Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-042 Atezolizumab

Stand: Mai 2022

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Atezolizumab
[Patienten mit vollständig reseziertem NSCLC nach adjuvanter Cisplatin-basierter Chemotherapie]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Im geplanten Anwendungsgebiet sind derzeit keine Arzneimittel explizit zugelassen.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Für einen Teil der Patienten im Anwendungsgebiet (Stadium II-IIIA mit mediastinaler N2 Erkrankung) kommt eine mediastinale Strahlentherapie nach der adjuvanten CT in Betracht.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Atezolizumab L01XC32 Tecentriq®	<u>Zugelassenes Anwendungsgebiet:</u> Nicht-kleinzelliges Lungenkarzinom (non-small cell lung cancer, NSCLC) im Frühstadium Tecentriq als Monotherapie wird angewendet zur adjuvanten Behandlung des NSCLC nach vollständiger Resektion und platinbasierter Chemotherapie bei erwachsenen Patienten mit hohem Risiko für ein Rezidiv und deren Tumoren eine PD-L1-Expression auf ≥ 50 % der Tumorzellen (tumour cells, TC) aufweisen und kein EGFR (epidermal growth factor receptor, epidermaler Wachstumsfaktorrezeptor)-mutiertes oder ALK(anaplastische-Lymphomkinase)-positives NSCLC haben
Vinorelbin L01CA04	Vinorelbin ist angezeigt bei Erwachsenen zur Behandlung von nicht kleinzelligem Lungenkrebs (Stadium 3 oder 4).

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-042 (Atezolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	10. März 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DFS	Disease free survival
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
OR	Odds Ratio
OS	Overall survival
PFS	Progression free survival
PORT	surgery plus radiotherapy
RCTs	randomized controlled trials
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Indikation der Synopse: zur Behandlung von Patienten mit vollständig reseziertem NSCLC Stadium IB (Tumore >/ 4 cm) - IIIA nach adjuvanter Cisplatin-basierter Chemotherapie.

Hinweis zur Synopse: Aufgrund der zusätzlichen Frage des pUs zur adjuvanten Therapie, sind ebenfalls systematische Übersichtsarbeiten und Leitlinienempfehlungen zu diesem Setting abgebildet.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *nicht-kleinzelliges Lungenkarzinom (NSCLC)* durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 21.09.2018 durchgeführt, die Folgerecherche am 24.07.2019 und 07.01.2020. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherche übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 2331 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 21 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es wurden keine relevanten G-BA Beschlüsse/IQWiG Berichte identifiziert.

3.2 Cochrane Reviews

Burdett S et al., 2016 [3].

Postoperative radiotherapy for non-small cell lung cancer.

Fragestellung

To evaluate the effects of PORT on survival and recurrence in patients with completely resected NSCLC. To investigate whether predefined patient subgroups benefit more or less from PORT.

Methodik

Population:

- individuals with histologically confirmed NSCLC who had undergone a potentially curative resection

Intervention:

- surgery

Komparator:

- surgery plus radiotherapy (PORT)

Endpunkte:

- overall survival, recurrence-free survival, local-regional recurrence, distant recurrence-free survival

Recherche/Suchzeitraum:

- MEDLINE and CANCERLIT searches (1965 to 8 July 2016)

Qualitätsbewertung der Studien:

- Cochrane approach

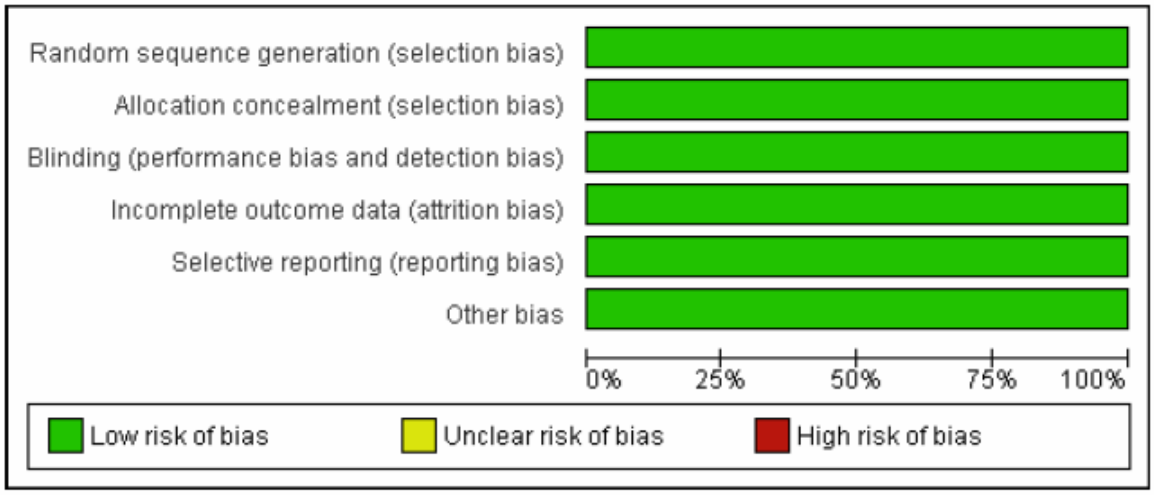
Ergebnisse

Anzahl eingeschlossener Studien:

- 11 trials and 2343 patients

Qualität der Studien:

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Studienergebnisse:

- Survival:
  - Survival data were available for all trials and included information from 2343 participants and 1511 deaths (777 PORT, 734 surgery alone). Although the confidence intervals (CIs) for individual trial results were wide, combined results showed a significant adverse effect of PORT on survival (P = 0.001), with a hazard ratio (HR) of 1.18 (95% CI 1.07 to 1.31), or an 18% relative increase in risk of death.
  - This was equivalent to an absolute detriment of 5% at two years (95% CI 2% to 9%), reducing overallsurvival from 58% to 53%. Survival curves appeared to diverge at around four months and remained apart for the five years to which they could be drawn with reasonable reliability.
  - There was some evidence of increased statistical heterogeneity between trials in the current update (I2 = 40%, P = 0.08), compared with the original 1998 meta-analysis. However, the random-effects result is similar (HR 1.17, 95% CI 1.02 to 1.34, P = 0.02), and heterogeneity appears largely driven by the Italian trial. A sensitivity analysis excluding this trial reduces heterogeneity (I2 = 31%, P = 0.16) and gives similar fixed-effect (HR 1.20, 95% CI 1.08 to 1.33, P = 0.0005) and random-effects results (HR 1.20, 95% CI 1.06 to 1.37, P = 0.005).
- Local recurrence-free survival:
  - Data on local-regional recurrence were available from all trials. Analysis of local-regional recurrence-free survival, based on 1556 events (498 local-regional recurrences (200 on PORT, 298 on surgery alone) and 1058 deaths (593 on PORT, 465 on surgery alone)), gave a HR of 1.12 (95% CI 1.01 to 1.24), significantly in favour of surgery alone (P = 0.03).
  - There was evidence of statistical heterogeneity between trials (I2 = 47%, P = 0.04), which was not apparent in the 1998 analysis (I2 = 29%, P = 0.19), and for this outcome, the random-effects result is less convincing (HR 1.10, 95% CI 0.95 to 1.27, P = 0.19) than the fixed-effect result. However, exclusion of the Italian trial again reduces heterogeneity to non-significant levels (I2 = 22%, P = 0.23), as well as giving similar fixed-effect (HR 1.15,

95% CI 1.04 to 1.27, P = 0.008) and random-effects estimates (HR 1.15, 95% CI 1.02 to 1.29, P = 0.02).

- Results may suggest an increase in local-regional recurrence on the PORT arm, but the number of local-regional recurrences alone shows less localregional recurrence on the PORT arm and more events when deaths without local-regional recurrence are included.

- Distant recurrence-free survival:
  - All trials provided data on distant recurrence. Analysis of distant recurrence-free survival based on 1570 events (892 distant recurrences (438 on PORT, 454 on surgery alone) and 678 deaths (361 on PORT, 317 on surgery alone)) gave an HR of 1.13 (95% CI 1.02 to 1.24) in favour of surgery alone (P = 0.02).
  - There was no evidence of gross statistical heterogeneity between trials (I2 = 31%, P = 0.15).
- Overall recurrence-free survival:
  - A total of 1597 events were observed, 810 on PORT and 787 on surgery alone. Of these, 445 first events were deaths, 260 participants had local-regional recurrences and 654 had distant recurrences (238 participants had both local-regional and distant recurrences, of which 110 were recorded on the same date). The overall HR of 1.10 (95% CI 0.99 to 1.21) potentially suggests an adverse effect of PORT (P = 0.07).
  - This 10% relative increase in risk of recurrence or death was equivalent to an absolute detriment of 3%at two years (95%CI 0%to 7%), reducing the recurrence-free survival rate from 48% to 45%.
  - As with local-regional recurrence-free survival, there was some evidence of increased statistical heterogeneity between trials (I2 = 44%, P = 0.06) that was not present in the 1998 analysis (I2 = 26%, P = 0.21), and a random-effects analysis produces a less convincing result (HR 1.09, 95% CI 0.95 to 1.25, P = 0.23). However, a sensitivity analysis excluding the Italian trial not only reduces heterogeneity (I2 = 20%, P = 0.26) but also gives similar fixed-effect (HR 1.13, 95% CI 1.02 to 1.24, P = 0.02) and random- effects (HR 1.13, 95% CI 1.00 to 1.26, P = 0.04) results.

Fazit der Autoren

Although the radiotherapy used in most of the included trials is now considered suboptimal, this update still provides the best evidence that postoperative radiotherapy (PORT) has an adverse effect on survival. There is now less compelling evidence that the effect of PORT varies by stage, and in particular nodal status, but PORT should not be used routinely unless supporting evidence can be obtained from an ongoing trial of modern PORT techniques.

3.3 Systematische Reviews

Li R et al., 2019 [11].

Comparing the benefits of postoperative adjuvant chemotherapy vs. observation for stage IB non-small cell lung cancer: a meta-analysis.

Fragestellung

to compare the benefits of postoperative adjuvant chemotherapy vs. observation for stage IB non-small cell lung cancer (NSCLC).

Methodik

Population:

- resected NSCLC patients; p-stage IB (T2N0M0) NSCLC

Intervention:

- adjuvant chemotherapy

Komparator:

- observation

Endpunkte:

- OS, DFS,local recurrence, distant metastasis

Recherche/Suchzeitraum:

- PubMed, Embase, and Cochrane Library databases from the earliest publications to June 2018

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- nine RCTs
- 1,645 patients who were assigned to the adjuvant chemotherapy (n=820) and observation (n=825) groups

Charakteristika der Population:

Table 1 Characteristics of the included studies for the meta-analysis

The study of stage IB	Year	Accrual year	Country	Study design	Postoperative adjuvant chemotherapy	Size	Outcome	Journal
Butts *et al.* (9)	2010	1994–2001	Canada	RCT	Cisplatin (50 mg/m^2) d1, d8, 4 weeks; vinorelbine (25 mg/m^2), weekly 16 weeks	219	5-year OS	*Journal of Clinical Oncology*
Strauss *et al.* (10)	2008	1996–2003	USA	RCT	Paclitaxel (200 mg/m^2), carboplatin (AUC =6); every 3 weeks	344	5-year OS; 5-year DFS	*Journal of Clinical Oncology*
Douillard *et al.* (11)	2006	1994–2000	France	RCT	Vinorelbine (30 mg/m^2), cisplatin (100 mg/m^2); every 4 weeks	301	5-year OS	*Lancet Oncology*
Roselli *et al.* (12)	2006	1988–1994	Italy	RCT	Cisplatin (100 mg/m^2) d1, etoposide (120 mg/m^2) d1, 2, 3; every 4 weeks	140	5-year OS; 5-year DFS; local recurrence; distant metastasis	*International Journal of Cancer*
Park *et al.* (13)	2005	1989–1998	Korea	RCT	Mitomycin C (10 mg/m^2) d1, vinblastine (6 mg/m^2) d1, cisplatin (100 mg/m^2) d1–d5; every 3 weeks	97	5-year OS; 5-year DFS	*European Journal of Cardio-thoracic Surgery*
Nakagawa *et al.* (14)	2005	1992–1994	Japan	RCT	Uracil and tegafur 400 mg/d	111	5-year OS	*Annals of Oncology*
Kato *et al.* (15)	2004	1994–1997	Japan	RCT	Uracil and tegafur 250 mg twice a day	263	5-year OS; 5-year DFS	*The New England journal of Medline*
Waller *et al.* (16)	2004	1995–2001	UK	RCT	Cisplatin (50 mg/m^2), mitomycin (6 mg/m^2), ifosfamide (3 g/m^2); vinblastine (6 mg/m^2); cisplatin (50 mg/m^2), vindesine (3 mg/m^2), vinorelbine (30 mg/m^2); 3 weeks	103	5-year OS	*European Journal of Cardio-thoracic Surgery*
Mineo *et al.* (17)	2001	1988–1994	Italy	RCT	Cisplatin (CDDP) (100 mg/m^2) given on day 1 and etoposide (VP16) (120 mg/m^2) administered on days 1–3; every 4 weeks	66	5-year OS; 5-year DFS; local recurrence; distant metastasis	*European Journal of Cardio-thoracic Surgery*

RCT, randomized controlled trial.

Qualität der Studien:

Table 2 The risk of bias analysis of the included RCTs

Study	A	B	C	D	E	F	G	Grade
Butts *et al.* (9)	+	+	+	?	+	+	?	B
Strauss *et al.* (10)	+	+	+	?	+	+	–	B
Douillard *et al.* (11)	+	+	+	+	+	+	+	A
Roselli *et al.* (12)	+	+	+	+	+	+	?	A
Park *et al.* (13)	+	+	+	+	–	+	?	B
Nakagawa *et al.* (14)	+	+	+	?	+	+	?	B
Kato *et al.* (15)	+	+	+	+	–	+	?	B
Waller *et al.* (16)	+	+	+	+	+	?	?	B
Mineo *et al.* (17)	+	+	+	+	?	?	?	B

A, random sequence generation; B, allocation concealment; C, blinding of participants and personnel; D, blinding of outcome assessment; E, incomplete outcome data; F, selective reporting; G, other bias; +, low risk of bias; –, high risk of bias; ?, uncertain risk of bias. RCT, randomized controlled trial.

Studienergebnisse:

- No significance in the 5-year OS and 5-year DFS between the postoperative adjuvant chemotherapy and observation groups.
- However, there was a significant difference in local recurrence (RR =0.43; 95% CI: 0.23–0.80; P=0.007) and distant metastasis (RR =0.68; 95% CI: 0.48–0.97; P=0.03) between the two groups.

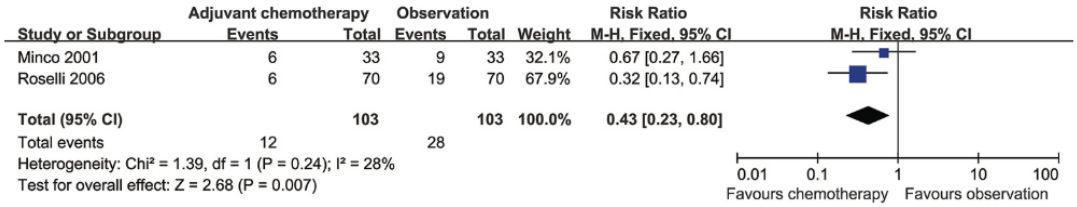


Figure 4 Forest plot of local recurrence associated with adjuvant chemotherapy compared with observation in stage IB NSCLC patients. NSCLC, non-small cell lung cancer.

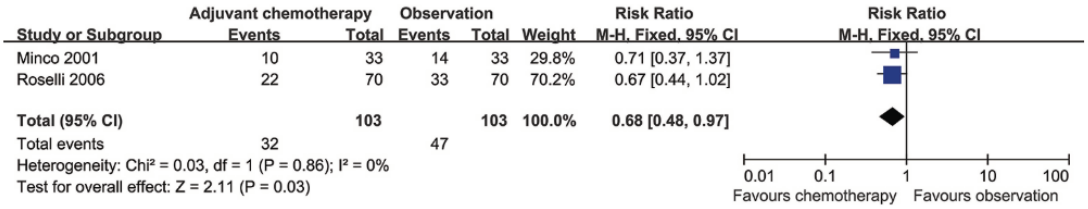


Figure 5 Forest plot of distant metastasis associated with adjuvant chemotherapy compared with observation in stage IB NSCLC patients. NSCLC, non-small cell lung cancer.

Anmerkung/Fazit der Autoren

The 5-year OS and 5-year DFS of stage IB NSCLC patients were not improved by adjuvant chemotherapy. In addition, there was not enough evidence to show that adjuvant chemotherapy reduced the risks of local recurrence and distant metastasis after surgery, because these results might be influenced by sample size in the meta-analysis. In conclusion, adjuvant chemotherapy might not be recommended for stage IB NSCLC patients.

Cheng H et al., 2019 [6].

A meta-analysis of adjuvant EGFR-TKIs for patients with resected non-small cell lung cancer.

Fragestellung

to compare adjuvant EGFR-TKIs with a placebo or adjuvant chemotherapy among patients with resected non-small cell lung cancer (NSCLC).

Methodik

Population:

- patients with resected NSCLC

Intervention:

- adjuvant EGFR-TKIs

Komparator:

- chemotherapy or a placebo

Endpunkte:

- DFS, OS, adverse events

Recherche/Suchzeitraum:

- PubMed, Scopus, EMBASE; between January 1, 2010 and June 30, 2019

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Five RCTs / RCTs including three RCTs that compared adjuvant EGFR-TKIs with a placebo, and two RCTs that compared adjuvant EGFR-TKIs with chemotherapy

Charakteristika der Population:

Table 1
Baseline characteristics of included studies. *NA, not assessable.

Trials	Intervention	No.	AgeMedian	Stage (No.)	Adjuvant chemotherapy		Primary endpoint	EGFR mutation positive patients	Median follow up(year)	Median TKI treatment duration (month)
					Yes	No				
RADIANT [10]	erlotinib	N = 623	62	IB to IIIA	315(50.6%)	308(49.4%)	DFS	N = 102	3.9	11.9
	Placebo	N = 350	62	IB to IIIA	200(57.1%)	150(42.9%)	DFS	N = 59		
Br.19 [11]	gefitinib	N = 251	66	IB to IIIA	43(17%)	208(83%)	OS and DFS	N = 7	4.7 (range, 0.1–6.3)	4.8
	placebo	N = 252	67	IB to IIIA	44(17%)	208(83%)	OS and DFS	N = 8		
Li [9]	chemotherapy-gefitinib	N = 30	59.5	IIIA N2	30	0	DFS	N = 30	2.5 (range, 0.3–4.39)	6
	chemotherapy	N = 30	54.6	IIIA N2	30	0	DFS	N = 30		
Feng [8]	Chemotherapy-Icotinib	N = 21	57	IB to IIIA	21	0	DFS	21	2	NA*(Range, 4–8)
	chemotherapy	N = 20	55	IB to IIIA	18	2	DFS	20		
CTONG1104 [12]	gefitinib	N = 111	58	II–IIIA (N1–N2)	0	0	DFS	N = 111	3.04(IQR 1.98–3.73)	21.9
	Vinorelbine plus cisplatin	N = 111	60	II–IIIA (N1–N2)	111	0	DFS	N = 111		
EVAN [13]	erlotinib	N = 51	59	IIIA	0	0	2 year DFS	N = 51	2.75(IQR1.48-3.59)	23.9(IQR20.7–24
	Vinorelbine plus cisplatin	N = 51	57	IIIA	51	0	2 year DFS	N = 51		

Qualität der Studien:

- The study by Li et al. was not a double-blinded trial and had a moderate risk of bias (performance bias and detective bias). The other four included trials were well designed and were at a low risk of bias.

Studienergebnisse:

- For unselected intent-to treat patients who received adjuvant EGFR-TKIs versus a placebo, the hazard ratio (HR) of disease-free survival (DFS) was 0.88 (n.s.).
- For patients with an EGFR mutation, the DFS after adjuvant EGFR-TKIs was superior to that after a placebo, with a HR of 0.59 (95% CI: 0.40–0.88; P=0.009).
- For patients with an EGFR mutation, the DFS after EGFR-TKIs was greater than that after chemotherapy, with a HR of 0.42 (95% CI: 0.19–0.93; P=0.03).
- For patients with wild-type EGFR, the DFS of adjuvant EGFR-TKIs was similar to the placebo, with a RR of 1.00 (n.s.).
- Treatment with EGFR-TKIs resulted in more adverse events compared with the placebo, with a risk ratio (RR) of 2.72, (95% CI: 2.23–3.33; P < 0.00001), but fewer adverse events compared with chemotherapy, with an RR of 0.26 (95% CI: 0.18–0.38; P < 0.00001).

Anmerkung/Fazit der Autoren

In conclusion, patients with resected EGFR-mutant NSCLC treated with adjuvant EGFR-TKIs had an improved DFS compared with placebo or adjuvant chemotherapy. Adjuvant EGFR-TKIs were not effective among patients with wild type EGFR NSCLC. Treatment with adjuvant EGFR-TKIs resulted in more adverse events than the placebo but fewer adverse events compared with adjuvant chemotherapy. Ongoing studies are therefore needed to further confirm the possible benefits of adjuvant EGFR-TKI therapy in patients with NSCLC.

Kommentare zum Review

- inhomogeneous study design including patients with wild type EGFR, different stage, different treatment regimen and duration
- still many questions that need to be answered regarding treatment with EGFR-TKIs. For patients with EGFR mutations, which stage of lung cancer benefits most from adjuvant EGFR-TKIs after radical resection?

Liu T et al., 2019 [13].

The role of postoperative radiotherapy for completely resected pIIIA-N2 non-small cell lung cancer patients with different clinicopathological features: a systemic review and meta-analysis.

Fragestellung

to assess the effect of PORT in patients with pIIIA-N2 NSCLC on the basis of clinicopathological features.

Methodik

Population:

- completely resected pIIIA-N2 NSCLC

Intervention/Komparator:

- surgical resection with or without PORT according to clinicopathological features

Endpunkte:

- OD, DFS

Recherche/Suchzeitraum:

- PubMed, PubMed Central (PMC), EMBASE, Web of Science, and Cochrane Library

Qualitätsbewertung der Studien:

- Newcastle–Ottawa Quality Assessment Scale (NOS) was used to assess the quality of retrospective studies / Cochrane risk of bias tool for RCTs

Ergebnisse

Anzahl eingeschlossener Studien:

- one RCT and 12 retrospective studies were included in the meta-analysis

Charakteristika der Population:

Table 1. Baseline characteristics of included studies

First author/ Year	Country of origin	Time range	No. of patients (PORT/non-PORT)	Study language	Study design	POCT (PORT/non-PORT)	RT techniques	RT dose median(Gy)	Type of surgery	NOS score
Matsuguma/2008 [14]	Japan	1986–2003	45/46	English	RS	26.7%/13%	NR	50.4	Lob/Pne	6
Wei/2017 [15]	USA	2004–2013	1244/2090	English	RS	NA	NR	NR	Sub/Lob/Pne	7
Kou/2018 [16]	USA	2004–2013	1106/1843	English	RS	NA	NR	NR	NR	7
Wang/2017 [17]	USA	2004–2013	1198/2179	English	RS	NA	NR	NR	Lob/Pne	7
Du/2009 [18]	China	2000–2005	104/255	Chinese	RS	73.1%/51.4%	2D	NR	Lob/Pne	6
Xu/2018 [19]	China	2009–2012	89/157	English	RS	98.9%/57.3%	3D	50.4	Lob/Pne	7
Sun/2017 [20]	Korea	2009–2014	51/50	English	RCT	100%*/100%	3D	50	Lob/Bilo/Pne	-
Kim/2014 [21]	Korea	2000–2011	41/178	English	RS	100%/NA	2D+3D	54	Lob/Bilo/Pne	7
Hui/2014 [22]	China	2003–2005	96/125	English	RS	NA	2D+3D	60	Lob/Pne	7
Cao/2014 [23]	China	2008–2009	39/179	English	RS	100%/71.5%	3D	50.4	Lob/Bilo/Pne/Wed	7
Pang/2017 [24]	USA	2004–2011	9040/5419	English	RS	NA	NR	NR	Lob/Bilo/Pne/Wed	7
Sawyer/1997 [25]	USA	1987–1993	88/136	English	RS	NA	NR	50.4	Lob/Pne/Wed	6
Chen/2009 [26]	China	1987–2004	46/46	Chinese	RS	NA	NR	56	Lob/Pne	6

Abbreviations: PORT, postoperative radiotherapy; POCT, postoperative chemotherapy; RT, radiotherapy; NOS, Newcastle–Ottawa Quality Assessment Scale score; NR, not reported; 2D, two-dimensional radiotherapy; 3D, three-dimensional conformed radiotherapy; Lob, lobectomy; Pne, pneumonectomy; Sub, sublobectomy; Bilo, Bilobectomy; Wed, wedge resection; RCT, randomized controlled trial; RS, retrospective cohort study.
*, concurrent chemoradiotherapy.

Qualität der Studien:

- All of the retrospective studies demonstrated a score of ≥6 (Table 2). The quality of the included RCT was relatively high (Adequate sequence generation: yes; Allocation concealment: Incomplete outcome: unclear; Free of selective reports: yes)

Table 2. Quality assessment of twelve retrospective studies using the Newcastle-Ottawa scale.

First author/	Selection				Comparablity		Outcome			Score
year	Item1	Item2	Item3	Item4	Item5	Item6	Item7	Item8	Item9	
Matsuguma/2008[14]	※	※	※	※	※	-	-	※	-	6
Wei/2017[15]	※	※	※	※	※	-	※	※	-	7
Kou/2018[16]	※	※	※	※	※	-	※	※	-	7
Wang/2017[17]	※	※	※	※	※	-	※	※	-	7
Du/2009[18]	※	※	※	※	※	-	-	※	-	6
Xu/2018[19]	※	※	※	※	※	-	※	※	-	7
Kim/2014[21]	※	※	※	※	※	-	※	※	-	7
Hui/2014[22]	※	※	※	※	※	-	※	※	-	7
Cao/2014[23]	※	※	※	※	※	-	※	※	-	7
Pang/2017[24]	※	※	※	※	※	-	※	※	-	7
Sawyer/1997[25]	※	※	※	※	※	-	-	※	-	6
Chen/2009[26]	-	-	※	※	※	-	※	※	※	6

Abbreviations: –, zero point; ※, one point. Item 1: representativeness of the exposed cohort; Item 2: selection of the nonexposed cohort; Item 3: ascertainment of exposure; Item 4: demonstrating that the outcome of interest was not present at the start of the study; Item 5: comparability of cohorts on the basis of the design (study controls for the most important factor); Item 6: comparability of cohorts on the basis of the design (study controls for other additional factors); Item 7: assessment of outcome; Item 8: follow-up long enough for outcomes to occur; and Item 9: adequacy of follow-up of cohorts.

Studienergebnisse:

- PORT significantly improved both OS [HR = 0.85; 95% confidence interval (CI): 0.79–0.92] and DFS (HR = 0.57; 95% CI: 0.38–0.85) compared with non-PORT treatment in patients with multiple N2 metastases or multiple N2 station involvement.
- No significant difference in either OS or DFS was found between PORT and non-PORT groups for patients with single N2 station involvement.
- No significant differences in OS were observed between PORT and non-PORT groups for patients of different ages, sex, tumor sizes or pT stages, and histological types.

Anmerkung/Fazit der Autoren

Evidences from the present meta-analysis supported a role for PORT in patients with completely resected pIIIA-N2 NSCLC having multiple N2 metastases and favored withholding PORT to patients with single N2 station involvement. Further prospective RCTs are needed to confirm the findings.

Kommentare zum Review

- almost all the available data were extracted from retrospective studies
- little trial on the effect of PORT in patients with pIIIA-N2 NSCLC on the basis of clinicopathological features.
- Siehe auch: Zhang H., et al. 2019 [19]

Tang, W. et al., 2019 [18].

EGFR inhibitors as adjuvant therapy for resected non-small cell lung cancer harboring EGFR mutations.

Fragestellung

to evaluate the role of EGFR inhibitors as an adjuvant therapy for targeted patients.

Methodik

Population:

- completely resected patients with EGFR mutation-positive NSCLC

Intervention:

- adjuvant EGFR-TKIs

Komparator:

- adjuvant non-EGFR therapy

Endpunkte:

- DFS, OS, (serious) adverse events

Recherche/Suchzeitraum:

- PubMed, ISI Web of Science, ScienceDirect, SpringerLink, The Cochrane library, AACR, and the Ovid databases as far back as they extend (k.A. zu genauem Zeitrahmen der Suche)

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 studies that assigned 1152 patients

Charakteristika der Population:

Table 1
Characteristics of the eligible studies.

Trial	Phase	Period	Patients Number	Mutation Type	Pathologic Stage	Experimental Events	Control Events	Outcome
Goss 2013	III	Sept.2002-Apr.2005	15	Exon19 deletion and Exon21 Leu858Arg	IB-IIIA	TKIs(Gefitinib)	Placebo	No statistic DFS or OS benefit
Janjigian 2011	Retrospective	May.2002-Aug.2008	167	Exon19 n = 93(56%) Exon21 n = 74(44%)	I-III	TKIs(Erlotinib/Gefitinib) + Chemotherapy	Chemotherapy	DFS benefit but no OS benefit
Kelly 2015	III	Nov.2007-Jul.2010	161	Exon19 n = 89(55.3%) Exon21 n = 72(44.7%)	IB-IIIA	TKIs (Erlotinib) + Chemotherapy	Placebo	DFS benefit; OS data immature
Li 2014	II	Aug.2008-Sept.2011	60	Exon19 n = 20(33.3%) Exon21n = 40(66.7%)	IIIA-N2	TKIs (Gefitinib) + Chemotherapy	Chemotherapy	DFS benefit but no OS benefit
Lv 2015	Retrospective	Sept.2004-May.2013	138	Exon18 n = 4(2.9%) Exon19 n = 58(42%) Exon21 n = 70(50.7) Complex Mutation n = 6 (4%)	I-IIIA	TKIs(Erlotinib/Gefitinib/Icotinib)	Chemotherapy	DFS benefit but no OS benefit
Waterhouse 2012	II	Tus.2008-Jan.2012	106	Mutation type not mentioned	IB-IIIA	TKIs + Chemotherapy (docetaxel, bevacizumab, and erlotinib)	Chemotherapy	No statistic DFS or OS benefit
Xie 2018	Retrospective	Jan.2013-Mar.2017	104	Exon19 n = 58(55.8%) Exon21 n = 46(44.2%)	II-IIIA	TKIs (Gefitinib)	Chemotherapy	DFS benefit but no OS benefit
Yue 2017	II	Sept.2012-May.2015	102	Exon19 n = 58(56.8%) Exon21 n = 43(42.2%) Complex Mutation n = 1 (1%)	IIIA	TKIs (Gefitinib)	Chemotherapy (vinorelbine plus cisplatin)	DFS benefit; OS data immature
Zhong 2018	II	Sept.2011-Apr.2014	222	Exon19 n = 58(52%) Exon21 n = 53(48%)	II-IIIA	TKIs (Gefitinib)	Chemotherapy (Vinorelbine plus cisplatin)	DFS benefit; OS data immature
Feng 2015	II	Feb.2011-Dec.2012	39	Exon18 n = 1(3%) Exon19 n = 16(41%) Exon21 n = 22(56%)	IB-IIIA	TKIs (Icotinib) + Chemotherapy	Chemotherapy	No statistic DES or OS benefit
Tsuboi 2005	III	Oct.2002-Mar.2003	38	Mutation type not mentioned	I-IIIA	TKIs (Gefitinib)	Placebo	No survival data

Qualität der Studien:

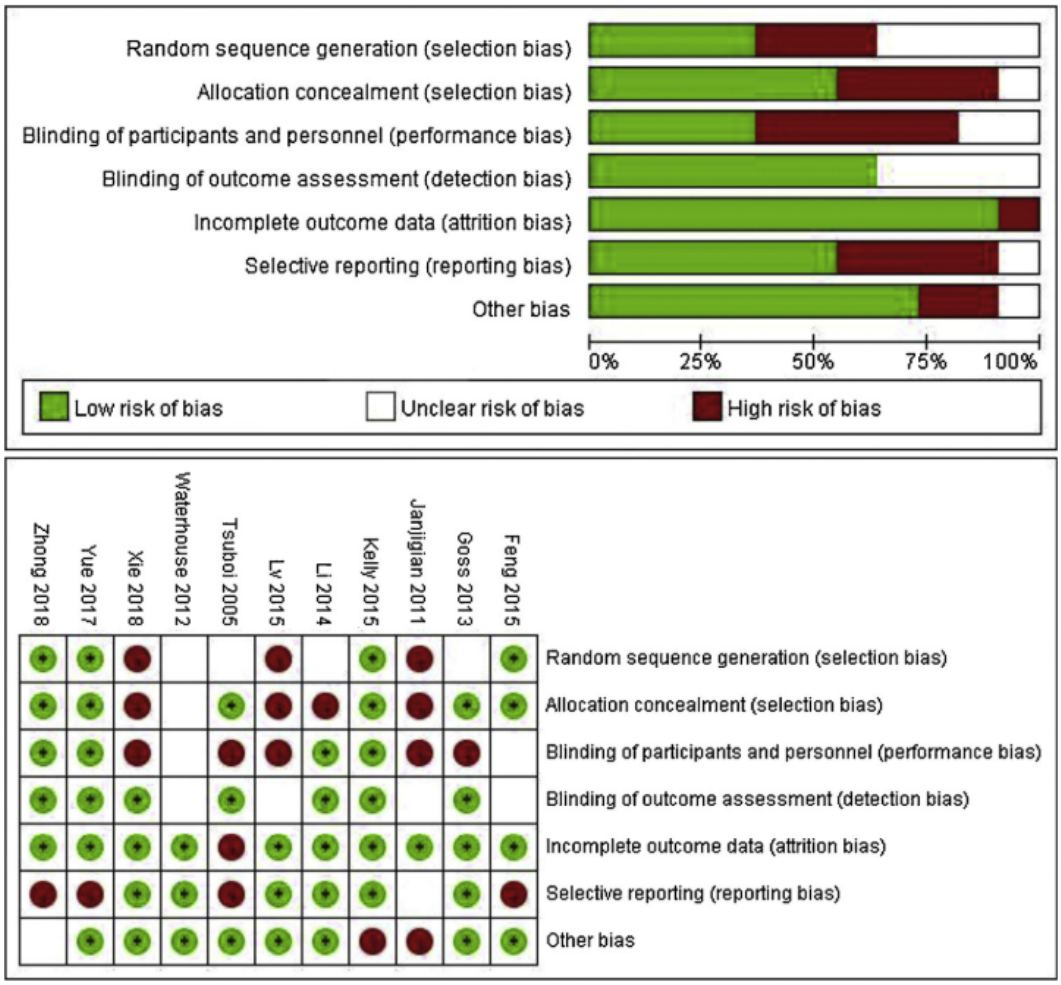


Fig. 6. The assessment of bias of included studies using the Cochrane Risk of Bias Assessment Tool.

Studienergebnisse:

- adjuvant treatment with EGFR-TKIs can prolong both the OS and DFS when compared to treatment without TKIs as an adjuvant therapy (OS: OR, 0.63; 95% CI, 0.46 to 0.87, P=0.004; heterogeneity I2=61%, P=0.008; DFS: OR, 0.56; 95% CI, 0.43 to 0.72, P < 0.00001; heterogeneity I2=37%, P=0.10).
- predefined subgroup analyses in this meta-analysis suggested a greater DFS with the mono EGFR-TKIs compared with chemotherapy, whereas the OS benefit failed to show a similar difference between the two arms (p=0.30).
- treatment with EGFR-TKIs plus chemotherapy was associated with a significantly longer DFS and OS compared to mono chemotherapy in patients with completely resected EGFR-mutant NSCLC (DFS: OR, 0.48; 95% CI, 0.34-0.68; P < 0.0001; heterogeneity I2=47%, P=0.07; OS: OR, 0.50; 95% CI, 0.31-0.78; P=0.003; heterogeneity I2=57%, P=0.05).
- less severe adverse events (SAEs) were observed in the TKIs group (OR, 0.22; 95% CI, 0.14 to 0.37, P < 0.00001; heterogeneity I2=22%, P=0.28).

Anmerkung/Fazit der Autoren

Adjuvant therapies are required to prevent disease recurrence and improve patient survival after surgery. Our results suggest a benefit in the DFS (and perhaps in the OS) when using adjuvant EGFR-TKIs, with or without the addition of chemotherapy, which indicates that adjuvant EGFR-TKIs could be a potential treatment option compared to adjuvant chemotherapy in completely resected patients with EGFR mutation positive NSCLC. It may not be curative, but adjuvant EGFR-TKIs do provide clinical benefit for most patients. Moreover, its safety and tolerability also make it an appealing treatment option for patients with resected EGFR-mutant NSCLC.

Kommentare zum Review

- there was a limited number of phase III studies available to be included in our study, so we included several phase II trials and retrospective studies as well, both of which increased the heterogeneity of this meta-analysis.
- OS benefit demonstrated in this meta-analysis appears to be mainly driven by two studies (Li et al. and Yue et al.), which enrolled only Stage III patients and represented a small scope of patients.
- number of studies available for comparison of mono EGFR-TKIs with chemotherapy was limited.

Raphael J et al., 2019 [17].

Adjuvant Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (TKIs) in Resected Non-Small Cell Lung Cancer (NSCLC): A Systematic Review and Meta-analysis.

Fragestellung

to perform a systematic review of the literature and meta-analysis of randomized controlled trials to assess the efficacy and safety of adjuvant EGFR TKIs in NSCLC.

Methodik

Population:

- patients aged 18 years or older with a stage IB to IIIA NSCLC (any histology), particularly patients harboring an EGFR activating mutation. All patients had to have their tumor completely resected before they received the TKI.

Intervention:

- adjuvant TKI

Komparator:

- no treatment, placebo or adjuvant chemotherapy

Endpunkte:

- DFS, OS, safety

Recherche/Suchzeitraum:

- from January 2000 till October 2017 without language restriction: Medline (OVID), and Embase

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 randomized trials and 1860 patients met the inclusion criteria and were included in this review. Among them, data of 599 patients with an activating EGFR mutation (ie, exon 19 deletion/exon 21 L858R) were included.

Charakteristika der Population:

TABLE 1. Characteristics of Included Trials

RCT Trial	Phase	TKI	D	Control	Stage	Primary Endpoint	N	EGFR-mutant	DFS Benefits
BR19	III	Gefitinib	2 y	Placebo	IB-IIIA	OS	503	15	No
RADIANT	III	Erlotinib	2 y	Placebo	IB-IIIA	DFS	973	161	No
P-C-G	II	Gefitinib	6 m	No trt	IIIA, N2	DFS	60	60	Yes
CKC-1102	II	Icotinib	4-8 m	No trt	IB-IIIA	DFS	39	39	No
CTONG-1104	III	Gefitinib	2 y	CT	II-IIIA	DFS	222	222	Yes
EVAN	II	Erlotinib	2 y	CT	IIIA	DFS	102	102	Yes

CT indicates computed tomography; D, duration of TKI; DFS, disease-free survival; EGFR, epidermal growth factor receptor; m, month; N, number; OS, overall survival; P-C-G, pemetrexed, carboplatin, and gefitinib trial; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor; trt, treatment.

Qualität der Studien:

- Overall, risk of bias was low, particularly in the random sequence generation and in the reporting of outcomes. Yet, the allocation concealment was not clearly stated in 4 studies and the blinding domain was not met in 4 studies. Furthermore, the OS data were reported in 4 studies so far.

Studienergebnisse:

- In patients harboring an EGFR mutation, adjuvant TKIs decreased the risk of disease recurrence by 48% (HR: 0.52, 95% confidence interval [CI]: 0.350.78), improved 2-year DFS (HR: 0.53, 95% CI: 0.43-0.66) but did not improve OS (HR: 0.64, 95% CI: 0.22-1.89).

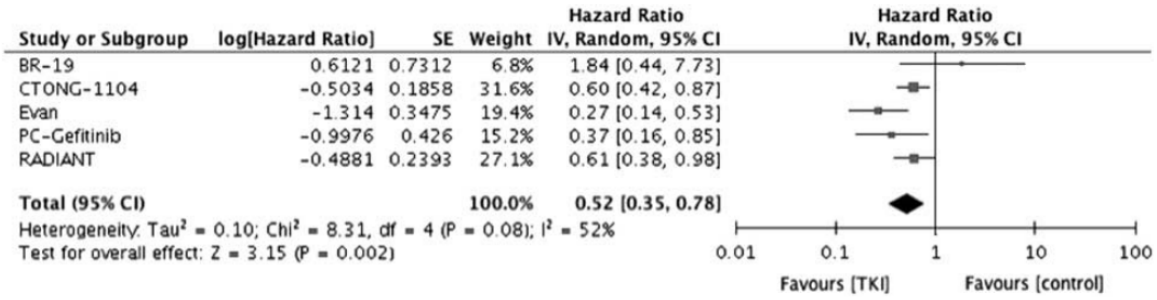


FIGURE 2. Forest plot for DFS in patients harboring an EGFR mutation. CI indicates confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

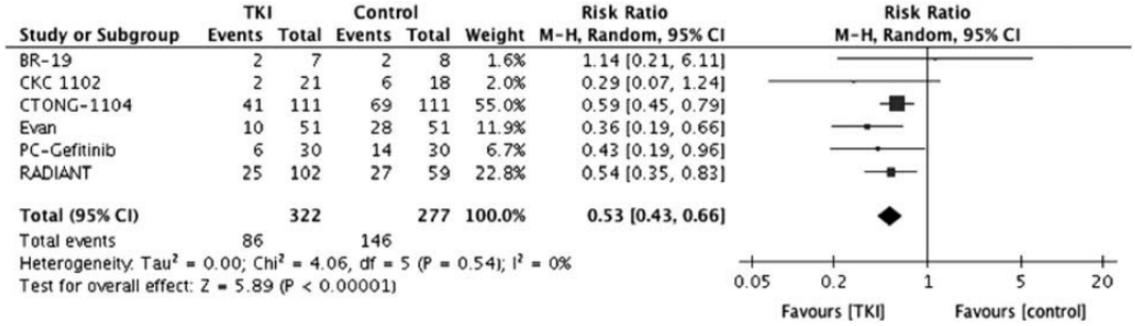


FIGURE 3. Forest plot for 2-year DFS in patients harboring an EGFR mutation. CI indicates confidence interval; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

- The risk of developing ≥ grade 3 skin toxicity (OR: 6.07, 95% CI: 4.34-8.51) and diarrhea (OR: 4.05; 95% CI: 2.44-6.74) was increased.
  - In subgroup analyses, the DFS benefit was more pronounced in trials using TKIs over chemotherapy compared with trials using TKIs postchemotherapy.

Anmerkung/Fazit der Autoren

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.

Lu D et al., 2019 [14].

Differential effects of adjuvant EGFR tyrosine kinase inhibitors in patients with different stages of non-small-cell lung cancer after radical resection: an updated meta-analysis.

Fragestellung

to compare the beneficial effects of adjuvant tyrosine kinase inhibitor (TKI) therapy with those of traditional therapy on NSCLC patients, specifically on EGFR-mutant and stage II–IIIA patients, who might benefit most from such treatment.

Methodik

Population:

- patients diagnosed with pathological stage I–IIIA NSCLC suitable for adjuvant chemotherapy or chemoradiotherapy

Intervention/Komparator:

- adjuvant EGFR-TKIs vs chemotherapy or placebo, or adjuvant combination of TKIs and chemotherapy vs chemotherapy alone

Endpunkte:

- DFS, OS

Recherche/Suchzeitraum:

- MEDLINE, Embase, and the Cochrane Library without any restrictions on publication status/date

Qualitätsbewertung der Studien:

- Newcastle–Ottawa scale / Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Six randomized control trials and three retrospective cohort studies of 2,467 patients

Charakteristika der Population:

- The overall EGFR mutation rate was 48.62%

Qualität der Studien:

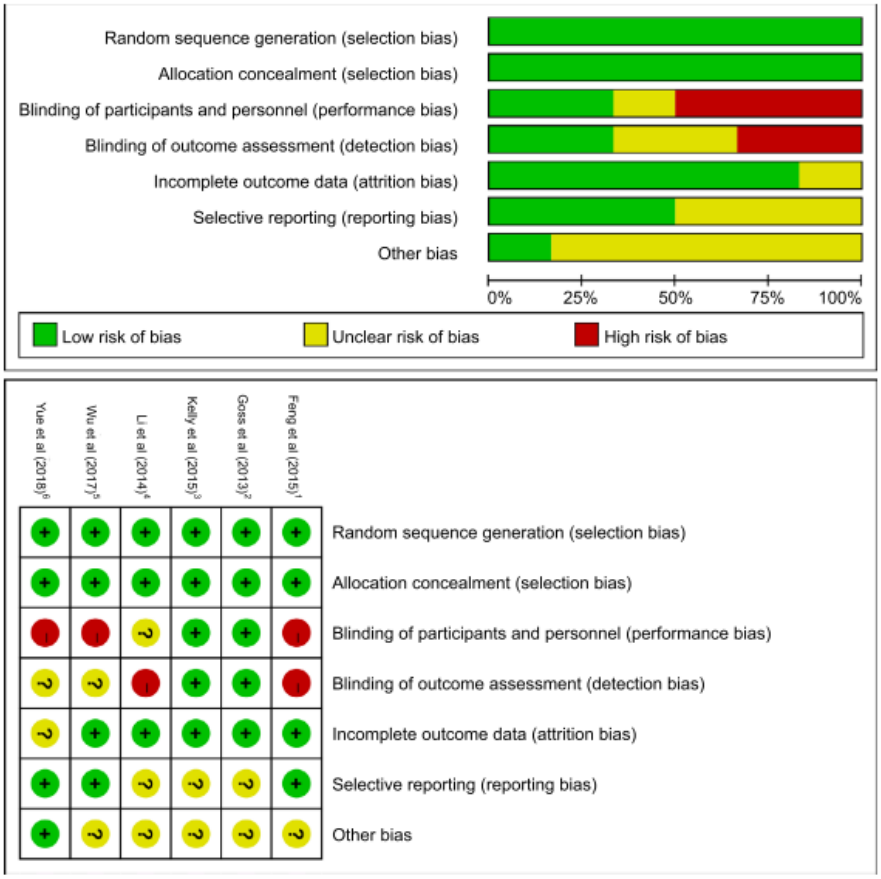


Figure S1 Risk-of-bias graph and summary for the included randomized control trials.

Table S1 Newcastle–Ottawa scale for quality assessment of non-randomized cohort studies

Study	Selection				Comparability	Exposure			Total score
	1	2	3	4	1	1	2	3	
D'Angelo et al (2012)[7]	b	a	a	b	ab	a	a	A	8
Janjigian et al (2011)[8]	b	a	a	a	ab	a	a	B	9
Lv et al (2015)[9]	b	a	a	b	a	a	a	A	7

Studienergebnisse:

- DFS was significantly improved in all the patients (HR, 0.77; 95% CI, 0.68–0.88) and in the subgroup of EGFR-mutant patients (HR, 0.49; 95% CI, 0.40–0.61).
- The difference of 5-year OS in the subgroup of EGFR-mutant patients (HR, 0.48; 95% CI, 0.31–0.72) was statistically significant, while in all the patients (HR, 1.01; 95% CI, 0.85–1.19), the difference was not significant.

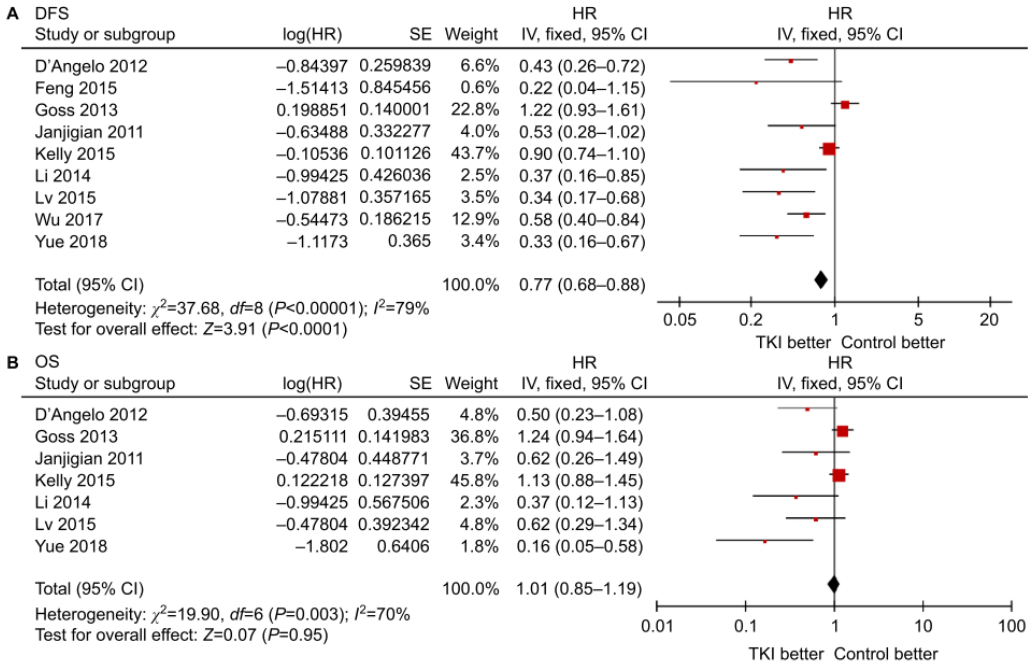


Figure 2 Forest plots of the HR of DFS (**A**) and OS (**B**) of adjuvant EGFR-TKI therapy vs control in patients with NSCLC after radical resection.
Abbreviations: DFS, disease-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor.

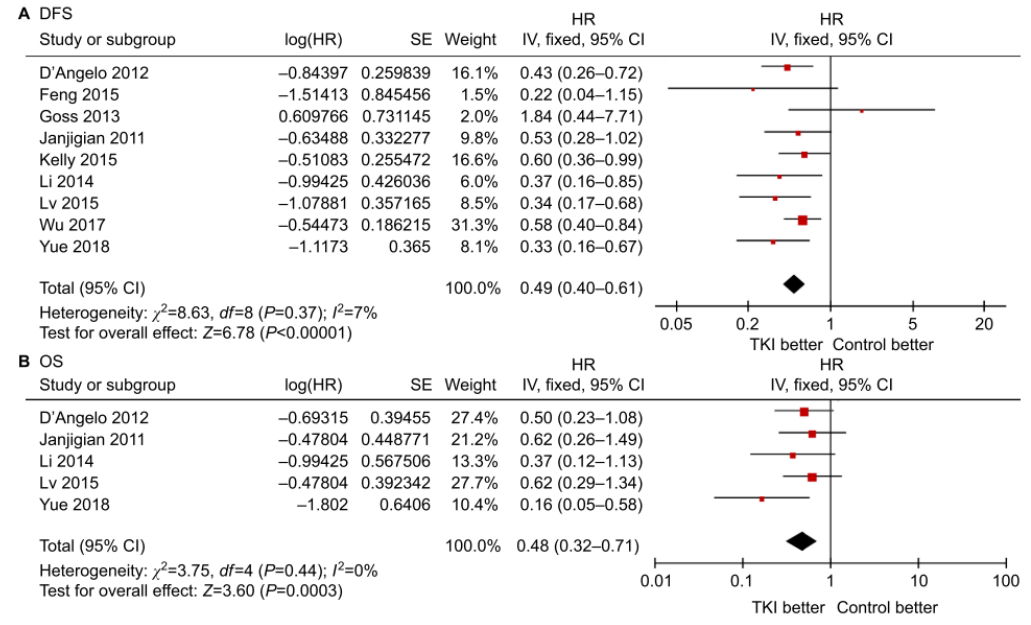


Figure 3 Forest plots of the HR of DFS (**A**) and OS (**B**) of adjuvant EGFR-TKI therapy vs control in patients with EGFR-mutant NSCLC after radical resection.
Abbreviations: DFS, disease-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor.

- In the subgroups of studies in which <50% of patients were in stage I (HR, 0.46; 95% CI, 0.35–0.60) and >30% of patients were in stage IIIA (HR, 0.46; 95% CI, 0.35–0.60), DFS was significantly improved, while in the subgroups of studies in which <30% of patients were in stage IIIA (HR, 0.90; 95% CI, 0.77–1.04) and >50% of patients were in stage I (HR, 0.90; 95% CI, 0.77–1.04), DFS was not significantly improved.

Table 2 Effects of adjuvant TKIs on DFS in relation to proportions of stage I and III NSCLC

Category		Studies divided into subgroups	HR [95% CI]
Stage I	>30	D'Angelo et al (2012)[28], Feng et al (2015)[18], Goss et al (2013) (BR19)[14], Janjigian et al (2011)[29], Kelly et al (2015) (RADIANT)[15], Lv et al (2015)[19]	0.85 [0.74–0.99]
	≤30	Li et al (2014)[27], Wu et al (2017) (ADJUVANT)[16], Yue et al (2018) (EVAN)[17]	0.49 [0.36–0.67]
	>40	D'Angelo et al (2012)[28], Feng et al (2015)[18], Goss et al (2013) (BR19)[14], Janjigian et al (2011)[29], Kelly et al (2015) (RADIANT)[15], Lv et al (2015)[19]	0.85 [0.74–0.99]
	≤40	Li et al (2014)[27], Wu et al (2017) (ADJUVANT)[16], Yue et al (2018) (EVAN)[17]	0.49 [0.36–0.67]
	>50	D'Angelo et al (2012)[28], Goss et al (2013) (BR19)[14], Janjigian et al (2011)[29], Kelly et al (2015) (RADIANT)[15]	0.90 [0.77–1.04]
	≤50	Wu et al (2017) (ADJUVANT)[16], Feng et al (2015)[18], Li et al (2014)[27], Lv et al (2015)[19], Yue et al (2018) (EVAN)[17]	0.46 [0.35–0.60]
Stage III	>30	Feng et al (2015)[18], Li et al (2014)[27], Lv et al (2015)[19], Wu et al (2017) (ADJUVANT)[16], Yue et al (2018) (EVAN)[17]	0.47 [0.36–0.60]
	≤30	D'Angelo et al (2012)[28], Goss et al (2013) (BR19)[14], Janjigian et al (2011)[29], Kelly et al (2015) (RADIANT)[15]	0.92 [0.79–1.07]
	>40	Li et al (2014)[27], Wu et al (2017) (ADJUVANT)[16], Yue et al (2018) (EVAN)[17]	0.49 [0.36–0.67]
	≤40	D'Angelo et al (2012)[28], Feng et al (2015)[18], Goss et al (2013) (BR19)[14], Kelly et al (2015) (RADIANT)[15], Lv et al (2015)[19], Janjigian et al (2011)[29]	0.85 [0.74–0.99]
	>50	Li et al (2014)[27], Wu et al (2017) (ADJUVANT)[16], Yue et al (2018) (EVAN)[17]	0.49 [0.36–0.67]
	≤50	D'Angelo et al (2012)[28], Feng et al (2015)[18], Goss et al (2013) (BR19)[14], Kelly et al (2015) (RADIANT)[15], Lv et al (2015)[19], Janjigian et al (2011)[29]	0.85 [0.74–0.99]

Abbreviations: DFS, disease-free survival; NSCLC, non-small-cell lung cancer; TKIs, tyrosine kinase inhibitors.

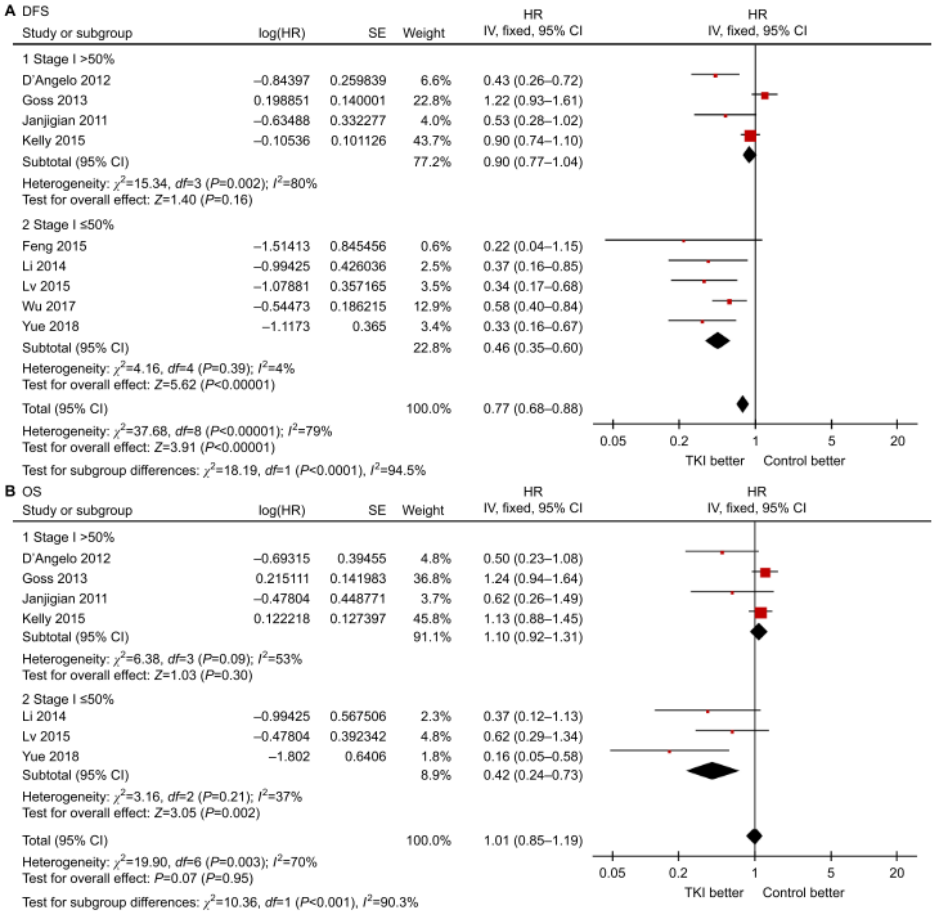


Figure 4 Forest plots of the HR of DFS (**A**) and OS (**B**) of adjuvant EGFR-TKI therapy vs control in subgroups in which >50% and <50% of patients were diagnosed with stage I NSCLC after radical resection.
Abbreviations: DFS, disease-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor.

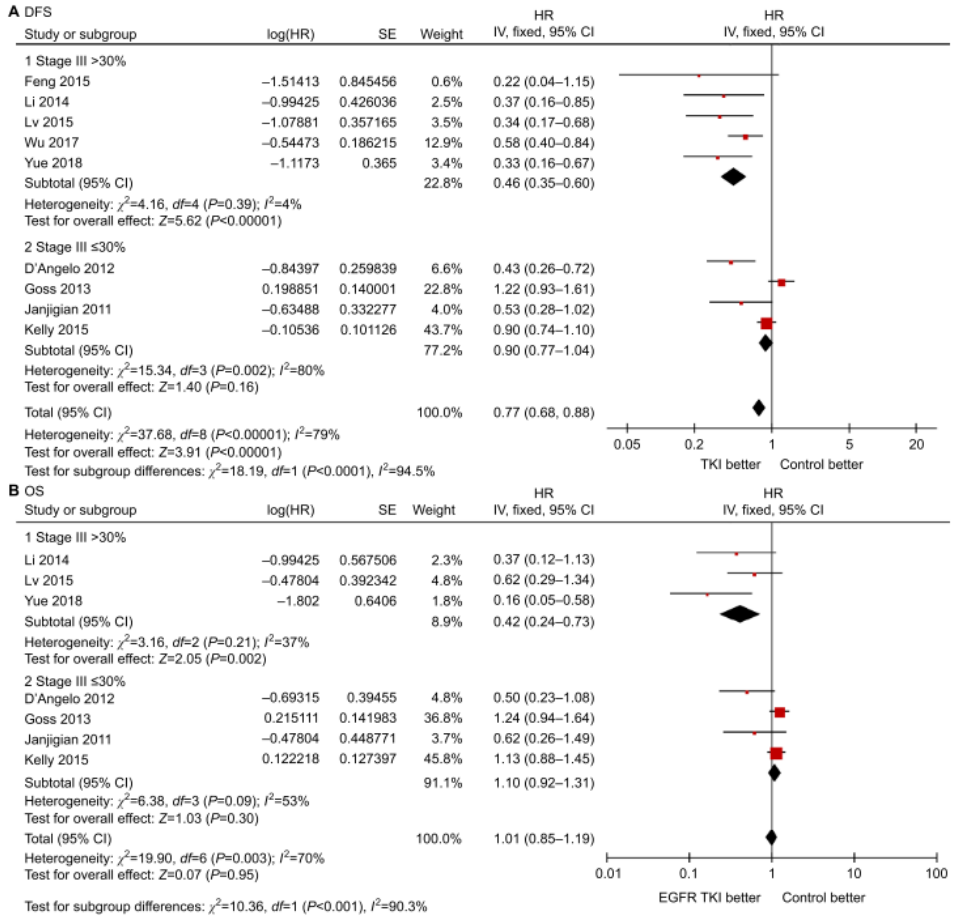


Figure 5 Forest plots of the HR of DFS (**A**) and OS (**B**) of adjuvant EGFR-TKI therapy vs control in subgroups in which >30% and <30% of patients were diagnosed with stage III NSCLC after radical resection.
Abbreviations: DFS, disease-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor.

Anmerkung/Fazit der Autoren

This meta-analysis indicated that postoperative adjuvant EGFR-TKI treatment may provide significant benefits in terms of DFS and OS in patients with EGFR-mutated NSCLC, especially those with regional lymph node metastasis (N1 and N2), but may not be beneficial in patients with stage I NSCLC.

Qie S et al., 2018 [16]

S-1 plus cisplatin with concurrent radiotherapy for stage III non-small cell lung cancer: A meta-analysis (PRISMA) of randomized control trials

Fragestellung

to assess the efficacy and safety of S-1 plus cisplatin as concurrent chemoradiation (experimental group [EG]) compared with standard concurrent chemoradiation regimens (control group[CG]) in patients with local advanced non-small cell lung cancer

Methodik

Population:

- all patients were histologically or pathologically confirmed locally advanced non-small cell lung cancer stage III

Intervention/Komparator:

- S-1-based or S-1 monotherapy concurrent chemoradiation regimens versus standard concurrent chemoradiation regimens

Endpunkte:

- PFS,OS, 1,2,3-year OS, and grade 3 or 4 toxicities

Recherche/Suchzeitraum:

- Embase and Pubmed databases between January, 1996 and February, 2018, and also searched the Cochrane Library databases

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 randomized control trials were included
- A total of 377 patients were included in the present meta-analysis, with 185 patients undergoing S-1-based or S-1 monotherapy concurrent regimens and 192 patients undergoing standard concurrent chemoradiation regimens

Charakteristika der Population:

Table 1
The characteristics of the studies included.

Trail	Patients enrolled	Gender M/F	PS	Interventions
Shukuya. 2012	Arm A 39 Arm B 50	Arm A 34/5 Arm B 37/13	0–1	Arm A: S-1 (p.o.q.d.40 mg/m^2, on days 1–14), cisplatin (60mg/m^2, on day 1). Arm B: Vinorelbine (20 mg/m^2, on days 1 and 8), cisplatin (80mg/m^2, on day 1). The treatment cycles in both arms were repeated every 4 weeks for a maximum of four cycles concurrent with radiotherapy.
Sugawara. 2013	Arm A 35 Arm B 31	Arm A 28/7 Arm B 26/5	0–1	Arm A: Cisplatin (80 mg/m^2 on days 8 and 36), UFT (p.o. 400 mg/m^2, on days 1–14 and 29–42). Arm B: Vinorelbine (20 mg/m^2) on days 1, 8, 29, and 36 and cisplatin (80 mg/m^2) on days 1 and 29. The schedule of concurrent thoracic radiotherapy was 60Gy in 30 fractions.
Seto. 2015	Arm A 55 Arm B 55	Arm A NG Arm B NG	0–1	Arm A: S-1 (40 mg/m^2/dose per oral, b.i.d, on days 1–14) and cisplatin (60 mg/m^2 on day 1) repeated every 4 weeks). Arm B: vinorelbine (20mg/m^2 on days 1, 8) and cisplatin (80 mg/m^{2}on day) repeated every 4 weeks. The schedule of concurrent thoracic radiotherapy was 60Gy in 30 fractions.
Yao. 2015	Arm A 20 Arm B 20	Arm A 15/5 Arm A 14/6	0–1	Arm A: Cisplatin (60 mg/m^2 on day1, every 4 weeks for 2 cycles), S-1 (p.o.b.i.d. 40 mg/m^2, on days1–14). Arm B: Cisplatin (60 mg/m^2 on day1, every 4 weeks for 2 cycles). Both arms received radiotherapy concurrently
Feng. 2016	Arm A 36 Arm B 36	Arm A 24/12 Arm A 21/15	0–1	Arm A: Cisplatin (60 mg/m^2 on day1 followed by at 4-week intervals), S-1 (p.o.b.i.d. 40 mg/m^2, on days1–14). Arm B: Cisplatin (60 mg/m^2 on day1 followed by at 4-week intervals). Both arms received radiotherapy concurrently

Qualität der Studien:

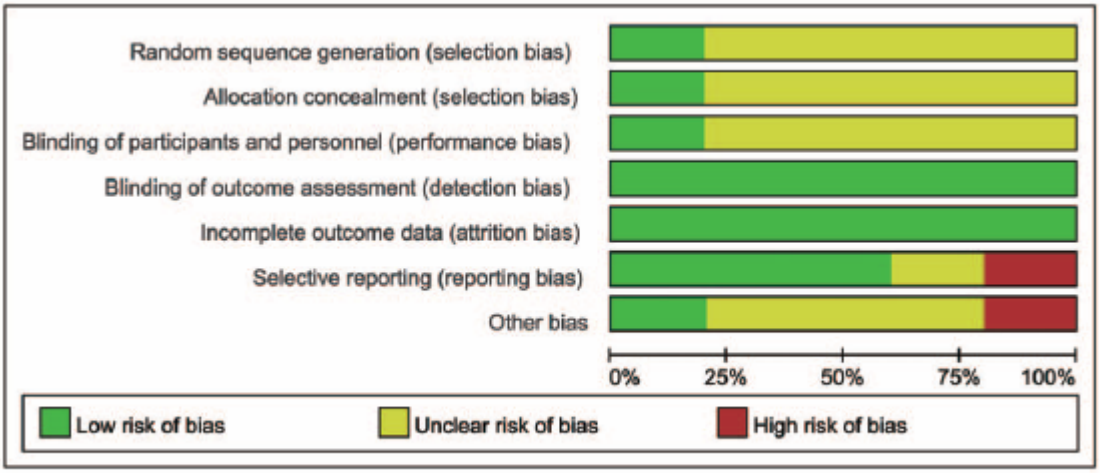


Figure 1. Risk of bias graph.

Studienergebnisse:

- Meta-analysis of the pooled date suggested that overall survival (OS), progressives free survival (PFS) and 1,2,3-year OS were not significantly different.
- The combination of S-1 and cisplatin had lower grade 3 or 4 leukocytopenia, neutropenia, (RR=0.54, 95% CI: 0.38–0.75, P=.0003; RR=0.23, 95% CI: 0.14–0.36, P<.00001, respectively).
- The rates of nausea, diarrhea, thrombocytopenia, pneumonitis, anorexia, anemia, febrile neutropenia were much the same in the 2 groups.

Anmerkung/Fazit der Autoren

No significant difference existed in OS, 1,2,3-year OS, and PFS. Compared with standard regimens, S-1plus cisplatin as concurrent chemoradiation is well tolerated with much lower grade 3 or 4 late toxicities in terms of leukocytopenia, and neutropenia

Kommentare zum Review

- Keine Angaben zu Metastasen

Zhao Y et al., 2019 [21]

The Optimal Treatment for Stage IIIA-N2 Non-Small Cell Lung Cancer: A Network Meta-Analysis

Fragestellung

The optimal treatment for stage IIIA-N2 non-small cell lung cancer (NSCLC) is controversial. We aimed to address this important issue through a Bayesian network meta-analysis.

Methodik

Population:

- pathologically or clinically suspected stage IIIA-N2 NSCLC

Intervention/Komparator:

- multiple treatments including surgery, radiotherapy, chemotherapy, and their multiple combinations

Endpunkte:

- survival data as endpoints

Recherche/Suchzeitraum:

- PubMed, Embase, MEDLINE, and Cochrane Central Register of Controlled Trials databases / ublished before March 25, 2018

Qualitätsbewertung der Studien:

- Adopted Cochrane Risk of Bias Tool

Ergebnisse

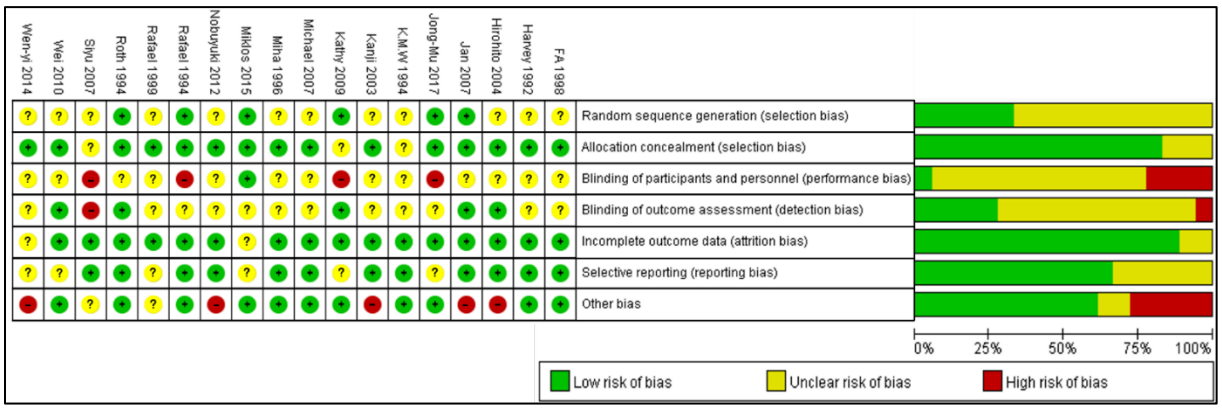
Anzahl eingeschlossener Studien:

- 18 RCTs with a total of 2,158 patients randomized to receive 1 of the following 13 treatments: surgery alone (S), radiotherapy alone (R), surgery followed by adjuvant chemotherapy (SC), surgery followed by adjuvant radiotherapy (SR), neoadjuvant chemotherapy followed by surgery (CS), sequential chemoradiotherapy (CR), concurrent chemoradiotherapy (C_R), neoadjuvant sequential chemoradiotherapy followed by surgery (CRS), neoadjuvant concurrent chemoradiotherapy followed by surgery (C_RS), neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy (CSC), neoadjuvant chemotherapy followed by surgery and adjuvant radiotherapy (CSR), surgery followed by adjuvant sequential chemoradiotherapy (SCR), and surgery followed by adjuvant concurrent chemoradiotherapy (SC_R).

Charakteristika der Population:

- Although 2 included studies recruited patients with stage IIIA but non-N2 NSCLC, N2 patients still accounted for more than 70% of the population of both studies.

Qualität der Studien:



Studienergebnisse:

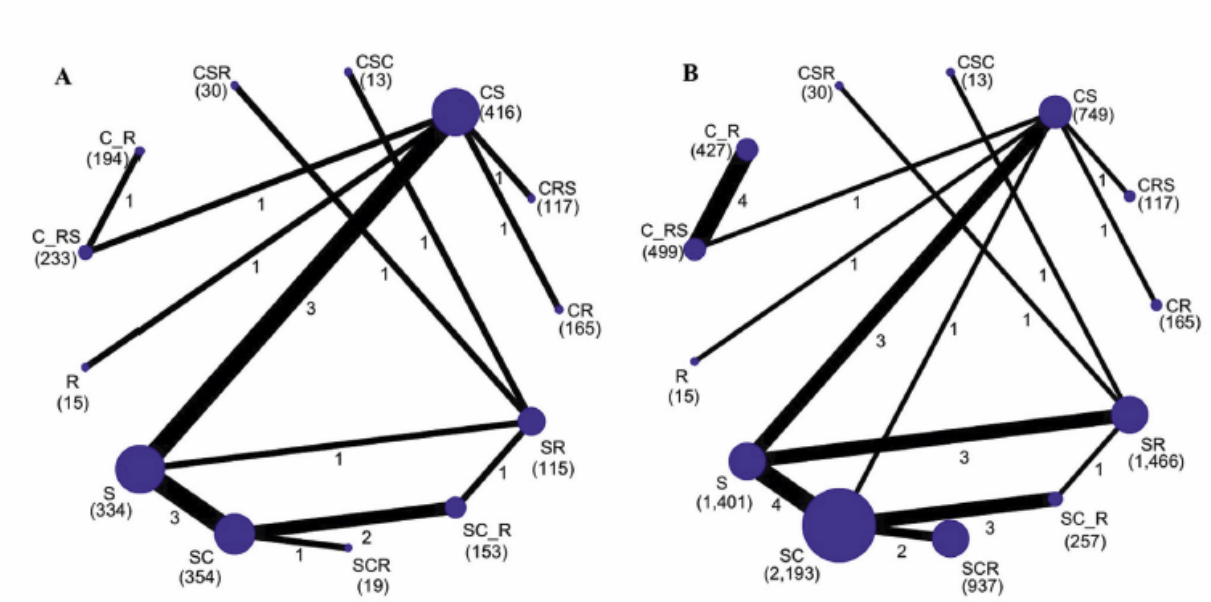


Fig 2. Network of comparisons established for (A) the original network meta-analysis and (B) first-sensitivity analysis. The first-sensitivity analysis additionally included nonrandomized controlled trials. Node size is proportional to the number of included patients (in parentheses). The width of the lines is proportional to the number of trials (beside the line) comparing the connected treatments. (C_R = concurrent chemoradiotherapy; C_RS = neoadjuvant concurrent chemoradiotherapy + surgery; CR = sequential chemoradiotherapy; CRS = neoadjuvant sequential chemoradiotherapy + surgery; CS = neoadjuvant chemotherapy + surgery; CSC = neoadjuvant chemotherapy + surgery + adjuvant chemotherapy; CSR = neoadjuvant chemotherapy + surgery + adjuvant radiotherapy; R = radiotherapy alone; S = surgery alone; SC = surgery + adjuvant chemotherapy; SC_R = surgery + adjuvant concurrent chemoradiotherapy; SCR = surgery + adjuvant sequential chemoradiotherapy; SR = surgery + adjuvant radiotherapy.)

- In terms of overall survival, neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy or radiotherapy, which tended to be consistent (hazard ratio [HR] 1.14, 95% credible interval [CrI] 0.21 to 5.93), ranked superior to other treatments.
- Notably, neoadjuvant chemotherapy followed by surgery and adjuvant radiotherapy was significantly more effective in prolonging survival than surgery alone (HR 0.38, 95% CrI 0.18 to 0.81), surgery plus adjuvant radiotherapy (HR 0.51, 95% CrI 0.29 to 0.92) and potentially surgery plus adjuvant chemotherapy (HR 0.49, 95% CrI 0.23 to 1.05).
- Overall, with 29% as the highest possibility of causing the fewest treatment-related deaths, neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy or radiotherapy was the safest treatment option.

Anmerkung/Fazit der Autoren

Although the debate on optimal treatment for stage IIIA-N2 NSCLC is certain to continue, this NMA indicates that CSR and CSC were preferentially recommended for teams with high efficacy-low risk profiles. Further investigation of CSR and CSC in the form of randomized trials is necessary. Through multidisciplinary consultation with thoracic and oncologic teams, resection of the primary tumors and metastatic lymph nodes in addition to reduction of recurrence and metastasis through other treatment regimens may be the keys to prolonging the survival of N2 disease.

Lei T et al., 2016 [8]

Adjuvant chemotherapy plus radiotherapy is superior to chemotherapy following surgical treatment of stage IIIA N2 non-small-cell lung cancer

Fragestellung

to investigate the role of PORT in N2 NSCLC patients who received adjuvant chemotherapy after radical resection.

Methodik

Population:

- patients with locally advanced N2 stage cancer

Intervention/Komparator:

- surgery followed by chemoradiotherapy to surgery followed by chemotherapy alone

Endpunkte:

- OS and/or disease-free survival (DFS)

Recherche/Suchzeitraum:

- PubMed, Embase, and Medline databases (last search updated in March 2015)

Qualitätsbewertung der Studien:

- The quality of the included randomized controlled trials (RCTs) was evaluated according to the PEDro scale. The quality of the included studies was evaluated according to the Methodological Index for Non-Randomized Studies. The Methodological Index for Non-Randomized Studies includes 12 items that are each scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate).

Ergebnisse

Anzahl eingeschlossener Studien:

- Six studies met our criteria for analysis: two RCTs and four retrospective reviews

Charakteristika der Population:

Table 1 Characteristics of the included studies

First author	Year	Study years	Country	Study design	Stage	Number of patients		DFS (HRs and 95% CIs)	OS (HRs and 95% CIs)	Sequencing of CT and RT	Quality assessment	
						Undergoing POCRT	Undergoing POCT				PEDro scale	MINORS
Robinson et al[13]	2015	2006–2010	USA	Retrospective	IIIA (N2)	1,850	2,633	NA	0.89 (0.80–0.99)	Sequential	/	20
Shen et al[14]	2014	2004–2009	People's Republic of China	RCT	IIIA (N2)	66	69	1.49 (1.01–2.20)	0.69 (0.46–1.04)	Concurrent	9	/
Kim et al[25]	2014	2000–2011	Korea	Retrospective	N2	38	178	0.75 (0.48–1.17)	1.50 (0.94–2.39)	Sequential	/	18
Zou et al[28]	2010	1998–2005	People's Republic of China	Retrospective	III (N2)	104	79	0.63 (0.46–0.86)	0.69 (0.50–0.96)	Sequential	/	19
Douillard et al[27]	2008	1998–2000	USA	Retrospective	N2	48	70	NA	0.93 (0.53–1.64)	Sequential	/	19
Perry et al[26]	2007	NA	France	RCT	IIIA (N2)	19	18	1.16 (0.37–3.65)	0.95 (0.33–2.74)	Sequential	8	/

Abbreviations: CI, confidence interval; CT, chemotherapy; DFS, disease-free survival; HR, hazard ratio; MINORS, Methodological Index for Non-Randomized Studies; NA, non-available; OS, overall survival; POCRT, postoperative chemoradiotherapy; POCT, postoperative chemotherapy; RCT, randomized controlled trial; RT, radiation therapy.

Qualität der Studien:

- Overall, the methodological quality of the two RCTs was good.
- Points were lost because the blinding of patients and investigators was not reported. The Methodological Index for Non-Randomized Studies scores of the other four non-RCTs ranged from 18 to 20 points and were deemed acceptable.

Studienergebnisse:

- Meta-analysis:

- a greater OS benefit associated with POCRT versus POCT (HR =0.87, 95% CI: 0.79–0.96, P=0.006).
- DFS was investigated in four studies, including two RCTs and two retrospective reviews. There was no significant difference in DFS between the two groups, as the combined HR for DFS. Significant heterogeneity (χ2=12.08, P=0.007, I2=75.2%) was observed between these four studies.

- Subgroup analyses:
  - The subgroup analysis was performed on two RCTs (n=172 patients), which demonstrated that adding radiation did not benefit either OS or DFS with adequate homogeneity.
  - In the four retrospective reviews, additional PORT significantly improved OS (HR =0.89, 95% CI: 0.81–0.98) with modest homogeneity (χ2=7.18, P=0.067, I2=58.2%). These four reviews did not report on how additional PORT affected DFS. The results of this pooled analysis demonstrated that the application of PORT in an adjuvant setting significantly improves DFS (HR =0.67, 95% CI: 0.52–0.86) with adequate homogeneity (I2=0.0%).

Anmerkung/Fazit der Autoren

In summary, compared to adjuvant chemotherapy alone, adjuvant chemotherapy plus radiotherapy significantly improves OS but not DFS in N2 NSCLC patients. Due to the lack of studies and especially of RCTs on the use of POCRT in N2 NSCLC, the therapeutic benefit of this strategy remains unclear. Thus, large-scale, multicenter clinical trials are urgently needed.

Liu T et al., 2019 [12].

Comparative efficacy and safety for different chemotherapy regimens used concurrently with thoracic radiation for locally advanced non-small cell lung cancer: a systematic review and network meta-analysis.

Fragestellung

to account for missing head-to-head data and multiple regimen comparisons. The study aimed to perform a network meta-analysis to estimate the relative efficacy and tolerability of different agents based concurrent chemotherapy regimens, attempting to identify the most preferable regimen used concurrently with thoracic radiation for locally advanced NSCLC.

Methodik

Population:

- locally advanced NSCLC

Intervention/Komparator:

- different agents based concurrent chemotherapy regimens (siehe Ergebnisteil)

Endpunkte:

- OS, PFS

Recherche/Suchzeitraum:

- PubMed, Embase, Cochrane Library, Web of Science, and major international scientific meetings were searched for the available studies published before October 31, 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 RCTs with 2975 patients randomized to receive the twelve categories of treatments were included in the meta-analysis
- The twelve treatments were EP, PC, pemetrexed-cisplatin/carboplatin (PP), S-1-cisplatin (SP), uracil/tegafur (UFT)-cisplatin (UP), vinorelbine-cisplatin (NP), gemcitabine-cisplatin (GP), docetaxel-cisplatin (DP), irinotecan-carboplatin (IC), mitomycin-vindesine-cisplatin (MVP), PC + cetuximab (PC-Cet), and PP + cetuximab (PP-Cet), respectively

Qualität der Studien:

- Seven trials were judged to be unclear risk of bias, as they had more than three domains indicating as unclear risk. The remaining trials were rated with a low risk of bias. No trial was judged to be high risk of bias.

Studienergebnisse:

- Conventional pairwise meta-analysis
  - Direct comparison meta-analysis was feasible only for EP vs. PC. EP was more effective than PC in terms of OS (HR = 0.85, 95% CI: 0.77–0.94) and PFS (HR = 0.66, 95% CI: 0.47–0.95).
  - No significant differences were observed in ORR and overall SAEs between the two arms. PC had a trend higher risk of causing grade≧3 radiation pneumonitis (RP) than EP (OR = 0.48, 95% CI: 0.21–1.1; P = 0.08).
- Network meta-analysis

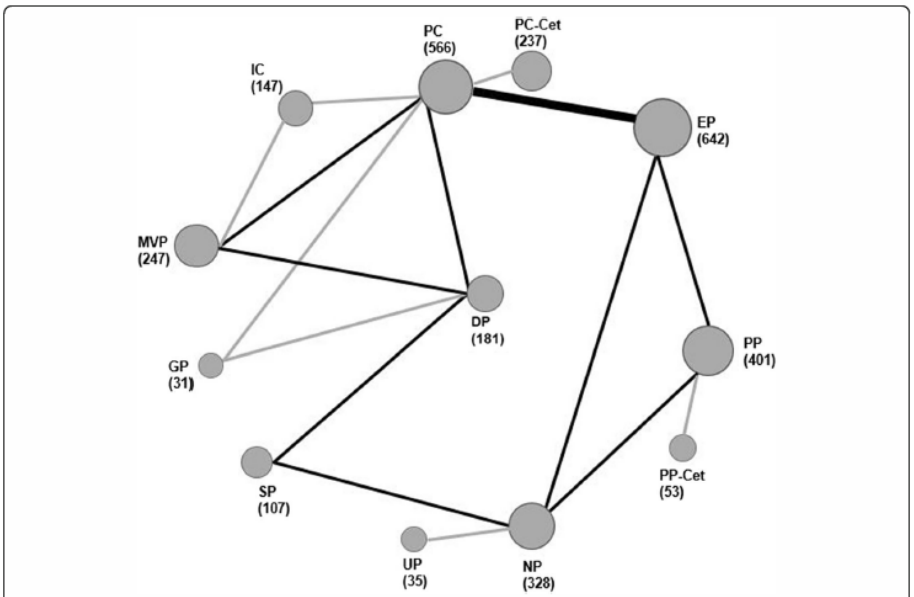


Fig. 2 Network of eligible comparisons for the Bayesian network meta-analysis. The size of the nodes is proportional to the number of patients (in parentheses) randomized to receive the treatment. The width of the lines is proportional to the number of trials (beside the line) comparing the connected treatments. EP, etoposide-cisplatin; PC, paclitaxel-cisplatin/carboplatin; SP, S-1-cisplatin; UP, uracil/tegafur (UFT)-cisplatin; PP, pemtrexed-cisplatin/carboplatin; NP, vinorelbine-cisplatin; DP, docetaxel-cisplatin; IC, irinotecan-carboplatin; GP, gemcitabine-cisplatin; MVP, mitomycin-vindesine-cisplatin; Cet, cetuximab

- In term of OS, EP showed a trend significant advantage over PC (HR = 0.83, 95% CI: 0.65–1.0; P =0.05). Other regimen comparisons did not produce statistically significant differences.
- With regard to PFS and ORR, no significant differences were observed for all regimen comparisons.
- As for overall SAEs and RP, MVP showed significantly higher risk of SAEs in comparison to each regimen except GP and PC-Cet. DP was more likely to cause SAEs than SP (OR = 0.51, 95% CI: 0.30–0.86) and UP (OR = 0.38, 95% CI: 0.15–0.96). NP resulted in a higher and a trend higher risk of SAEs than UP (OR = 0.47, 95% CI: 0.24–0.94) and SP (OR = 0.63, 95% CI: 0.38–1.0; P = 0.05), respectively. PC had a trend higher risk of grade≧3 RP than PP (OR = 0.053, 95% CI: 0.00064–1.0; P = 0.05) and EP (OR = 0.19, 95% CI: 0.016–1.1; P = 0.06).

Anmerkung/Fazit der Autoren

Based on efficacy and tolerability, SP is likely to be the most preferable regimen used concurrently with thoracic radiation for locally advanced NSCLC, followed by UP and PP. GP and PC-Cet appeared to be the worst and second-worst regimens for this population. Further direct head-to-head, well-designed, prospective studies are needed to confirm these findings.

Chen Y et al., 2018 [4]

Comparing the benefits of chemoradiotherapy and chemotherapy for resectable stage III A/N2 non-small cell lung cancer: a meta-analysis.

Fragestellung

updated meta-analysis by specifically including only randomized control trials of patients exclusively diagnosed with stage IIIA/N2 NSCLC, to ascertain whether addition of preoperative radiotherapy to chemotherapy would improve the survival outcome in these stage IIIA/N2 patients.

Methodik

Population:

- resectable stage IIIA (T1–3, N2, M0) non-small cell lung cancer patients

Intervention/Komparator:

- preoperative induction chemoradiotherapy with chemotherapy alone in the treatment

Endpunkte:

- tumor response, pathological complete response, mediastinal nodule downstaging, pathological complete response of mediastinal lymph node, progression free survival (PFS), and OS at 2, 4, and 6 years

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Library databases up to July 2017

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- three RCTs were finally included in our meta-analysis
- 334 patients, where 157 underwent induction chemotherapy and 177 underwent induction chemoradiotherapy

Charakteristika der Population:

Table 1 Summary of three randomized controlled trials included in the meta-analysis

Study	Publication year	Stage	CT regimen	CRT regimen	Number of patients		Median survival	
					CT	CRT	CT	CRT
Girard et al.	2010	cN2 IIIA	GC	VP or PC + Con RT(46Gy)	14	32	24.2	–
Katakami et al.	2012	pN2 IIIA	DC	DC + Con RT(40Gy)	28	28	29.9	39.6
Pless et al.	2015	pN2 IIIA	DP	DP + Seq RT(44Gy)	115	117	26.2	31.7

Abbreviations: *GC* gemcitabine + cisplatin, *DP* docetaxel + cisplatin, *DC* docetaxel + carboplatin, *VP* vinorelbine + cisplatin, *PC* paclitaxel + carboplatin, *Seq RT* sequential radiochemotherapy, *Con RT* concomitant radiochemotherapy

Qualität der Studien:

- The quality of the RCT by Girard et al. was of level B, due to incomplete outcome data that resulted in high attrition bias. However, the other two RCTs were assessed as level A.

Studienergebnisse:

- The pooled results demonstrated that, in comparison to induction chemotherapy, induction chemoradiotherapy has a significant benefit in tumor response, mediastinal downstaging, and pathological complete response of mediastinal lymph nodes.

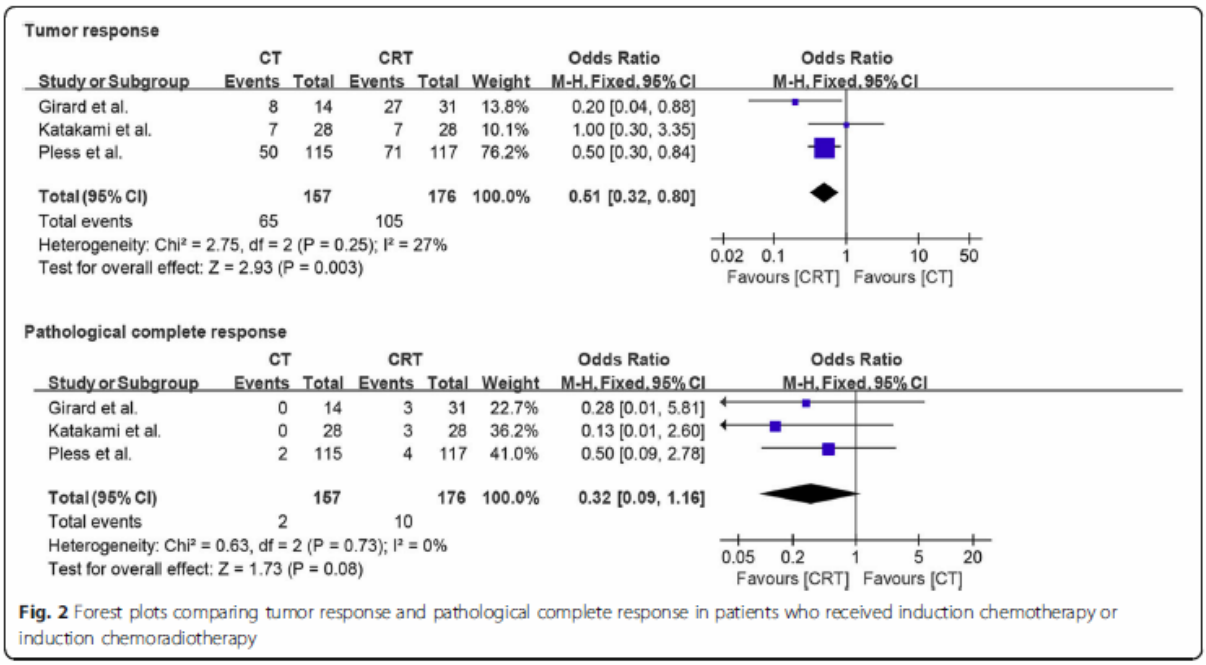


Fig. 2 Forest plots comparing tumor response and pathological complete response in patients who received induction chemotherapy or induction chemoradiotherapy

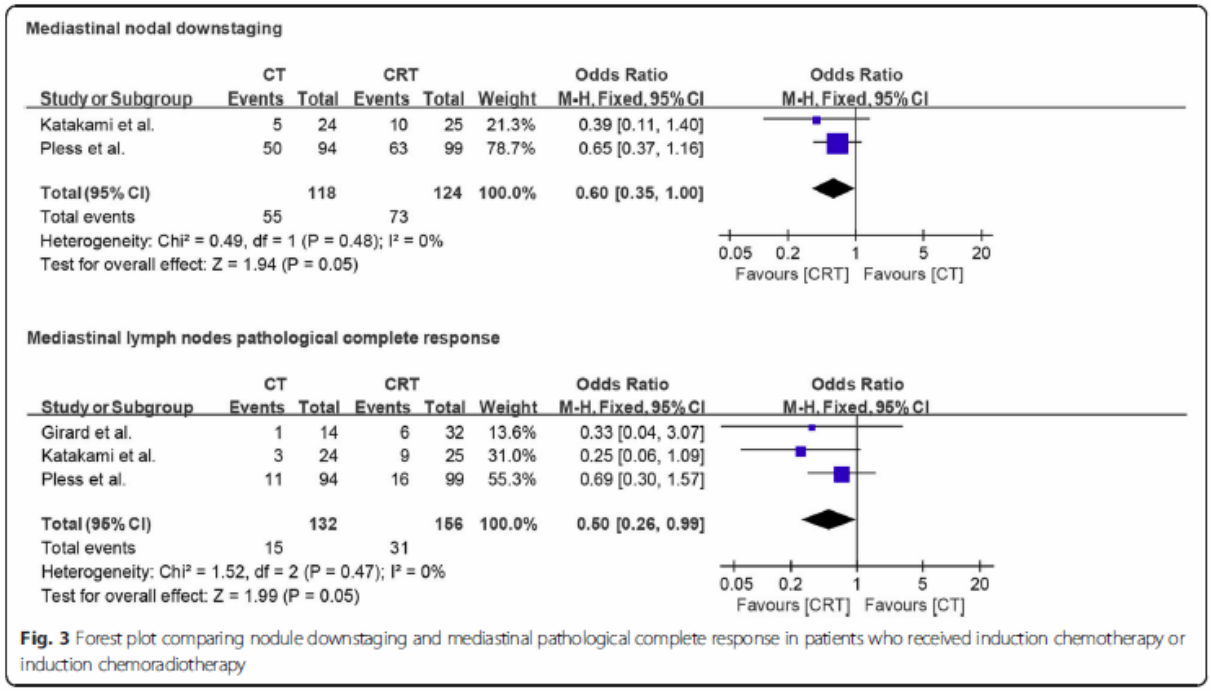


Fig. 3 Forest plot comparing nodule downstaging and mediastinal pathological complete response in patients who received induction chemotherapy or induction chemoradiotherapy

- In addition, no more peri-intervention mortality was detected in patients from chemoradiotherapy group, and a higher number of patients from this group had R0 resection.

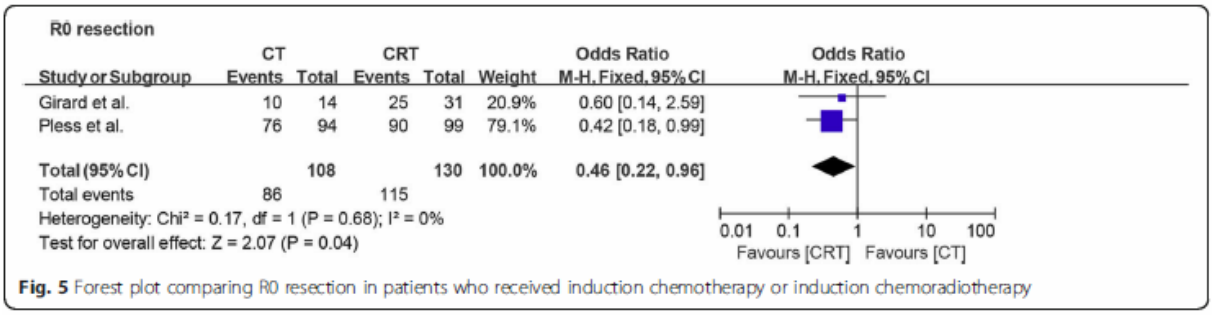


Fig. 5 Forest plot comparing R0 resection in patients who received induction chemotherapy or induction chemoradiotherapy

- However, our results did not show any difference between overall survival and progression-free survival after 2, 4, and 6 years of follow-ups, in patients undergoing radiation therapy vs. induction chemotherapy.

Fazit der Autoren

Preoperative chemoradiotherapy, as compared to chemotherapy alone, can increase the pathological response and mediastinal downstaging in patients with resectable stage IIIA/N2 NSCLC, without increasing peri-interventional mortality. However, it does not improve long-term survival. Going forward, additional high-quality randomized controlled trials should be undertaken to further confirm the validity of our results.

Chen YY et al., 2015 [5]

Meta-analysis of postoperative adjuvant chemotherapy without radiotherapy in early stage non-small cell lung cancer.

Fragestellung

to assess the effect of postoperative chemotherapy without radiotherapy in early stage patients.

Methodik

Population:

- histologically confirmed NSCLC (including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) with radically resection;
- pathologic stage I and/or II with an Eastern Cooperative Oncology Group performance status of 2 or less;
- no major organ (liver, kidney, or heart) dysfunction;
- no preoperative anticancer treatment;
- no other cancer site besides lung;

Intervention/Komparator:

- surgery plus postoperative chemotherapy versus surgery alone

Endpunkte:

- OS, DFS, adverse events

Recherche/Suchzeitraum:

- RCTs published after January 1, 1992 were enrolled

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Fourteen trials with 3,923 patients

Qualität der Studien:

- All RCTs included a statement about randomization, and detailed descriptions were listed in eleven trials. Blinding of participants and personnel assessment was only described in one trial.[14] However, it was not always feasible to blind in studies involving surgery. No quality difference was observed in the included RCTs except for in the study of Strauss et al which had a higher risk than others due to early termination (data not shown).

Studienergebnisse:

- Compared with surgery alone, postoperative chemotherapy significantly improved DFS and OS with HR of 0.71 (P=0.005) and 0.74 (P,0.00001), respectively.

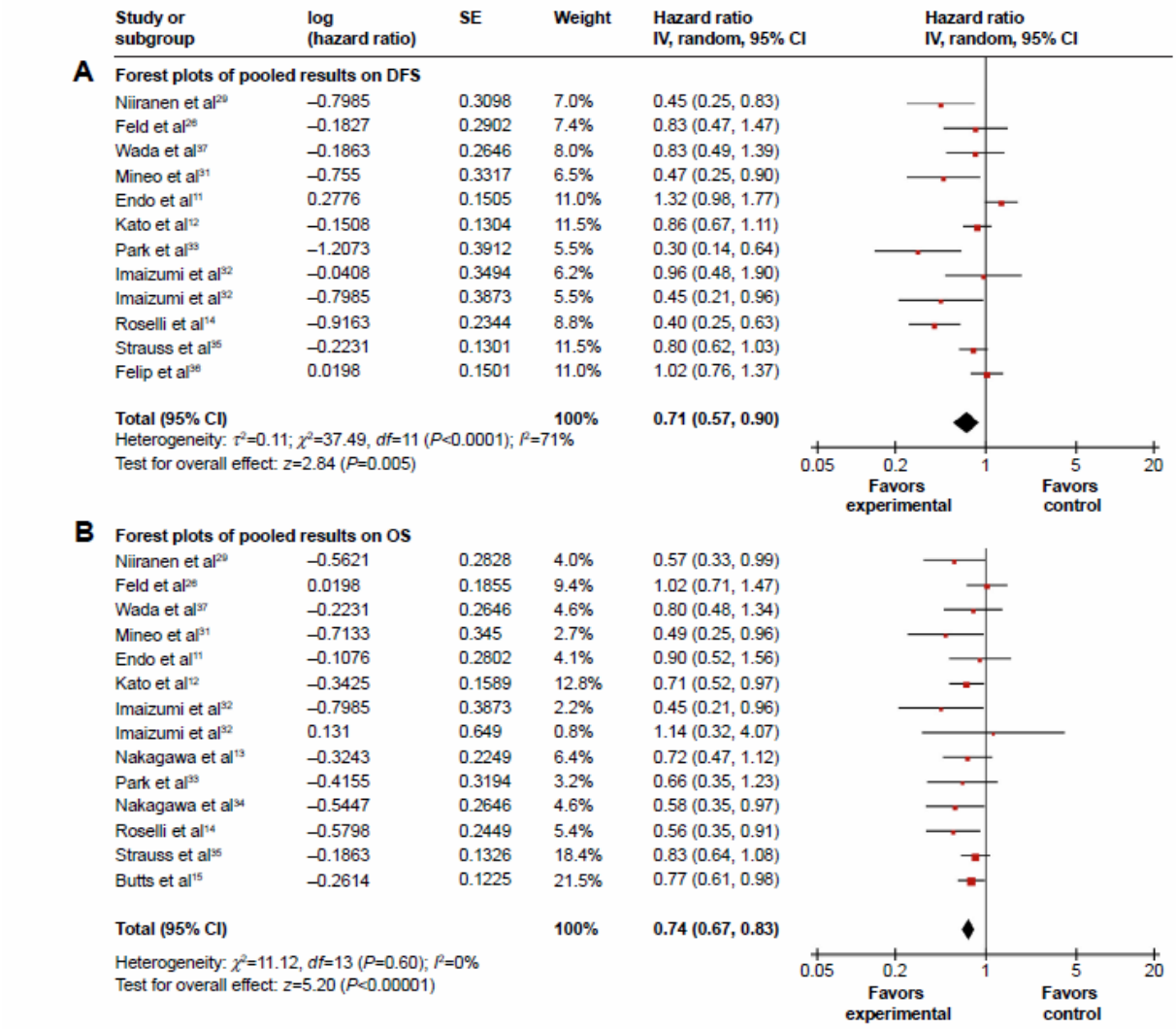


Figure 2 Forest plots of pooled results on DFS (**A**) and OS (**B**) comparing chemotherapy and control groups.
Abbreviations: CI, confidence interval; DFS, disease-free survival; IV, inverse variance; OS, overall survival; SE, standard error.

- Subgroup analysis by regimen:
  - Cisplatin-based chemotherapy showed results consistent with the overall DFS, which favored postoperative chemotherapy (HR: 0.61, 95% CI, 0.47–0.81, *P*=0.0005). There was evidence of publication bias by Egger's test (*P*=0.029). However, single UFT chemotherapy did not show a DFS benefit without publication bias.
  - Compared with control groups, both cisplatin-based (HR: 0.75, P,0.0001) and single UFT (HR: 0.72, P=0.002) chemotherapy showed survival benefits in the combined OS analysis. Some evidence of publication bias was identified in DFS analysis of cisplatin-based chemotherapy by Begg's (P=0.048) and Egger's tests (P=0.045). ITC demonstrated that cisplatin-based chemotherapy had a longer DFS than single UFT chemotherapy (HR: 0.587, 95% CI, 0.387–0.89, P=0.04), but it failed to show difference of OS between the two regimen types.
- Subgroup analysis of survival by stage: (…) An evaluation of DFS for stage IA and II patients could not be conducted due to the limited data. (…) In this analysis, the OS data on stage II patients was not sufficient to perform a reliable analysis.

- Grade 3–4 neutropenia, nausea and vomiting, thrombocytopenia, and infection were observed in 16.4%, 10.7%, 2%, and 1.9% of the patients who received cisplatin-based chemotherapy, respectively. Incidence of other adverse effects like sensory neuropathy, anemia, and diarrhea were less than 1%. Incidence of grade 3 or 4 nausea/vomiting and anorexia were observed in 0.8% and 0.7% of the patients who received single UFT chemotherapy, respectively. Only four treatment-related deaths (0.2%) occurred in chemotherapy group (data not shown). These findings indicate that chemotherapy toxicity was mild and well tolerated.

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis demonstrates the positive efficacy of postoperative chemotherapy alone in stage I–II, I, and IB NSCLC with mild toxicity, but a significant benefit was not found in IA patients. Meanwhile, this meta-analysis also indicates that efficacy of cisplatin-based chemotherapy is comparable to single UFT chemotherapy in OS, but better than single UFT chemotherapy in DFS; however, further studies are needed to verify these findings in clinical practice. In view of few trials that have assessed the effects of postoperative chemotherapy alone in stage IA and II patients, we suggest that more trials should be conducted to confirm the effectivity of postoperative chemotherapy in stage IA and II NSCLC patients in future.

Zhang T et al., 2018 [20]

Meta-analysis of adjuvant chemotherapy versus surgery alone in T2aN0 stage IB non-small cell lung cancer

Fragestellung

Meta-analysis aimed to compare the effects of adjuvant chemotherapy versus surgery alone in patients with Stage IB NSCLC.

Methodik

Population:

- Patients with NSCLC Stage IB

Intervention:

- Adjuvant platinum-based chemotherapy after surgery

Komparator:

- Surgery alone (included wedge resection, lobectomy and pneumonectomy)

Endpunkte:

- OS, disease-free survival (DFS)

Recherche/Suchzeitraum:

- PubMed, EMBASE, Medline and Cochrane Library from inclusion to July 2016

Qualitätsbewertung der Studien:

- Quality of RCTs was independently assessed by two investigators, and discrepancies were resolved by consensus. Using Cochrane approach to analyse the allocation concealment. Investigators evaluated blinding of outcome assessment and adequate description of withdrawals. Randomization method assessed by Jadad et al. Intention to treat analysis was assessed.

Ergebnisse

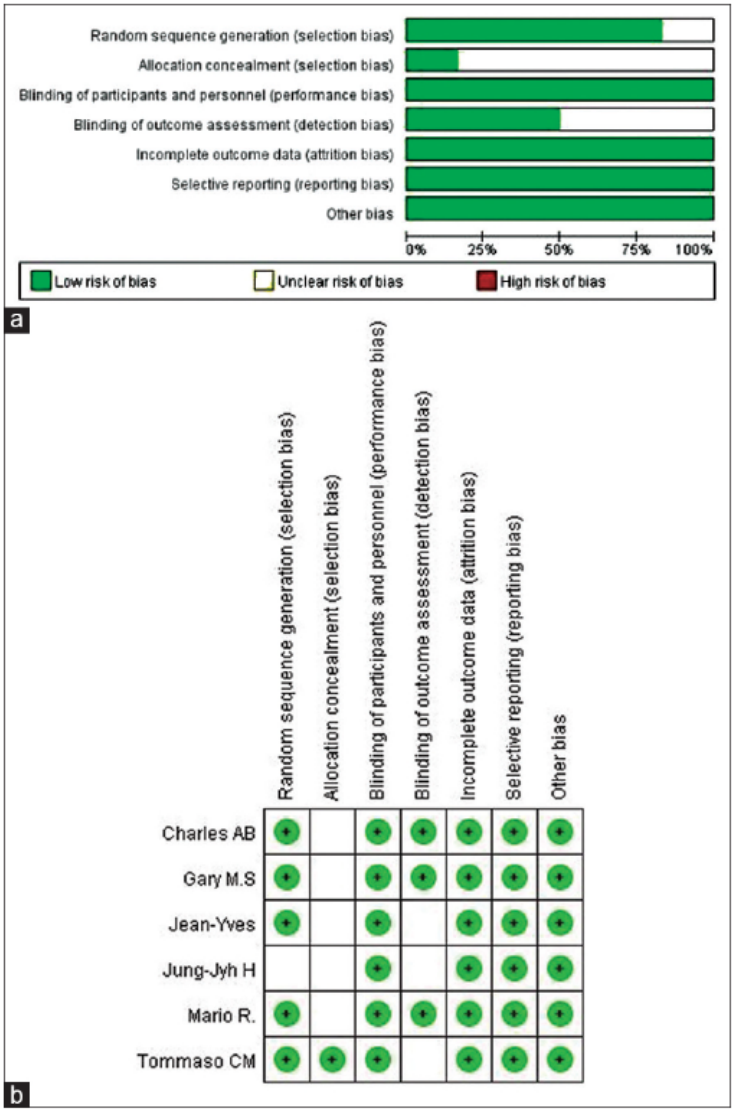
Anzahl eingeschlossener Studien:

- 6 RCTs, 2007 patiens included

Charakteristika der Population:

- Two of the six trials also included patients with stage IB-IIIA and IB-II; OS and DFS of stage IB could not be obtained in these two trials; these data were not included in the meta-analysis
- Meta-analysis based on four trials with 685 patients

Qualität der Studien:



Studienergebnisse:

- OS (n= 4 Studien): Adjuvant chemotherapy was beneficial to the patients with stage IB disease, RR = 1,19; 95 %-CI: 1,03-1,37; p = 0,02
- DFS (n= 4 Studien): 5-year DFS RR = 1,36; 95 %-CI: 1,13-1,63; p = 0,001

Anmerkung/Fazit der Autoren

Adjuvant chemotherapy after surgery, as compared with surgery alone, can definitely improve OS and PFS-rates. In other words, distant survival could be prolonged with adjuvant chemotherapy due to decreasing locoregional progression and distant recurrences. Thus, we positively recommend that this treatment strategy should be considered in the patients with Stage IB NSCLC.

Kommentare zum Review

- According to the results heterogeneity tests showed high-level heterogeneity.

3.4 Leitlinien

AWMF, 2018 [9,10]

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF))

Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms. S3-Leitlinie; Langversion 1.0.

Leitlinienorganisation/Fragestellung

Therapieempfehlungen des Lungenkarzinoms

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

LoE/GoR

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) inception cohort studies; CDR validated in different populations	SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centers	SR (with homogeneity) of prospective cohort studies	SR (with homogeneity) of Level 1economic studies
1b	Individual RCT (with narrow Confidence Interval)	Individual inception cohort study with > 80 % follow-up; CDR validated in a single population	Validating cohort study with good reference standards; or CDR tested within one clinical centre	Prospective cohort study with good follow-up	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or	SR (with homogeneity) of Level >2 diagnostic studies	SR (with homogeneity) of Level 2b and better studies	SR (with homogeneity) of Level >2 economic studies

		untreated control groups in RCTs			
2b	Individual cohort study (including low quality RCT; e.g., <80 % follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR or validated on split-sample only	Exploratory cohort study with good reference standards; CDR after derivation, or validated only on split-sample or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity) of case-control studies		SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study; or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
4	Case-series (and poor quality cohort and case-control studies)	Case-series (and poor quality prognostic cohort studies)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Tabelle 6: Schema der Empfehlungsgraduierung für Empfehlungen 2018

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Tabelle 7: Konsensusstärke

Konsenstärke	Prozentuale Zustimmung
Starker Konsens	> 95 % der Stimmberechtigten
Konsens	> 75 – 95 % der Stimmberechtigten
Mehrheitliche Zustimmung	50 – 75 % der Stimmberechtigten
Dissens	< 50 % der Stimmberechtigten

Sonstige methodische Hinweise

- Für den Aktualisierungsprozess 2013-2018 erfolgte keine systematische Aufarbeitung und Berücksichtigung existierender evidenzbasierter Leitlinien.

Empfehlungen

Postoperative Chemotherapie

Eine adjuvante Chemotherapie mit einem cisplatinhaltigen Regime führte in 3 randomisierten Studien bei Patienten im Stadium IB-IIIA (inzidentell) zu einer signifikanten Verlängerung der Überlebenszeit mit einem Anstieg der 5-Jahres Überlebensrate von 4,1 % - 15 %. Dieser Effekt wurde bestätigt durch zwei Metaanalysen, wobei die Datenlage im Stadium IB nicht konsistent ist.

Bei älteren Patienten, Patienten mit Z.n. Pneumonektomie und Patienten im reduzierten Allgemeinzustand war die Verträglichkeit schlechter und die Dosis der applizierten Chemotherapie erniedrigt, so dass auf diese Faktoren genauso wie auf ein postoperatives Zeitintervall von maximal 60 Tagen zu achten ist.

8.20.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **A**	Nach R0-Resektion und systematischer Lymphknotendissektion sollten Patienten im Stadium II bzw. $IIIA_1$ / $IIIA_2$ (vgl. 8.5.1) in gutem Allgemeinzustand (ECOG 0/1) eine adjuvante Chemotherapie erhalten.	

8.21.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **D**	Im Stadium IB wird eine individuelle Therapieentscheidung unter Berücksichtigung der Komorbidität, des Alters und der kardiopulmonalen Funktion empfohlen.	

8.22.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **D**	Die adjuvante Chemotherapie sollte nach Abschluss der Wundheilung innerhalb von 60 Tagen nach der Resektion beginnen.	

8.23.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **A**	In der adjuvanten Chemotherapie wird die Gabe einer cisplatinhaltigen Kombination über 4 Zyklen empfohlen. In der Mehrzahl der positiven Studien wurde eine Kombination mit Vinorelbin verwendet.	

8.24.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **D**	Bei Patienten mit bedeutsamer Komorbidität aufgrund der vorangegangenen Resektion oder vorbestehender Erkrankungen wird empfohlen, die adjuvante Chemotherapie in einer interdisziplinären Behandlungsgruppe mit entsprechender Erfahrung in der Durchführung von multimodalen Therapien durchführen zu lassen.	

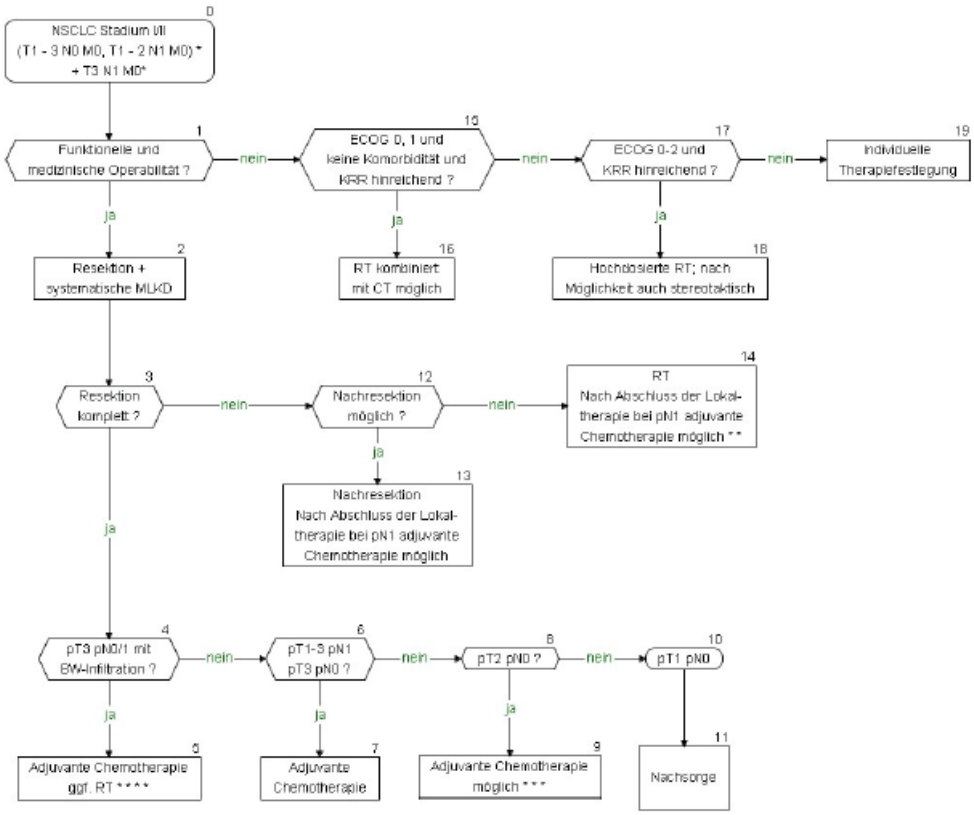
Postoperative Radiotherapie und Radio-/Chemotherapie

Weder eine postoperative Radiotherapie noch eine postoperative Chemoradiotherapie führen nach der vorliegenden Evidenz im Stadium I oder II zu einer Verlängerung der Überlebens- bzw. der rezidivfreien Überlebenszeit.

8.25.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **B**	Im Stadium I, II wird nach R0-Resektion eine adjuvante Strahlentherapie nicht empfohlen.	

8.26.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **B**	Im Stadium I, II wird nach R0-Resektion eine simultane adjuvante Chemoradiotherapie nicht empfohlen.	

8.3.6. Algorithmus Stadium I/II + T3N1M0



MLKD: Mediastinale Lymphknotendissektion; RT: Radiotherapie; CT: Chemotherapie, KRR: Kardiorespiratorische Reserve; BW-Infiltration: Brustwandinfiltration.

Operabilität und Resektabilität wird präoperativ seitens Thoraxchirurgie gemeinsam mit Pneumologie beurteilt. Bis auf pT1 pN0 werden alle Patienten postoperativ bzw. bei Inoperabilität in einer interdisziplinären Konferenz (zumindest mit Pneumologie, Onkologie, Thoraxchirurgie, Radioonkologie und diagnostischer Radiologie) vorgestellt und das weitere Vorgehen (Indikation Radiotherapie; Indikation Chemotherapie) festgelegt und dokumentiert.

* sensitiv mediastinal gestagt gemäß Diagnostikkapitel.

** pN1 impliziert ein hohes systemisches Rezidivrisiko; nach R0-Resektion profitieren Patienten mit pN1 (pT1-3) am besten von einer adjuvanten Chemotherapie, daher kann diese im Einzelfall auch nach Abschluss der Lokaltherapie bei vorangegangener R1/2-Resektion empfohlen werden.

*** pT2pN0 zeigt in explorativen Subgruppenanalysen der adjuvanten Therapiestudien keinen konsistenten Überlebensvorteil mit adjuvanter Therapie. Eine Empfehlung kann im Einzelfall ausgesprochen werden.

Stadium III (T1-3N2 / T1-3N3 / T4N0-3):

Die ursprünglich von Mountain beschriebene und von der UICC übernommene Stadienunterteilung in **IIIA** und IIIB unterscheidet technisch **resektable** - jedoch prognostisch ungünstige - Tumorausbreitungen im Stadium IIIA von in der Regel technisch inoperablen Erkrankungsausdehnungen (Stadium IIIB). (…)

Ergänzt 2017: Für die neue TNM-Klassifikation in der 8. Auflage wurden die Subklassen daher neu gruppiert und drei Untergruppen des Stadiums III definiert. **Stadium IIIA umfasst die lokal fortgeschrittenen, im Rahmen eines multimodalen Therapieansatzes jedoch in der Regel resektablen Tumorkonstellationen T1-2 N2, T3 N1 und T4 N0-1**; Stadium IIIB die in der Regel inoperablen Untergruppen T1-2 N3 und T3-4 N2 und Stadium IIIC die lokal fortgeschrittenen Tumorbefunde (T3,4 N3) ohne Rolle für die Chirurgie. (…)

8.34.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **B**	Die Unterscheidung von Subgruppen speziell im Stadium IIIA(N2) ist für Therapiewahl und Prognose von großer Bedeutung.	

8.35.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **A**	Eine adjuvante Chemotherapie wird im Stadium III (T1-3) mit inzidentellem N2-Status ($IIIA_1$ bzw. $IIIA_2$) nach kompletter Resektion (R0) und systematischer Lymphknotendissektion empfohlen.	

8.36.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **D**	Ein Beginn der Chemotherapie nach Abschluss der Wundheilung innerhalb von 60 Tagen nach Resektion wird empfohlen.	

8.37.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **A**	In der adjuvanten Chemotherapie wird die Gabe einer cisplatinhaltigen Kombination über 4 Zyklen empfohlen. In der Mehrzahl der positiven Studien wurde eine Kombination mit Vinorelbin verwendet.	

8.38.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **D**	Bei Patienten mit bdeutsamer Komorbidität aufgrund der vorangegangenen Resektion oder vorbestehender Erkrankungen wird empfohlen, die adjuvante Chemotherapie in einem interdisziplinär ausgerichteten Behandlungskontext mit entsprechender Erfahrung in der Durchführung von multimodalen Therapien durchführen zu lassen.	

8.39.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **B**	Für Patienten mit mediastinalem Lymphknotenbefall im Stadium $IIIA_1$ bzw. $IIIA_2$ sollte zusätzlich zur adjuvanten Chemotherapie die Indikation zur postoperativen Mediastinalbestrahlung geprüft werden.	

8.40.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **B**	Die Bestrahlung sollte bis spätestens 4 Wochen nach Abschluss der adjuvanten Chemotherapie beginnen und eine Dosis von 50 – 60 Gy nach CT gestützter 3-dimensionaler Bestrahlungsplanung umfassen. Komorbiditäten müssen bei diesem Vorschlag ausreichend berücksichtigt werden.	

8.41.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **D**	Patienten im Stadium $IIIA_3$ sollten präferentiell im Rahmen von Studien zur weiteren Definition des Therapiealgorithmus behandelt werden.	

8.42.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **B**	Außerhalb von Studien können Patienten im Stadium $IIIA_3$ und technisch resektabler Tumorausdehnung individuell mit einem Induktionsprotokoll (Induktionschemotherapie oder Induktionschemostrahlentherapie) behandelt und anschließend operiert werden. Grundsätzlich erfordern solche Behandlungsansätze zur sicheren Indikationsstellung vor Therapiebeginn eine interdisziplinäre Diskussion und Festlegung (zumindest Beteiligung von Pneumologie, Onkologie, Thoraxchirurgie und Radioonkologie und diagnostischer Radiologie). Präoperativ soll die Indikation zur Resektion im interdisziplinären Kontext gleichermaßen überprüft werden. Die Durchführung sollte an Zentren mit entsprechender Erfahrung und hinreichendem Behandlungsvolumen erfolgen.	

8.43.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **B**	In den Subgruppen T4N0 und T4N1 (jeweils Stadium IIIA) ist die primäre Operation bzw. die Integration der Operation in das Gesamtbehandlungskonzept bei medizinischer und funktioneller Operabilität in folgenden Fällen möglich: Karinabefall, resektabler Trachealbefall, resektabler Befall des Atrium, Infiltration der V. cava oder der Pulmonalarterie, ipsilobäre Metastase im tumortragenden Lungenlappen.	

8.44.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **B**	Nach Operation und R0-Resektion sollte im Stadium $IIIA_3$ bei alleiniger Induktionschemotherapie eine mediastinale Radiotherapie erfolgen. Bei Induktionschemostrahlentherapieprotokollen sollten nach R0-Resektion keine weitere postoperative Radiotherapie durchgeführt werden.	

8.45.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **A**	Patienten im Stadium $IIIA_3$ – insbesondere bei multiplem N2-Befall – können gleichermaßen mit einer Kombination aus Strahlentherapie und Chemotherapie (definitive Chemo-/Radiotherapie) behandelt werden.	

Erläuterungen:

- Adjuvante Radiotherapie: Eine adjuvante Chemotherapie wird im Stadium IIIA mit inzidentellem N2-Status (IIIA1 bzw. IIIA2) empfohlen. Für Patienten mit mediastinalem Lymphknotenbefall im Stadium IIIA1 bzw. IIIA2 sollte zusätzlich zur adjuvanten Chemotherapie die Indikation für eine postoperative Mediastinalbestrahlung geprüft werden. Die Bestrahlung sollte etwa 4 Wochen nach Abschluss der adjuvanten Chemotherapie beginnen und eine Dosis von 50–60 Gy nach CT gestützter 3-dimensionaler Bestrahlungsplanung umfassen. Komorbiditäten müssen bei diesem Vorschlag ausreichend berücksichtigt werden.
- In dem Stadium IIIA (T4N0/1) ist die primäre Operation bei medizinischer und funktioneller Operabilität in folgenden Fällen möglich: Karinabefall, minimaler Trachealbefall, minimaler Befall des rechten Atrium, Infiltration der V. cava oder der Pulmonalarterie, ipsilobäre Metastase im tumortragenden Lungenlappen.

(…)

- Therapiewahl
  - Chemotherapie: Die weitaus meisten Daten sind bisher für Cisplatin-basierte Chemotherapieschemata publiziert worden. Routinemäßiger Einsatz Carboplatin-basierter Protokolle ist hinsichtlich Effektivität insbesondere in der simultanen Therapiephase mit der Strahlentherapie in diesem Zusammenhang noch nicht ausreichend abgesichert. Präliminäre Daten sind für neuere Chemotherapiekombinationen (Cisplatin/Paclitaxel, Cisplatin/Vinorelbin) mitgeteilt worden. Abschließend dürfte die größte Datenbasis für eine Kombination aus Cisplatin und Etoposid vorhanden sein.
  - Radiotherapie: Die präoperativ eingesetzte Strahlentherapie verwendet typische Dosen zwischen 40 und 50 Gy. Konventionelle Fraktionierungen (1,8 bzw. 2,0 Gy pro die, qd)

sind beschrieben worden, ebenfalls aber auch hyperfraktioniert akzelerierte Radiotherapieverfahren (45 Gy, 2 x 1,5 Gy, bid). Ein Standard-Behandlungsprotokoll kann derzeit nicht abgeleitet werden.

- o Chemoradiotherapie: Die weitaus meisten klinischen Daten liegen bisher für die Kombination aus zwei Zyklen Cisplatin und Etoposid mit Strahlentherapie bis 45 Gy vor.

- Zusammenfassung und Empfehlungen: Eine präoperative Chemoradiotherapie ist im Stadium IIIA3 durchführbar und führt im Vergleich zur alleinigen präoperativen Chemotherapie wohl zu höheren klinischen und histopathologischen Ansprechraten ohne dass bisher ein signifikanter Überlebensvor-teil gesichert werden konnte. Eine Überlegenheit gegenüber einer definitiven simultanen Chemoradiotherapie ist hinsichtlich des Gesamtüberleben nicht ableitbar; allerdings zeigte bei primär resektablen Patienten ein Ansatz aus Radio-/Chemotherapie gefolgt von Operation im Vergleich zur definitiven Radio-/Chemotherapie ohne Operation eine signifikante Verlängerung des progressionsfreien Überlebens (Evidenzgrad 1b). Damit verbunden sind jedoch auch nennenswerte Morbiditäts- und Letalitäts-raten – insbesondere in Verbindung mit einer Pneumonektomie. Daher bedürfen solche Behandlungsansätze vor Therapiebeginn der interdisziplinären Diskussion und Festlegung (Beteiligung von Pneumologie, Thoraxonkologie, Thoraxchirurgie und Radioonkologie). Letztlich sollte die Durchführung an Zentren mit entsprechender Erfahrung und hinreichendem Behandlungsvolumen gebunden sein.

<u>Kombination aus Chemo- und Strahlentherapie im Stadium III</u>

8.50.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **A**	Patienten im Stadium $IIIA_3$ – insbesondere bei multiplem N2-Befall – können mit einer Kombination aus Strahlentherapie und Chemotherapie (definitive Chemo-/Radiotherapie) behandelt werden.	

8.51.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **A**	Patienten im Stadium $IIIA_4$ / IIIB sollten – wenn Allgemeinzustand und Tumorausdehnung dies zulassen – eine Kombination aus Strahlentherapie und Chemotherapie erhalten.	

8.52.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad **D**	Für selektionierte Patienten im Stadium $IIIA_4$ / IIIB kann im begründeten Ausnahmefall ein multimodaler Behandlungsansatz unter Integration der Operation (möglichst nur in Studien) erfolgen.	

8.53.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad A	Im direkten Vergleich ist bei geeigneten Patienten die simultane Radio-/Chemotherapie der sequentiellen überlegen. Bei der Patientenselektion ist auf Komorbiditätsspektrum und Allgemeinzustand zu achten.	

8.54.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad B	Die Sequenz von Chemotherapie gefolgt von definitiver Strahlentherapie kann im Vergleich zur alleinigen Strahlentherapie sowohl medianes Überleben als auch 5-Jahresüberlebensraten signifikant verbessern.	

8.55.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad B	Für die sequentielle und simultane Chemostrahlentherapie sollten cisplatinbasierte Chemotherapieprotokolle gewählt werden (Kombinationspartner bei simultaner Therapie in der Regel Etoposid oder Vincaalkaloid).	

8.56.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad B	Sowohl bei der sequentiellen als auch simultanten Behandlung werden typischerweise zwei Zyklen einer voll-dosierten cisplatinhaltigen Kombinationschemotherapie (Zyklusintervall 3-4 Wochen) appliziert.	

8.57.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad D	Angesichts des hohen systemischen Rezidivrisikos nach definitiver Chemostrahlentherapie kann im Einzelfall eine konsolidierende platinbasierte Kombinationschemotherapie aufgrund der im historischen Vergleich vielversprechenden Daten des Kontrollarms in einer multizentrischen randomisierten Phase-III-Studie (INT 0139) durchgeführt werden.	

8.58.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad A	Im Vergleich zur alleinigen simultanen Chemo- / Radiotherapie ist der Stellenwert einer zusätzlichen konsolidierenden Chemotherapie in randomisierten Studien bisher nicht belegt. Die zusätzliche Konsolidierung in Form der Monotherapie mit einem Taxan nach stattgehabter Radio-/Chemotherapie führt zu deutlicher und inakzeptabler Toxizität und wird nicht empfohlen.	

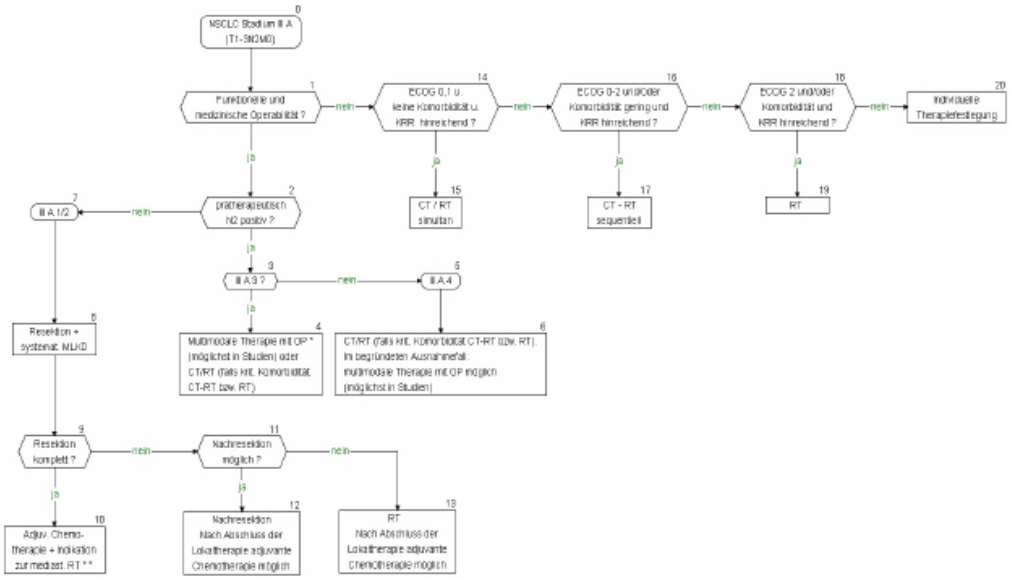
Erläuterungen:

- Patienten im Stadium IIIA4/IIIB sollten – wenn Allgemeinzustand und Tumorausdehnung dies zulassen – eine Kombination aus Strahlentherapie und Chemotherapie erhalten.

- Die Chemotherapie simultan zur Strahlentherapie verbessert im Vergleich zur alleinigen Radiotherapie sowohl medianes Überleben als auch 5-Jahresüberlebensraten signifikant und klinisch relevant. Bei der Patientenselektion ist auf Komorbiditätsspektrum und Allgemeinzustand zu achten.
- Die Sequenz von Chemotherapie gefolgt von definitiver Strahlentherapie kann im Vergleich zur alleinigen Strahlentherapie sowohl medianes Überleben als auch 5-Jahres-überlebensraten signifikant verbessern. Im direkten Vergleich ist bei geeigneten Patienten die simultane Radio-/ Chemotherapie der sequentiellen Therapie überlegen.
- Präferentiell sollten cisplatinbasierte Chemotherapieprotokolle für die simultane wie auch sequentielle Chemostrahlentherapie gewählt werden (z.B. Cisplatin/Etoposid oder Cisplatin/Vincaalkaloid). Während der definitiven Chemostrahlentherapie sollten zwei Zyklen einer voll-dosierten cisplatinhaltigen Kombinationschemotherapie im Abstand von 3-4 Wochen appliziert werden. Die fortlaufende (wöchentlich bzw. täglich) niedrig dosierte Chemotherapie simultan zur Bestrahlung wird außerhalb von Studien nicht bzw. nur dann empfohlen, wenn weder ein simultaner noch ein sequentieller Therapie-ansatz mit einem Zyklusintervall von 3-4 Wochen aufgrund von Komorbidität möglich ist.
- Die Strahlentherapie sollte eine Dosis zwischen 60 und 66 Gy bei einmal täglicher Fraktionierung haben. Die Zeitdauer hängt von der Einzelfraktionierung ab und liegt bei 6-7 Wochen. Eine Unterbrechung der Strahlentherapie sollte vermieden werden.
- Für eine zusätzliche konsolidierende Chemotherapie nach definitiver Chemostrahlentherapie existieren bislang keine randomisierten Daten, die einen Vorteil bezüglich des Gesamtüberlebens nachweisen. Eine Monotherapie mit Taxan als Konsolidierungsbehandlung nach definitiver Chemostrahlentherapie verbesserte nicht die Überlebensergebnisse und erhöhte signifikant Mortalität/ Morbidität.

8.5.6. Algorithmus Stadium IIIA

Cave: Stadieneinteilung nach der 7. Auflage der TNM-Klassifikation



Indikationsstellung und Therapie nur in Zentren. Grundsätzlich bedürfen die o.g. Behandlungsansätze zur sicheren Indikationsstellung vor Behandlungsbeginn wie auch im Staging vor der Operation der interdisziplinären Diskussion und Festlegung (Konferenz mit Dokumentation; Beteiligung von zumindest Pneumologie, Onkologie, Thoraxchirurgie, Radioonkologie und diagnostischer Radiologie). Insbesondere im Stadium IIIA3/IIIA4 sollte die Durchführung an Zentren mit entsprechender Erfahrung und hinreichendem Behandlungsvolumen erfolgen.

Subklassifikation nach Robinson:

III A1/2: inzidenteller N2-Status;III A3: prätherapeutischer gesicherter N2-Status, jedoch nicht III A4 ;III A4: positive Lymphknoten (LK) > 2cm mit Kapseldurchbruch ; N2 in multiplen Positionen; Gruppen multipler positiver LK (1-2 cm) in einer Position;

MLKD: Mediastinale Lymphknotendissektion; KRR: Kardiorespiratorische Reserve;CT: Chemotherapie;RT: Radiotherapie

* Multimodale Therapie mit Operation (OP): CT-OP-RT; CT-RT/CT-OP; CT/RT-OP; OP-CT-RT; vgl. Kap. 8.5.2.2.1.

* * Vgl. Kap. 8.5.2.1.2.

NICE, 2019 [15]

National Institute for Health and Care Excellence (NICE)

Lung cancer: diagnosis and management

Leitlinienorganisation/Fragestellung

Treamtent recommendations for Lung Cancer.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

LoE/GoR

- Methodenreport beschreibt systematische Evidenzaufbereitung und Konsensusprozesse (je nach Bedarf fomal oder informal) - eigene Checklisten - Anwendung von GRADE - GoR schlagen sich in den Formulierungen wider "To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.“ Interventionen werden mittels GRADE-Methodik bewertet und in SoF-Tabellen dargestellt.

Recommendations

Radical radiotherapy for people not having surgery

- (…) 1.4.27 For people with stage I–IIA (T1a–T2b, N0, M0) NSCLC who decline surgery or in whom any surgery is contraindicated, offer SABR. If SABR is contraindicated, offer either conventional or hyperfractionated radiotherapy. [2019]
- 1.4.28 For eligible people with stage IIIA NSCLC who cannot tolerate or who decline chemoradiotherapy (with or without surgery), consider radical radiotherapy (either conventional or hyperfractionated). [2019]
- 1.4.29 For eligible people with stage IIIB NSCLC who cannot tolerate or who decline chemoradiotherapy, consider radical radiotherapy (either conventional or hyperfractionated). [2019]

Combination treatment for non-small-cell lung cancer

- 1.4.32 Consider chemoradiotherapy for people with stage II or III NSCLC that are not suitable for or decline surgery. Balance potential benefit in survival with the risk of additional toxicities. [2011]

- 1.4.33 Ensure that all people for whom multimodality treatment is potentially suitable (surgery, radiotherapy and chemotherapy in any combination) are assessed by a thoracic oncologist and by a thoracic surgeon. [2011]
- 1.4.34 Offer postoperative chemotherapy to people with good performance status (WHO 0 or 1) and T1a–4, N1–2, M0 NSCLC. [2011]
- 1.4.35 Consider postoperative chemotherapy for people with good performance status (WHO 0 or 1) and T2b–4, N0, M0 NSCLC with tumours greater than 4 cm in diameter. [2011]
- 1.4.36 Offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy. [2011]
- 1.4.37 For people with stage I–II NSCLC that are suitable for surgery, do not offer neoadjuvant treatment outside a clinical trial. [2011, amended 2019]
- 1.4.38 Ensure eligible people have the benefit of detailed discussion of the risks and benefits of adjuvant chemotherapy. [2011]
- 1.4.39 Treat Pancoast tumours in the same way as other types of NSCLC. Offer multimodality therapy according to resectability, stage of the tumour and performance status of the person. [2011]
- 1.4.40 For people with operable stage IIIA–N2 NSCLC who can have surgery and are well enough for multimodality therapy, consider chemoradiotherapy with surgery. [2019]
- 1.4.41 Discuss the benefits and risks with the person before starting chemoradiotherapy with surgery, including that:
  - chemoradiotherapy with surgery improves progression-free survival
  - chemoradiotherapy with surgery may improve overall survival. [2019]
- 1.4.42 For people with stage IIIA–N2 NSCLC who are having chemoradiotherapy and surgery, ensure that their surgery is scheduled for 3 to 5 weeks after the chemoradiotherapy. [2019]

Kris MG et al., 2017 [7]

American Society of Clinical Oncology (ASCO)

Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non-Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update

Siehe auch: Bradbury, P. et al. (2017) [2]

Leitlinienorganisation/Fragestellung

What is the role of adjuvant systemic therapy and adjuvant radiation therapy in patients with completely resected stage I to IIIA non–small-cell lung cancers (NSCLCs)?

Methodik

<u>Grundlage der Leitlinie</u>

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;

- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- To update the evidence base, a search for any additional adjuvant radiation therapy trials that were published between March 2013 and June 2016 was conducted.

LoE/GoR

Type of Recommendation	Definition
Evidence-based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in an online data supplement.
Informal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No Recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Recommendations

- Adjuvant systemic therapy for NSCLCs:

- Recommendation 1.1. Stage IA: Adjuvant chemotherapy is not recommended (Type: Evidence based and Panel consensus; Harms outweigh benefits; Evidence quality: Moderate; Strength of recommendation: Strong).
- Recommendation 1.2. Stage IB: Adjuvant cisplatin-based chemotherapy is not recommended for routine use. A postoperative multimodality evaluation, including a consultation with a medical oncologist, is recommended to assess benefits and risks of adjuvant chemotherapy for each patient. Factors other than tumor stage to consider when making a recommendation for adjuvant chemotherapy are outlined after the adjuvant systemic therapy section of this guideline (Type: Evidence based and Panel consensus; Benefits outweigh harms, especially in patients with larger tumors; Evidence quality: Intermediate; Strength of recommendation: Moderate).
- Recommendation 1.3. Stages IIA/B and IIIA: Adjuvant cisplatin-based chemotherapy is recommended (Type: Evidence based and Panel consensus; Benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

- Adjuvant radiation therapy for NSCLCs:
  - Recommendation 2.1. Stages IA/B and IIA/B: Adjuvant radiation therapy is not recommended (Type: Evidence based and Panel consensus; Harms outweigh benefits; Evidence quality: Intermediate; Strength of recommendation: Strong).
  - Recommendation 2.2. Stage IIIA (N2): Adjuvant radiation therapy is not recommended for routine use. A postoperative multimodality evaluation, including a consultation with a radiation oncologist, is recommended to assess benefits and risks of adjuvant radiotherapy for each patient with N2 disease (Type: Evidence based and Panel consensus; Benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Australian Government Cancer Council Australia, 2017 [1]

Australian Government Cancer Council Australia

Clinical practice guidelines for the treatment of lung cancer

Leitlinienorganisation/Fragestellung

What is the role of chemotherapy before surgery in the treatment of operable stage II NSCLC?

What is the clinical benefit of the addition of surgery to definitive chemoradiotherapy in stage IIIA (N2) NSCLC?

What is the clinical benefit of neoadjuvant chemotherapy for patients with stage III operable NSCLC?

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;

- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

LoE/GoR

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP (practice point)	Where no good-quality evidence is available but there is consensus among Guideline committee members, consensus-based guidance points are given, these are called "Practice points"

Level of evidence was assigned according to the following criteria from the NHMRC Evidence Hierarchy[1]:

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study

Recommendations

What is the role of radiotherapy after surgery in the treatment of operable stage I NSCLC?

Recommendation	Grade
In patients who have had complete resection of stage I NSCLC, postoperative radiotherapy is not recommended. Last reviewed December 2015	A

Practice point(s)
In the absence of any evidence regarding the treatment of incompletely resected stage I disease (positive margins) unsuitable for further surgery, expert consensus opinion recommends that radiotherapy be given to the site of residual disease using the same dose and technique as if no resection had been performed. Last reviewed December 2015

What is the role of postoperative radiotherapy (PORT) in resected stage III NSCLC?

Recommendation	Grade
Post-operative radiation therapy in patients with pN2 disease is not recommended for routine use because of the lack of prospective randomised clinical trial data demonstrating an improvement in survival. The use of PORT could be considered in selected patients with pN2 disease. Last reviewed December 2015	C

Practice point(s)
Post-operative radiation therapy may be considered in the setting of a positive margin. Last reviewed December 2015

What is the role of prophylactic cranial irradiation in patients with stage III NSCLC?

Recommendation	Grade
In patients with stage III NSCLC, the use of prophylactic cranial irradiation is not recommended. Last reviewed December 2015	B

What is the clinical benefit of adjuvant chemotherapy for patients with stage III operable NSCLC?

Recommendation	Grade
Patients who have a good performance status (WHO 1, 2) and completely resected stage III non-small cell lung cancer should be offered adjuvant cisplatin-based chemotherapy. Last reviewed December 2015	A
Patients with superior sulcus NSCLC may be considered for induction chemoradiotherapy. Last reviewed December 2015	C

Practice point(s)
Caution is advised in recommending adjuvant cisplatin-based chemotherapy to good performance status patients who are 70 years of age or older and/or who have clinically significant cardio-respiratory or renal co-morbidities. Last reviewed December 2015

Patients with resectable stage III non-small cell lung cancer, who are being considered for preoperative chemotherapy and surgery or surgery and postoperative chemotherapy, should have their treatment plan reviewed in a lung cancer-specific multidisciplinary meeting. The recommended treatment plan may need to be individualized to take account of such patient-specific factors as treatment preference, availability and timing of surgery, and geographically remote location.

Last reviewed December 2015

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 1 of 12, January 2020) am 07.01.2020

#	Suchfrage
1	[mh “Carcinoma, Non-Small-Cell Lung”]
2	(((non NEXT small) OR nonsmall) NEXT cell NEXT lung):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions* OR malignan*):ti,ab,kw
4	#1 OR (#2 AND #3)
5	#4 with Cochrane Library publication date from January 2015 to present

Systematic Reviews in Medline (PubMed) am 07.01.2020

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[mh]
2	((((non[tiab]) AND small[tiab]) OR nonsmall[tiab]) AND cell[tiab]) AND lung[tiab]
3	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesions*[tiab]) OR malignan*[tiab]
4	#1 OR (#2 AND #3)
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review[ti] OR meta-analysis [pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review [tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw] AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR

	(systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
6	((#5) AND ("2015/01/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 07.01.2020

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[mh]
2	((((non[tiab]) AND small[tiab]) OR nonsmall[tiab]) AND cell[tiab]) AND lung[tiab]
3	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesions*[tiab]) OR malignan*[tiab]
4	#1 OR (#2 AND #3)
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
6	(((#5) AND ("2015/01/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

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