed".ab.	
14	placebo.ab.	
15	drug therapy.fs	
16	randomly.ab.	
17	Trial.ab.	
18	groups.ab.	
19	systematic review.ti.	
20	Systematic review.pt.	
21	(meta-analy* or metaanaly*).ti.	
22	Meta analysis.pt.	
23	or/11-22	4 594 703
24	(animals not (humans and animals)).sh.	
25	23 not 24	
26	7 and 10 and 25	1347
27	26 not (comment or editorial).pt.	
28	**limit 27 to yr="2015 -Current"**	**858**

Tabelle 19: Suche in Medline, Fragestellung 1 zur Therapieauswahl auf Grundlage der Histologie, einer ALK Translokation oder ROS-Mutation

Nr.	Suchbegriffe (21.9.2020) – Medline (Therapieauswahl auf Grundlage der Histologie, ALK translocation oder ROS1mutation ab 2000)	Treffer
1	exp Carcinoma, Non-Small-Cell Lung/	
2	(non-small adj3 cell adj3 (lung$ adj3 canc$)).ti,ab.	
3	(non-small adj3 cell adj3 lung$ adj3 carcinoma$).ti,ab.	
4	(non-small adj3 cell adj3 lung$ adj3 tumo?r$).ti,ab.	
5	(non-small adj3 cell adj3 lung$ adj3 neoplasm$).ti,ab.	

Nr.	Suchbegriffe (21.9.2020) – Medline (Therapieauswahl auf Grundlage der Histologie, ALK translocation oder ROS1mutation ab 2000)	Treffer
6	NSCLC.ti,ab.	
7	**OR/1-6**	**57588**
8	((squamous adj cell) adj (canc* or carcinoma* or tumo?r$ or neoplasm$)).ti	
9	(adenocarcinoma or (adeno adj3 (canc* or carcinoma* or tumo?r$ or neoplasm$))).ti	
10	ALK.ti	
11	ROS1.ti	
12	OR/8-11	87880
13	“randomi*ed controlled trial".pt	
14	controlled clinical trial.pt	
15	randomi*ed".ab.	
16	placebo.ab.	
17	drug therapy.fs	
18	randomly.ab.	
19	Trial.ab.	
20	groups.ab.	
21	systematic review.ti.	
22	Systematic review.pt.	
23	(meta-analy* or metaanaly*).ti.	
24	Meta analysis.pt.	
25	or/13-24	4 594 703
26	(animals not (humans and animals)).sh.	
27	25 not 26	
28	7 and 12 and 27	1018
29	28 not (comment or editorial).pt.	
30	**limit 29 to yr="2000 -Current"**	**970**

Fragestellung 2

Tabelle 20: Suche in CENTRAL nach systematischen Übersichten, Fragestellung 2a

Nr.	Suchbegriffe (15.10.2020) - CENTRAL	Treffer
#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	
#2	NSCLC	
#3	non-small cell lung cancer	
#4	**#1 or #2 or #3**	**13 595**
#5	MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees	
#6	MeSH descriptor: [Chemoradiotherapy, Adjuvant] explode all trees	
#7	adjuvant near/3 chemotherap*	
#8	(sequential or postoperative) near/3 chemotherap*	
#9	#5 or #6 or #7 or #8	13474
#10	#4 and #9	1035
	20 Cochrane Reviews exportiert, 0 other reviews identifiziert	**20**

Tabelle 21: Suche in CENTRAL nach systematischen Übersichten, Fragestellung 2b

	Suchbegriffe (15.10.2020) - CENTRAL	Treffer
#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	
#2	NSCLC	
#3	non-small cell lung cancer	
#4	**#1 or #2 or #3**	**13 595**
#5	MeSH descriptor: [Neoadjuvant Therapy] explode all trees	
#6	(neoadjuvant or induct*) near (chemotherap* or chemoradiotherap*)	
#7	(preoperative or pre-operative) near/3 (chemotherap* or chemoradiotherap*)	
#8	chemotherap* near/3 surg*	
#9	#5 or #6 or #7 or #8	12363
#10	#4 and #9	979
	31 Cochrane Reviews exportiert, 0 other reviews identifiziert	**31**

Tabelle 22: Suche in Medline, Fragestellungen 2a und 2b

Nr.	Suchbegriffe (15.10.2020) - Medline	Treffer
1	exp Carcinoma, Non-Small-Cell Lung/	
2	(non-small adj3 cell adj3 (lung$ adj3 canc$)).ti,ab.	
3	(non-small adj3 cell adj3 lung$ adj3 carcinoma$).ti,ab.	
4	(non-small adj3 cell adj3 lung$ adj3 tumo?r$).ti,ab.	
5	(non-small adj3 cell adj3 lung$ adj3 neoplasm$).ti,ab.	
6	NSCLC.ti,ab.	
7	**OR/1-6**	**57141**
8	exp Chemotherapy,Adjuvant/	
9	exp Chemoradiotherapy/	
10	exp Neoadjuvant therapy/	
11	((adjuvant or sequential or postoperative) adj3 (chemotherap$ or chemoradiotherap$ or radiochemotherap$)).ti.	
12	((neoadjuvant or induct$ or preoperative or pre-operative) adj3 (chemotherap$ or chemoradiotherap$ or radiochemotherap$)).ti.	
13	or/8-12	72 052
14	“randomi*ed controlled trial".pt	
15	controlled clinical trial.pt	
16	randomi*ed".ab.	
17	placebo.ab.	
18	drug therapy.fs	
19	randomly.ab.	
20	Trial.ab.	
21	groups.ab.	
22	systematic review.ti.	
23	Systematic review.pt.	
24	(meta-analy* or metaanaly*).ti.	
25	Meta analysis.pt.	
26	or/14-25	4 610 864

Nr.	Suchbegriffe (15.10.2020) - Medline	Treffer
27	(animals not (humans and animals)).sh.	
28	36 not 27	3 975 586
29	7 and 13 and 28	2354
30	29 not (comment or editorial).pt.	2242
31	**limit 30 to yr="2014 -Current"**	**784**

Fragestellung 3

Tabelle 23: Suche in CENTRAL, Fragestellung 3

Nr.	Suchbegriffe (23.11.2020) - CENTRAL	Treffer
#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	
#2	NSCLC	
#3	non-small cell lung cancer	
#4	**#1 or #2 or #3**	**13 776**
#5	MeSH descriptor: [Thoracic Surgery, Video-Assisted] explode all trees	
#6	VATS	
#7	Robotic assisted	
#8	MeSH descriptor: [Surgery, Computer-Assisted] explode all trees	
#9	RATS	
#10	Robotic near assist* thorac* surg*	
#11	#5 or #6 or #7 or #8 or #9 or #10	5362
#12	#4 and #9	170
	11 Cochrane Reviews und 154 Studien exportiert (keine Protokolle oder klinischen Antworten)	**20**

Tabelle 24: Suche in Medline, Fragestellung 3

Nr.	Suchbegriffe (23.11.2020) - Medline	Treffer
1	exp Carcinoma, Non-Small-Cell Lung/	
2	(non-small adj3 cell adj3 (lung$ adj3 canc$)).ti,ab.	
3	(non-small adj3 cell adj3 lung$ adj3 carcinoma$).ti,ab.	
4	(non-small adj3 cell adj3 lung$ adj3 tumo?r$).ti,ab.	
5	(non-small adj3 cell adj3 lung$ adj3 neoplasm$).ti,ab.	
6	NSCLC.ti,ab.	
7	**OR/1-6**	**58344**
8	exp Thoracic Surgery, Video-assisted/	
9	((Video near assist$ thorac$ surg$) or VATS).ti,ab	
10	Exp robotic surgical procedures/	
11	(Robotic near assist$ thorac$ surg$).ti,ab	

Nr.	Suchbegriffe (23.11.2020) - Medline	Treffer
12	RATS.ti	
13	or/8-12	368365
14	“randomi*ed controlled trial".pt	
15	controlled clinical trial.pt	
16	randomi*ed".ab.	
17	placebo.ab.	
18	drug therapy.fs	
19	randomly.ab.	
20	Trial.ab.	
21	groups.ab.	
22	systematic review.ti.	
23	Systematic review.pt.	
24	(meta-analy* or metaanaly*).ti.	
25	Meta analysis.pt.	
26	or/14-25	4 671 954
27	(animals not (humans and animals)).sh.	
28	36 not 27	
29	**7 and 13 and 28**	**314**

Fragestellung 4

Tabelle 25: Suche in Medline, Fragestellung 4

Nr.	Suchbegriffe (7.9.2020) - Medline	Treffer
1	exp Carcinoma, Non-Small-Cell Lung/	
2	(non-small adj3 cell adj3 (lung$ adj3 canc$)).ti,ab.	
3	(non-small adj3 cell adj3 lung$ adj3 carcinoma$).ti,ab.	
4	(non-small adj3 cell adj3 lung$ adj3 tumo?r$).ti,ab.	
5	(non-small adj3 cell adj3 lung$ adj3 neoplasm$).ti,ab.	
6	NSCLC.ti,ab.	
7	**OR/1-6**	**67 361**
8	(consolidat* adj3 therapy).ti,ab.	
9	(consolidat* adj3 (chemotherapy or chemoradiotherapy or immunotherapy)).ti,ab.	
10	(durvalumab adj3 (chemotherapy or chemoradiotherapy or immunotherapy)).ti,ab.	
11	or/8-10	3444
12	“randomi*ed controlled trial".pt	506 727
13	controlled clinical trial.pt	
14	randomi*ed".ab.	
15	placebo.ab.	
16	drug therapy.fs	
17	randomly.ab.	
18	Trial.ab.	
19	groups.ab.	
20	systematic review.ti.	
21	Systematic review.pt.	
22	(meta-analy* or metaanaly*).ti.	
23	Meta analysis.pt.	
24	or/12-23	4 584 552
25	(animals not (humans and animals)).sh.	
26	24 not 25	3 953 125
27	7 and 11 and 26	186

Nr.	Suchbegriffe (7.9.2020) - Medline	Treffer
28	27 not (comment or editorial).pt.	184
29	**limit 28 to yr="2000 -Current"**	**175**

Tabelle 26: Suche in CENTRAL, Fragestellung 4

Nr.	Suchbegriffe (7.9.2020) - CENTRAL	Treffer
#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	
#2	NSCLC	
#3	non-small cell lung cancer	
#4	**#1 or #2 or #3**	**13 556**
#5	MeSH descriptor: [Consolidation Chemotherapy] explode all trees	
#6	consolidation near/3 (chemotherap* or chemoradiotherap* or immunotherap*)	
#7	(durvalumab near/3 (chemotherap* or chemoradiotherap* or immunotherap*))	
#8	#6 or #7 or #5	950
#9	#4 and #8	187
	1 Cochrane Review (anderes Thema), 4 Cochrane Protokolle, 162 Trials (exportiert)	

Anhang 2: Liste der eingeschlossenen Studien

Eingeschlossene Systematische Übersichten: Fragestellung 1

Cheng 2019

Cheng H, Li XJ, Wang XJ, Chen ZW, Wang RQ, Zhong HC, et al. A meta-analysis of adjuvant EGFR-TKIs for patients with resected non-small cell lung cancer. Lung Cancer. 2019;137:7-13.

Eingeschlossene Studien:

N. Li, et al., Pemetrexed-carboplatin adjuvant chemotherapy with or without gefitinib in resected stage IIIA-N2 non-small cell lung cancer harbouring EGFR mutations: a randomized, phase II study, Ann. Surg. Oncol. 21 (6) (2014) 2091–2096.

K. Kelly, et al., Adjuvant erlotinib versus placebo in patients with stage IB-IIIA nonsmall-Cell lung Cancer (RADIANT): a randomized, double-blind, phase III trial, J. Clin. Oncol. 33 (34) (2015) 4007–4014.

G.D. Goss, et al., Gefitinib versus placebo in completely resected non-small-cell lung cancer: results of the NCIC CTG BR19 study, J. Clin. Oncol. 31 (27) (2013) 3320–3326.

W.Z. Zhong, et al., Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study, Lancet Oncol. 19 (1) (2018) 139–148.

D. Yue, et al., Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): a randomised, open-label, phase 2 trial, Lancet Respir. Med. 6 (11) (2018) 863–873.

Elliot 2020

Elliott J, Bai Z, Hsieh SC, Kelly SE, Chen L, Skidmore B, et al. ALK inhibitors for non-small cell lung cancer: A systematic review and network meta-analysis. PLoS ONE. 2020;15(2):e0229179.

Eingeschlossene Studien:

Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. The New England journal of medicine. 2017; 377 (9):828–38.

Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. New England Journal of Medicine. 2013; 368:2385–94. https://doi. org/10.1056/NEJMoa1214886 PMID: 23724913

Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. New England Journal of Medicine. 2014; 371:2167–77.

Zhao J, Zhang K, Zhang L, Wang H. Clinical Efficacy of Crizotinib in Advanced ALK Positive Non-small Cell Lung Cancer. Zhongguo Fei Ai Za Zhi. 2015; 18:616–20.

Hida T, Nakagawa K, Seto T, Satouchi M, Nishio M, Hotta K, et al. Pharmacologic study (JP28927) of alectinib in Japanese patients with ALK+ non-small-cell lung cancer with or without prior crizotinib therapy. Cancer Science. 2016; 107:1642–6.

Cho BC, Kim DW, Bearz A, Laurie SA, McKeage M, Borra G, et al. ASCEND-8: A Randomized Phase 1 Study of Ceritinib, 450 mg or 600 mg, Taken with a Low-Fat Meal versus 750 mg in Fasted State in Patients with Anaplastic Lymphoma Kinase (ALK)-Rearranged Metastatic Non-Small Cell Lung Cancer (NSCLC). J Thorac Oncol. 2017; 12(9):1357–67.

Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, Seto T, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet. 2017.

Kim DW, Tiseo M, Ahn MJ, Reckamp KL, Hansen KH, Kim SW, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. J Clin Oncol. 2017;JCO2016715904.

Shaw AT, Kim TM, Crino L, Gridelli C, Kiura K, Liu G, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and

crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncology. 2017.
Soria JC, Tan DS, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017; 389:917–29.
Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS, et al. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. New England Journal of Medicine. 2018; 379(21):2027–39.
Novello S, Mazieres J, Oh IJ, Castro JD, Migliorino MR, Helland A, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. Ann Oncol. 2018; 29(6):1409–16.
Singhi EK, Horn L. Background and rationale of the eXalt3 trial investigating X-396 in the treatment of ALK+ non-small-cell lung cancer. Fut Oncol. 2018; 14(18):1781–7.
Wu YL, Lu S, Lu Y, Zhou J, Shi YK, Sriuranpong V, et al. Results of PROFILE 1029, a Phase III Comparison of First-Line Crizotinib versus Chemotherapy in East Asian Patients with ALK-Positive Advanced Non-Small Cell Lung Cancer. J Thorac Oncol. 2018; 13(10):1539–48.
Zhou C, Kim SW, Reungwetwattana T, Zhou J, Zhang Y, He J, et al. Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study. Lancet Respir Med. 2019; 7(5):437–46.

Greenhalgh 2016

Greenhalgh J, Dwan K, Boland A, Bates V, Vecchio F, Dundar Y, et al. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. Cochrane Database of Systematic Reviews. 2016(5):CD010383.

Eingeschlossene Studien (nur primäre Veröffentlichungen):

Khambata-Ford S, Harbison CT, Hart LL, Awad M, Xu L-A, Horak CE, et al. Analysis of potential predictive markers of cetuximab benefit in BMS099, a phase III study of cetuximab and first-line taxane/carboplatin in advanced non-small-cell lung cancer. Journal of Clinical Oncology 2010;28(6):918-27.
Lynch TJ, Patel T, Dreisbach L, McCleod M, Heim WJ, Hermann RC, et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small cell lung cancer: results of the randomized multicenter phase III trial BMS099. Journal of Clinical Oncology 2010;28(6):911-7.
Chen YM, Tsai CM, Fan WC, Shih JF, Liu SH, Wu CH, et al. Phase II randomized trial of erlotinib or vinorelbine in chemonaive, advanced, non-small cell lung cancer patients aged 70 years or older. Journal of Thoracic Oncology 2012;7(2):412-8.
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Eingeschlossene Studien: Fragestellung 4

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Flentje 2016
Flentje M, Huber RM, Engel-Riedel W, Andreas S, Kollmeier J, Staar S, et al. GILT--A randomised phase III study of oral vinorelbine and cisplatin with concomitant radiotherapy followed by either consolidation therapy with oral vinorelbine and cisplatin or best supportive care alone in stage III non-small cell lung cancer. Strahlenther Onkol. 2016;192(4):216-22.

Hanna 2008
Hanna N, Neubauer M, Yiannoutsos C, McGarry R, Arseneau J, Ansari R, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non–small-cell lung cancer: the Hoosier Oncology Group and US Oncology. J Clin Oncol. 2008;26(35):5755-60.
Jalal SI, Riggs HD, Melnyk A, Richards D, Agarwala A, Neubauer M, et al. Updated survival and outcomes for older adults with inoperable stage III non-small-cell lung cancer treated with cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel: analysis of a phase III trial from the Hoosier Oncology Group (HOG) and US Oncology. Annals of oncology : official journal of the european society for medical oncology. 2012;23(7):1730-8.

Anhang 3: Liste der ausgeschlossenen Studien (mit Gründen)

Ausgeschlossene Studien: Fragestellung 1

Einschluss in systematische Übersichtsarbeiten (28 Veröffentlichungen)

Blackhall F, Kim DW, Besse B, Nokihara H, Han JY, Wilner KD, et al. Patient-reported outcomes and quality of life in PROFILE 1007: a randomized trial of crizotinib compared with chemotherapy in previously treated patients with ALK-positive advanced non-small-cell lung cancer. J Thorac Oncol. 2014;9(11):1625-33.

Camidge DR, Dziadziuszko R, Peters S, Mok T, Noe J, Nowicka M, et al. Updated Efficacy and Safety Data and Impact of the EML4-ALK Fusion Variant on the Efficacy of Alectinib in Untreated ALK-Positive Advanced Non-Small Cell Lung Cancer in the Global Phase III ALEX Study. J Thorac Oncol. 2019;14(7):1233-43.

Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS, et al. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2018;379(21):2027-39.

Chen YM, Liu JM, Chou TY, Perng RP, Tsai CM, Whang-Peng J. Phase II randomized study of daily gefitinib treatment alone or with vinorelbine every 2 weeks in patients with adenocarcinoma of the lung who failed at least 2 regimens of chemotherapy. Cancer. 2007;109(9):1821-8.

Feng S, Wang Y, Cai K, Wu H, Xiong G, Wang H, et al. Randomized Adjuvant Chemotherapy of EGFR-Mutated Non-Small Cell Lung Cancer Patients with or without Icotinib Consolidation Therapy. PLoS ONE. 2015;10(10):e0140794.

Gadgeel S, Peters S, Mok T, Shaw AT, Kim DW, Ou SI, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. Ann Oncol. 2018;29(11):2214-22.

Guetz GD, Landre T, Uzzan B, Chouahnia K, Nicolas P, Morere JF. Is There a Survival Benefit of First-Line Epidermal Growth Factor Receptor Tyrosine-Kinase Inhibitor Monotherapy Versus Chemotherapy in Patients with Advanced Non-Small-Cell Lung Cancer?: A Meta-Analysis. Target. 2016;11(1):41-7.

Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, Seto T, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet. 2017;390(10089):29-39.

Lee YC, Hsieh CC, Lee YL, Li CY. Which Should Be Used First for ALK-Positive Non-Small-Cell Lung Cancer: Chemotherapy or Targeted Therapy? A Meta-Analysis of Five Randomized Trials. Medicina (Kaunas). 2019;55(2):29.

Liu J, Sheng Z, Zhang Y, Li G. The Efficacy of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors for Molecularly Selected Patients with Non-Small Cell Lung Cancer: A Meta-Analysis of 30 Randomized Controlled Trials. Target. 2016;11(1):49-58.

Miyauchi E, Inoue A, Kobayashi K, Maemondo M, Sugawara S, Oizumi S, et al. Efficacy of chemotherapy after first-line gefitinib therapy in EGFR mutation-positive advanced non-small cell lung cancer-data from a randomized Phase III study comparing gefitinib with carboplatin plus paclitaxel (NEJ002). Jpn J Clin Oncol. 2015;45(7):670-6.

Mok T, Camidge DR, Gadgeel SM, Rosell R, Dziadziuszko R, Kim DW, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. Ann Oncol. 2020;31(8):1056-64.

Nakagawa K, Hida T, Nokihara H, Morise M, Azuma K, Kim YH, et al. Final progression-free survival results from the J-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. Lung Cancer. 2020;139:195-9.

Novello S, Mazieres J, Oh IJ, de Castro J, Migliorino MR, Helland A, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. Ann Oncol. 2018;29(6):1409-16.

Paz-Ares L, Tan EH, O'Byrne K, Zhang L, Hirsh V, Boyer M, et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol. 2017;28(2):270-7.

Perol M, Pavlakis N, Levchenko E, Platania M, Oliveira J, Novello S, et al. Patient-reported outcomes from the randomized phase III ALEX study of alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer. Lung Cancer. 2019;138:79-87.

Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(9):829-38.

Popat S, Mellemgaard A, Reck M, Hastedt C, Griebsch I. Nintedanib plus docetaxel as second-line therapy in patients with non-small-cell lung cancer of adenocarcinoma histology: a network meta-analysis vs new therapeutic options. Fut Oncol. 2017;13(13):1159-71.

Shaw AT, Kim TM, Crino L, Gridelli C, Kiura K, Liu G, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2017;18(7):874-86.

Solomon BJ, Kim DW, Wu YL, Nakagawa K, Mekhail T, Felip E, et al. Final Overall Survival Analysis From a Study Comparing First-Line Crizotinib Versus Chemotherapy in ALK-Mutation-Positive Non-Small-Cell Lung Cancer. J Clin Oncol. 2018;36(22):2251-8.

Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014;371(23):2167-77.

Soria JC, Tan DSW, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017;389(10072):917-29.

Soria JC, Wu YL, Nakagawa K, Kim SW, Yang JJ, Ahn MJ, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol. 2015;16(8):990-8.

Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(11):1454-66.

Wu YL, Saijo N, Thongprasert S, Yang JC, Han B, Margono B, et al. Efficacy according to blind independent central review: Post-hoc analyses from the phase III, randomized, multicenter, IPASS study of first-line gefitinib versus carboplatin/paclitaxel in Asian patients with EGFR mutation-positive advanced NSCLC. Lung Cancer. 2017;104:119-25.

Wu YL, Zhou C, Liam CK, Wu G, Liu X, Zhong Z, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol. 2015;26(9):1883-9.

Yue D, Xu S, Wang Q, Li X, Shen Y, Zhao H, et al. Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): a randomised, open-label, phase 2 trial. Lancet Respir Med. 2018;6(11):863-73.

Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). Ann Oncol. 2015;26(9):1877-83.

Design (9 Veröffentlichungen)

Bearz A, Berretta M, Tirelli U. Clinical Effectiveness and Cost-effectiveness of Target Therapies for Adult Patients with Locally Advanced or Metastatic Non-small Cell Lung Cancer: A Systematic Review. Curr Cancer Drug Targets. 2018;18(5):405-9.

Fan J, Fong T, Xia Z, Zhang J, Luo P. The efficacy and safety of ALK inhibitors in the treatment of ALK-positive non-small cell lung cancer: A network meta-analysis. Cancer Med. 2018;7(10):4993-5005.

Hoang T, Myung SK, Pham TT, Park B. Efficacy of Crizotinib, Ceritinib, and Alectinib in ALK-Positive Non-Small Cell Lung Cancer Treatment: A Meta-Analysis of Clinical Trials. Cancers (Basel). 2020;12(3):25.

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Li G, Dai WR, Shao FC. Effect of ALK-inhibitors in the treatment of non-small cell lung cancer: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2017;21(15):3496-503.

Shukuya T, Takahashi T, Kaira R, Ono A, Nakamura Y, Tsuya A, et al. Efficacy of gefitinib for non-adenocarcinoma non-small-cell lung cancer patients harboring epidermal growth factor receptor mutations: a pooled analysis of published reports. Cancer Sci. 2011;102(5):1032-7.

Vestergaard HH, Christensen MR, Lassen UN. A systematic review of targeted agents for non-small cell lung cancer. Acta Oncol. 2018;57(2):176-86.

Wang M, Wang G, Ma H, Shan B. Crizotinib Versus Chemotherapy on ALK-positive NSCLC: A Systematic Review of Efficacy and Safety. Curr Cancer Drug Targets. 2019;19(1):41-9.

Yang YL, Xiang ZJ, Yang JH, Wang WJ, Xiang RL. Effect of alectinib versus crizotinib on progression-free survival, central nervous system efficacy and adverse events in ALK-positive non-small cell lung cancer: a systematic review and meta-analysis. Ann. 2020;9(4):1782-96.

Andere Intervention (2 Veröffentlichungen)

1. Lee CK, Brown C, Gralla RJ, Hirsh V, Thongprasert S, Tsai C-M, et al. Impact of EGFR inhibitor in non–small cell lung cancer on progression-free and overall survival: a meta-analysis. J Natl Cancer Inst. 2013;105(9):595-605.

2. Liu GF, Li XF, Yu SN, Miao YY, Zhang SH. Efficacy and adverse events of five targeted agents in the treatment of advanced or metastatic non-small-cell lung cancer: A network meta-analysis of nine eligible randomized controlled trials involving 5,059 patients. J Cell Physiol. 2019;234(4):3445-57.

Keine Volltextveröffentlichung (1 Veröffentlichung)

1. Breadner D, Blanchette P, Shanmuganathan S, Boldt RG, Raphael J. Efficacy and safety of ALK inhibitors in ALK-rearranged non-small cell lung cancer: A systematic review and meta-analysis. Lung Cancer. 2020;144:57-63.

Ausgeschlossene Studien: Fragestellung 2a

Bereits aktualisierte systematische Übersichtsarbeiten (1 Veröffentlichung)

Burdett S, Stewart L, Rydzewska L. Chemotherapy and surgery versus surgery alone in non-small cell lung cancer. Cochrane Database of Systematic Reviews. 2007(3).

Design (1 Veröffentlichung)

Bradbury P, Sivajohanathan D, Chan A, Kulkarni S, Ung Y, Ellis PM. Postoperative Adjuvant Systemic Therapy in Completely Resected Non-Small-Cell Lung Cancer: A Systematic Review. Clin Lung Cancer. 2017;18(3):259-73.e8.

Andere (aktive) Kontrollgruppe (1 Veröffentlichung)

Toyooka S, Okumura N, Nakamura H, Nakata M, Yamashita M, Tada H, et al. A Multicenter Randomized Controlled Study of Paclitaxel plus Carboplatin versus Oral Uracil-Tegafur as the Adjuvant Chemotherapy in Resected Non-Small Cell Lung Cancer. J Thorac Oncol. 2018;13(5):699-706.

Ausgeschlossene Studien: Fragestellung 2b

In umfassenderer und aktuellerer systematischer Übersicht enthalten (4 Veröffentlichungen)

Berghmans T, Van Houtte P, Paesmans M, Giner V, Lecomte J, Koumakis G, et al. A phase III randomised study comparing concomitant radiochemotherapy as induction versus consolidation treatment in patients with locally advanced unresectable non-small cell lung cancer. Lung Cancer. 2009;64(2):187-93.

Senan S, Cardenal F, Vansteenkiste J, Stigt J, Akyol F, De Neve W, et al. A randomized phase II study comparing induction or consolidation chemotherapy with cisplatin-docetaxel, plus radical concurrent chemoradiotherapy with cisplatin-docetaxel, in patients with unresectable locally advanced non-small-cell lung cancer. Ann Oncol. 2011;22(3):553-8.

Souquet PJ, Chavaillon JM, Bozonnat MC, Daures JP, Fournel P, Talabard JN, et al. Induction or consolidation chemotherapy for unresectable stage III non-small-cell lung cancer patients treated with concurrent chemoradiation: a randomised phase II trial GFPC - IFCT 02-01. Eur J Cancer. 2016;52:181-7.Wang T, Yan T, Ma S, Wang K, Wang J, Song J, et al. The efficacy and safety of preoperative chemotherapy for patients with nonsmall cell lung cancer: A meta-analysis. Indian J Cancer. 2017;54(1):223-7.

Anderer Vergleich (2 Veröffentlichungen)

Pless M, Stupp R, Ris HB, Stahel RA, Weder W, Thierstein S, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. Lancet. 2015;386(9998):1049-56.

Xu YP, Li B, Xu XL, Mao WM. Is There a Survival Benefit in Patients With Stage IIIA (N2) Non-small Cell Lung Cancer Receiving Neoadjuvant Chemotherapy and/or Radiotherapy Prior to Surgical Resection: A Systematic Review and Meta-analysis. Medicine (Baltimore). 2015;94(23):e879.

Ausgeschlossene Studien: Fragestellung 3

Einschluss in systematische Übersichtsarbeiten (11 Veröffentlichungen)

Bu L, Li Y, Yang F, Zhao H, Jiang GC, Li JF, et al. Completely video-assisted thoracoscopic lobectomy versus open lobectomy for non-small cell lung cancer greater than 5 cm: a retrospective study. Chin Med J. 2012;125(3):434-9.

Cao C, Manganas C, Ang SC, Peeceeyen S, Yan TD. Video-assisted thoracic surgery versus open thoracotomy for non-small cell lung cancer: a meta-analysis of propensity score-matched patients. Interact Cardiovasc Thorac Surg. 2013;16(3):244-9.

Falcoz PE, Puyraveau M, Thomas PA, Decaluwe H, Hurtgen M, Petersen RH, et al. Video-assisted thoracoscopic surgery versus open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. Eur J Cardiothorac Surg. 2016;49(2):602-9.

Jiang G, Yang F, Li X, Liu J, Li J, Zhao H, et al. Video-assisted thoracoscopic surgery is more favorable than thoracotomy for administration of adjuvant chemotherapy after lobectomy for non-small cell lung cancer. World J Surg Oncol. 2011;9:170.

Jing X, Lin Y, Zhang B, Zhang G. Video-assisted thoracoscopic lobectomy mitigates adverse oncological effects of delayed adjuvant chemotherapy for nonsmall cell lung cancer patients. J. 2016;21(6):1524-9.

Lee PC, Nasar A, Port JL, Paul S, Stiles B, Chiu YL, et al. Long-term survival after lobectomy for non-small cell lung cancer by video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg. 2013;96(3):951-60; discussion 60-1.

Long H, Tan Q, Luo Q, Wang Z, Jiang G, Situ D, et al. Thoracoscopic Surgery Versus Thoracotomy for Lung Cancer: short-Term Outcomes of a Randomized Trial. Ann Thorac Surg. 2018;105(2):386-92.

Nwogu CE, D'Cunha J, Pang H, Gu L, Wang X, Richards WG, et al. VATS lobectomy has better perioperative outcomes than open lobectomy: CALGB 31001, an ancillary analysis of CALGB 140202 (Alliance). Ann Thorac Surg. 2015;99(2):399-405.

Pages PB, Delpy JP, Orsini B, Gossot D, Baste JM, Thomas P, et al. Propensity Score Analysis Comparing Videothoracoscopic Lobectomy With Thoracotomy: A French Nationwide Study. Ann Thorac Surg. 2016;101(4):1370-8.

Rodgers-Fischl PM, Martin JT, Saha SP. Video-Assisted Thoracoscopic versus Open Lobectomy: Costs and Outcomes. South Med J. 2017;110(3):229-33.

Xue Y, Wang YY, Zhang K, Cong W, He B, Zeng FC. A Study of Complete Video-Assisted Thoracoscopic Surgery Lobectomy in Treatment of Elderly Patients with Non-Small Cell Lung Cancer: curative Effect and Impact on Clinical Prognosis. Cell biochemistry and biophysics. 2015;73(2):399-404.

In umfassenderer und aktuellerer systematischer Übersicht enthalten (6 Veröffentlichungen)

Guo F, Ma D, Li S. Compare the prognosis of Da Vinci robot-assisted thoracic surgery (RATS) with video-assisted thoracic surgery (VATS) for non-small cell lung cancer: A Meta-analysis. Medicine (Baltimore). 2019;98(39):e17089.

Hu X, Wang M. Efficacy and Safety of Robot-assisted Thoracic Surgery (RATS) Compare with Video-assisted Thoracoscopic Surgery (VATS) for Lung Lobectomy in Patients with Non-small Cell Lung Cancer. Comb Chem High Throughput Screen. 2019;22(3):169-78.

Wang Z, Pang L, Tang J, Cheng J, Chen N, Zhou J, et al. Video-assisted thoracoscopic surgery versus muscle-sparing thoracotomy for non-small cell lung cancer: a systematic review and meta-analysis. BMC surg. 2019;19(1):144.

Wei S, Chen M, Chen N, Liu L. Feasibility and safety of robot-assisted thoracic surgery for lung lobectomy in patients with non-small cell lung cancer: a systematic review and meta-analysis. World J Surg Oncol. 2017;15(1):98.

Ye B, Wang M. Video-assisted Thoracoscopic Surgery versus Thoracotomy for Non-Small Cell Lung Cancer: A Meta-Analysis. Comb Chem High Throughput Screen. 2019;22(3):187-93.

Zhang Z, Zhang Y, Feng H, Yao Z, Teng J, Wei D, et al. Is video-assisted thoracic surgery lobectomy better than thoracotomy for early-stage non-small-cell lung cancer? A systematic review and meta-analysis. Eur J Cardiothorac Surg. 2013;44(3):407-14.

Andere Population (13 Veröffentlichungen)

Gazala S, Pelletier JS, Storie D, Johnson JA, Kutsogiannis DJ, Bedard EL. A systematic review and meta-analysis to assess patient-reported outcomes after lung cancer surgery. ScientificWorldJournal. 2013;2013:789625.

Kamel MK, Nasar A, Stiles BM, Altorki NK, Port JL. Video-Assisted Thoracoscopic Lobectomy Is the Preferred Approach Following Induction Chemotherapy. J Laparoendosc Adv Surg Tech A. 2017;27(5):495-500.

Kato M, Onishi H, Furugaki K, Yunotani S, Matsumoto K, Tsuruta N, et al. New Approach to Complete Video-assisted Thoracoscopic Lobectomy in T2 and T3 Non-Small Cell Lung Cancer. Anticancer Res. 2015;35(6):3585-9.

Papiashvilli M, Stav D, Cyjon A, Haitov Z, Gofman V, Bar I. Lobectomy for non-small cell lung cancer: differences in morbidity and mortality between thoracotomy and thoracoscopy. Innovations. 2012;7(1):15-22.

Park BJ, Yang HX, Woo KM, Sima CS. Minimally invasive (robotic assisted thoracic surgery and video-assisted thoracic surgery) lobectomy for the treatment of locally advanced non-small cell lung cancer. J. 2016;8(Suppl 4):S406-13.

Qiu T, Zhao Y, Xuan Y, Qin Y, Niu Z, Shen Y, et al. Robotic sleeve lobectomy for centrally located non-small cell lung cancer: A propensity score-weighted comparison with thoracoscopic and open surgery. J Thorac Cardiovasc Surg. 2020;160(3):838-46.e2.

Scott WJ, Allen MS, Darling G, Meyers B, Decker PA, Putnam JB, et al. Video-assisted thoracic surgery versus open lobectomy for lung cancer: a secondary analysis of data from the American College of Surgeons Oncology Group Z0030 randomized clinical trial. Journal of thoracic and cardiovascular surgery. 2010;139(4):976-81; discussion 81-3.

Teh E, Abah U, Church D, Saka W, Talbot D, Belcher E, et al. What is the extent of the advantage of video-assisted thoracoscopic surgical resection over thoracotomy in terms of delivery of adjuvant chemotherapy following non-small-cell lung cancer resection? Interact Cardiovasc Thorac Surg. 2014;19(4):656-60.

Wu L, Wang H, Cai H, Fan J, Jiang G, He Y, et al. Comparison of Double Sleeve Lobectomy by Uniportal Video-Assisted Thoracic Surgery (VATS) and Thoracotomy for NSCLC Treatment. Cancer Manag Res. 2019;11:10167-74.

Xue Y, Wang YY, Zhang K, Cong W, He B, Zeng FC. A Study of Complete Video-Assisted Thoracoscopic Surgery Lobectomy in Treatment of Elderly Patients with Non-Small Cell Lung Cancer: curative Effect and Impact on Clinical Prognosis. Cell biochemistry and biophysics. 2015;73(2):399-404.

Yan TD, Black D, Bannon PG, McCaughan BC. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. J Clin Oncol. 2009;27(15):2553-62.

Yang CF, Meyerhoff RR, Mayne NR, Singhapricha T, Toomey CB, Speicher PJ, et al. Long-term survival following open versus thoracoscopic lobectomy after preoperative chemotherapy for non-small cell lung cancer. Eur J Cardiothorac Surg. 2016;49(6):1615-23.

Yang H, Liu X, Meng X, Feng W. Efficacy of video-assisted thoracoscopic surgery for radical resection of non-small cell lung cancer in elderly patients. International journal of clinical and experimental medicine. 2019;12(3):2675-82.

Andere Intervention (1 Veröffentlichung)

Chen K, Wang X, Yang F, Li J, Jiang G, Liu J, et al. Propensity-matched comparison of video-assisted thoracoscopic with thoracotomy lobectomy for locally advanced non-small cell lung cancer. J Thorac Cardiovasc Surg. 2017;153(4):967-76.e2.

Anderer Vergleich (4 Veröffentlichungen)

Veronesi G, Park B, Cerfolio R, Dylewski M, Toker A, Fontaine JP, et al. Robotic resection of Stage III lung cancer: an international retrospective study. Eur J Cardiothorac Surg. 2018;54(5):912-9.

Whitson BA, Groth SS, Duval SJ, Swanson SJ, Maddaus MA. Surgery for early-stage non-small cell lung cancer: a systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. Ann Thorac Surg. 2008;86(6):2008-16; discussion 16-8.

Yang C, Mo L, Ma Y, Peng G, Ren Y, Wang W, et al. A comparative analysis of lung cancer patients treated with lobectomy via three-dimensional video-assisted thoracoscopic surgery versus two-dimensional resection. J. 2015;7(10):1798-805.

Zhang L. Short- and long-term outcomes in elderly patients with locally advanced non-small-cell lung cancer treated using video-assisted thoracic surgery lobectomy. Ther Clin Risk Manag. 2018;14:2213-20.

Anderer Endpunkt (1 Veröffentlichung)

Han L, Cheng H, Liu J, Gao W, Wang H, Xie H, et al. Effect of video-assisted thoracoscopic surgery on immune function and trauma in patients with non-small cell lung cancer. International journal of clinical and experimental medicine. 2018;11(11):12437-44.

Anderes Design (2 Veröffentlichungen)

Watanabe A, Miyajima M, Mishina T, Tsuruta K, Takahashi Y, Maki R, et al. Video-assisted thoracoscopic surgery node dissection for lung cancer treatment. Surg. 2017;47(12):1419-28.

West D, Rashid S, Dunning J. Does video-assisted thoracoscopic lobectomy produce equal cancer clearance compared to open lobectomy for non-small cell carcinoma of the lung? Interact Cardiovasc Thorac Surg. 2007;6(1):110-6.

Andere Sprache oder keine Volltextveröffentlichung (2 Veröffentlichungen)

Long H, Lin ZC, Lin YB, Situ DR, Wang YN, Rong TH. Quality of life after lobectomy for early stage non-small cell lung cancer--video-assisted thoracoscopic surgery versus minimal incision thoracotomy. Ai zheng [Chinese journal of cancer]. 2007;26(6):624-8.

Situ D, Long H, Tan Q, Luo Q, Wang Z, Jiang G, et al. OA13.02 Video-Assisted Thoracoscopic Surgery vs. Thoracotomy for Non-Small Cell Lung Cancer: survival Outcome of a Randomized Trial. Journal of thoracic oncology. 2019;14(10):S240-.

Ausgeschlossene Studien: Fragestellung 4

Design (1 Veröffentlichung)

Tsujino K, Kurata T, Yamamoto S, Kawaguchi T, Kubo A, Isa S, et al. Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small-cell lung cancer? A pooled analysis of the literature. J Thorac Oncol. 2013;8(9):1181-9.

Andere Intervention (1 Veröffentlichung)

Kelly K, Chansky K, Gaspar LE, Albain KS, Jett J, Ung YC, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J Clin Oncol. 2008;26(15):2450-6.

Anderer Vergleich (8 Veröffentlichungen)

Berghmans T, Van Houtte P, Paesmans M, Giner V, Lecomte J, Koumakis G, et al. A phase III randomised study comparing concomitant radiochemotherapy as induction versus consolidation treatment in patients with locally advanced unresectable non-small cell lung cancer. Lung Cancer. 2009;64(2):187-93.

Fournel P, Vergnenegre A, Robinet G, Lena H, Gervais R, Le Caer H, et al. Induction or consolidation chemotherapy for unresectable stage III non-small-cell lung cancer patients treated with concurrent chemoradiation: a randomised phase II trial GFPC - IFCT 02-01. Eur J Cancer. 2016;52:181-7.

Garrido P, Rosell R, Arellano A, Andreu F, Domine M, Perez-Casas A, et al. Randomized phase II trial of non-platinum induction or consolidation chemotherapy plus concomitant chemoradiation in stage III NSCLC patients: mature results of the Spanish Lung Cancer Group 0008 study. Lung Cancer. 2013;81(1):84-90.

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