Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-063-z Pembrolizumab

Stand: Mai 2024

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

Pembrolizumab
[zur neoadjuvanten und anschließend zur adjuvanten Behandlung des resezierbaren NSCLC mit hohem Rezidivrisiko]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Prä-operative (neoadjuvante) Strahlentherapie Post-operative (adjuvante) Strahlentherapie (Stadium III)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: - Nivolumab: Beschluss vom 01.02.2024 - Atezolizumab: Beschluss vom 05.01.2023
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:	
Pembrolizumab L01FF02 Keytruda	<u>Anwendungsgebiet laut Zulassung:</u> Pembrolizumab ist in Kombination mit Platinbasierter Chemotherapie zur neoadjuvanten und anschließend als Monotherapie zur adjuvanten Behandlung des resezierbaren nicht-kleinzelligen Lungenkarzinoms mit hohem Rezidivrisiko bei Erwachsenen angezeigt (hinsichtlich Selektionskriterien siehe Abschnitt 5.1).
Zytostatika	
Vinorelbin L01CA04 Navelbine	Vinorelbin ist bei erwachsenen Patienten angezeigt zur Behandlung von: als **adjuvante Behandlung** von nicht-kleinzelligem Bronchialkarzinom in Kombination mit einer platinbasierten Chemotherapie
Antikörper	
Atezolizumab L01FF05 Tecentriq	<u>Nicht-kleinzelliges Lungenkarzinom (non-small cell lung cancer, NSCLC) im Frühstadium</u> 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 (siehe Abschnitt 5.1 zu den Auswahlkriterien).
Nivolumab L01FF01 Opdivo	<u>Neoadjuvante Behandlung des NSCLC</u> Opdivo ist in Kombination mit platinbasierter Chemotherapie für die **neoadjuvante Behandlung** des resezierbaren nicht-kleinzelligen Lungenkarzinoms mit Tumorzell-PD-L1-Expression ≥ 1 % bei Erwachsenen mit hohem Rezidivrisiko indiziert (Auswahlkriterien siehe Abschnitt 5.1).
Pembrolizumab L01FF02 Keytruda	<u>Nicht-kleinzelliges Lungenkarzinom (non small cell lung carcinoma, NSCLC)</u> Keytruda ist als Monotherapie zur **adjuvanten Behandlung** des nicht-kleinzelligen Lungenkarzinoms mit hohem Rezidivrisiko nach vollständiger Resektion und Platin-basierter Chemotherapie bei Erwachsenen angezeigt (hinsichtlich Selektionskriterien siehe Abschnitt 5.1).

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V
Vorgang: 2024-B-063z (Pembrolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	10. April 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

ALK	Anaplastic Lymphoma Kinase
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CI/KI	Konfidenzintervall
CRS	Neoadjuvant chemotherapy followed by surgery and adjuvant radiotherapy
CrI	Kredibilitätsintervall
CSC	Neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy
DFS	Disease-free survival
EBMC	Evidence Based Medicine Committee
EGFR	Epidermal Growth Factor Receptor
G-BA	Gemeinsamer Bundesausschuss
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LA	Locally advanced
LRFS	Local-regional recurrence survival
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
NMA	Netzwerkmetaanalyse
NSCLC	Non-small Cell Lung Cancer
OR	Odds Ratio
OS	Overall Survival
PD-L1	Programmed cell death ligand-1
PFS	Progression Free Survival
PORT	Postoperative radiation therapy
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
TNM	Tumor, Nodes, Metastases
WHO	World Health Organization

1 Indikation

Zur neoadjuvanten und anschließend zur adjuvanten Behandlung des resezierbaren nicht-kleinzelligen Lungenkarzinoms mit hohem Rezidivrisiko bei Erwachsenen.

Hinweis zur Synopse: „Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt".

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Nicht-kleinzelliges Lungenkarzinom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.ecosia.org/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 13.06.2023 durchgeführt, die folgende am 27.11.2023. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 2689 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Nachträglich wurde die aktualisierte S3-Leitlinie des Leitlinienprogramms Onkologie vom März 2024 identifiziert und in die Synopse aufgenommen. Basierend darauf, wurden insgesamt 12 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Wang Z et al., 2022 [11].

The efficacy of postoperative radiotherapy for patients with non-small cell lung cancer: An updated systematic review and meta-analysis

Fragestellung

The present study reassessed the overall survival (OS) and disease-free survival (DFS) data to investigate whether PORT can improve survival in resectable non-small cell lung cancer (NSCLC) patients.

Methodik

Population:

- patients with NSCLC who underwent a complete resection

Intervention/Komparator

- PORT

Endpunkte:

- kein PORT

Recherche/Suchzeitraum:

- bis Juli 2021 (PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), and Embase)

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool (RCTs); Newcastle Ottawa scale (Kohortenstudien)

Ergebnisse

Anzahl eingeschlossener Studien:

- n=13 RCTs (N=1318) / n=19 retrospektive Studien

Charakteristika der Population:

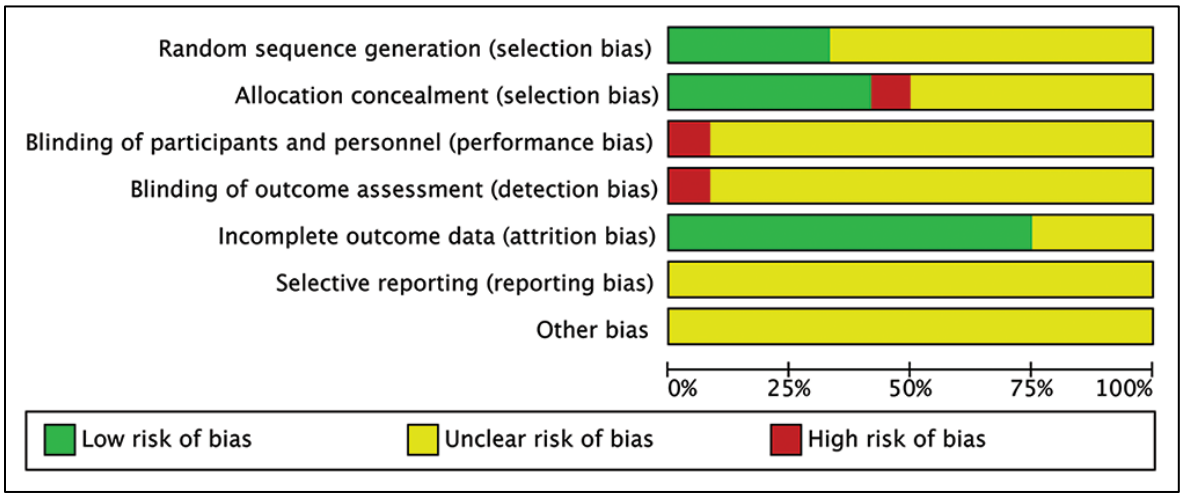
Table 1: Characteristics of the included studies

Author/year	Continent	No. of PORT/non-PORT	Study type	Pathology	Chemotherapy	Dose	NOS score
Weisenburger 1986[18]	America	110/120	RCT	II–III	None	TD::50 Gy	-
Debevec 1996[19]	Europe	35/39	RCT	IIIA-pN2	None	TD: <50 Gy	-
Lafitte 1996[20]	Europe	60/72	RCT	T2 N0 M0	None	-	-
Stephens 1996[21]	Europe	154/154	RCT	T1–2 N1–2 M0	None	TD: <50 Gy	-
Mayer 1997[22]	Oceania	83/72	RCT	T1–3 N0–2	None	-	-
Dautzenberg 1999[23]	Europe	373/355	RCT	I–III	Unknown	TD: 60 Gy	-
Feng 2000[24]	Asia	134/162	RCT	pN1–pN2	Unknown	TD: 60 Gy	-
Trodella 2002[25]	Europe	46/52	RCT	I	Unknown	TD: 50.4 Gy	-
Perry 2007[26]	America	19/18	RCT	IIIA-pN2	POCT	TD: 50 Gy	-
Shen 2013[27]	Asia	66/69	RCT	IIIA-pN2	POCT	TD: 50.4 Gy	-
Sun 2017[28]	Asia	51/50	RCT	IIIA-pN2	POCT	-	-
Hui 2021[8]	Asia	184/180	RCT	IIIA-pN2	POCT	TD: 50 Gy	-
Pechoux 2020[7]	France	249/252	RCT	pN2	Unknown	TD: 54 Gy	
Matsuguma 2008[29]	Asia	45/46	RS	IIIA-pN2	Not clearly stated	MD: 50.4 Gy	7
Zou 2010[30]	Asia	104/79	RS	III-pN2	POCT	MD: 50 Gy	7
Dai 2011[31]	Asia	96/125	RS	IIIA-pN2	POCT	TD: 60 Gy	7
Wisnivesky 2012[32]	America	810/597	RS	IIIA-pN2	POCT	-	7
Kim 2014[33]	Asia	38/111	RS	pN2	POCT	MD: 54 Gy	7
Feng 2015[34]	Asia	70/287	RS	IIIA-pN2	Not clearly stated	MD: 50.4 Gy	7
Robinson 2015[35]	Asia	1850/2633	RS	IIIA-pN2	Not clearly stated	MD: 54 Gy	6
Herskovic 2017[36]	America	516/2175	RS	IIIA-pN2	POCT	MD: 54 Gy	7
Park 2017[37]	Asia	155/85	RS	IIIA-pN2	POCT	TD: 50 Gy	7
Wang 2017[38]	Asia	1198/2179	RS	IIIA-pN2	Unknown	-	7
Wei 2017[39]	Asia	1244/2090	RS	IIIA-pN2	Unknown	-	7
Pang 2017[40]	Asia	9040/5419	RS	IIIA-cN2	Unknown	-	7
Xu 2018[41]	Asia	89/156	RS	pN2	Not clearly stated	MD: 50.4 Gy	6
Kou 2018[42]	Asia	1100/1100	RS	III-pN2	Unknown	-	7
Bao 2019[43]	Asia	112/103	RS	ypN2	Neoadjuvant chemotherapy	-	7
Men 2019[44]	Asia	341/1093	RS	pN2	Unknown	-	7
Wang 2019[45]	Asia	32/87	RS	IIIA-pN2	Not clearly stated	-	7
Gao 2020[46]	Asia	1568/1877	RS	IIIA-pN2	Not clearly stated	-	6
Mankuzhy 2020[47]	America	4269/4779	RS	pN2	Not clearly stated	-	7

MD=median radiation dose, POCT=postoperative chemotherapy, RCT=randomized controlled trial, TD=total radiation dose. None, none of the patients received chemotherapy; unknown, chemotherapy was not reported in the literature, RS=Retrospective cohort study

Qualität der Studien:

- RCTs:



- Retrospektiven Studien → siehe Table 1

Studienergebnisse:

- **OS and DFS**

  - OS data were obtained from 31 studies, and DFS data were extracted from 16 studies. PORT, in comparison with the non-PORT group, improved DFS in NSCLC patients (16 studies with 4111 patients; HR: 0.84, 95% CI: 0.75–0.93). But PORT did not reveal an evident difference in OS when compared with the non-PORT group (31 studies with 49,342 patients; HR: 0.94, 95% CI: 0.86–1.04). The random-effects model was used because the heterogeneity test result of OS was significant, while DFS revealed small heterogeneity when fixed-effect model was used

- **OS by chemotherapy**
  - 10 and five studies reported the efficacy of PORT in NSCLC patients who did not receive POCT and who received POCT, respectively. In patients who did not receive POCT, the combined HR was 1.03 and the 95% CI was 0.84–1.23, indicating no difference. A survival benefit was detected for PORT in patients who underwent POCT (HR: 0.89, 95% CI: 0.80–0.98), and the heterogeneity was moderate.
- **OS by pathology type**
  - PORT significantly promoted OS (HR: 0.89, 95% CI: 0.83–0.96) in patients with pathologic lymph node stage of pN2 (22 studies with 32,719 patients). The remaining studies on patients with other pathologic types (nine studies with 16,623 patients) showed a significant heterogeneity. The pooled HR was 1.10, and the 95% CI was 0.92–1.31.
- **OS by study type**
  - 19 retrospective studies that included 46,682 patients and 12 RCTs that included 2660 patients were used to explore the efficacy of PORT in NSCLC patients. No significant difference was observed in both RCTs and retrospective studies. The pooled HR for OS in retrospective cohort studies was 0.9 (95% CI: 0.80–1.01). The combined HR for RCT studies was 1.07, and the 95% CI was 0.91–1.25

Fazit der Autoren

Our findings illustrate that in the postoperative treatment for patients with stage III-N2 NSCLC, PORT contributes to a significantly increased DFS and LR and may not associate with an improved OS, indicating a cautious selection.

Kommentare zum Review

- Vielzahl an Studien aus Asien
- Gepoolte Effektschätzer unter Einschluss nicht-randomisierter Studien zeigen gleichgerichtete Ergebnisse für OS wie die Effektschätzer für RCT
- Aussagen für OS-Vorteil nach Pathologietyp schwierig, da keine Auswertung nach Studientyp vorliegt.

Lei T et al., 2021 [2].

Postoperative radiotherapy for patients with resectable stage III-N2 non-small cell lung cancer: a systematic review and meta-analysis.

Fragestellung

Meta-analysis to reassess the data of PORT in stage III-N2 NSCLC patients, to figure out whether these patients can benefit from PORT.

Methodik

Population:

- completely resected III-N2 NSCLC patients

Intervention/Komparator

- postoperative radiotherapy ((neo-) adjuvant chemotherapy was allowed)

Endpunkte:

- overall survival (OS) or disease-free survival (DFS) or local-regional recurrence survival (LRFS)

Recherche/Suchzeitraum:

- EMBASE, PubMed, and the Cochrane Library published studies before November 6, 2020

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- n=7 RCTs (N=1318)

Charakteristika der Population:

- All trials included participants with completely resected tumours for which the disease stage was no greater than **IIIB(N2) according to the 8th edition** of the AJCC/TNM staging system.

Author	Recruitment	Phase of trials	Median age	N	RT technique	Chemotherapy Regimen	Primary end-point	DFS	OS	LRFS
				Patients				HR	HR	HR
Debevec et al. (13)	1988 to 1992	NA	59 (35–80)	35	Linac	without chemotherapy	NA	NA	0.91 (0.44–1.87), NA	NA
				39	–			–	–	–
Stephens et al. (14)	July 1986 to October 1993	NA	62	52	megavoltage x-ray /Cobalt	without chemotherapy	NA	NA	0.74 (0.48–1.15), P = 0.18	0.55 (0.29–1.05), P = 0.07
				54	–			–	–	–
Perry et al. (15)	May 1998 to June 2000	Phase III	NA	19	NA	sequential chemoradiotherapy	NA	NA	0.95 (0.40–2.28), P = 0.91	NA
				18	–			–	–	–
Shen et al. (16)	April 2004 to March 2009	Phase III	NA	66	3DCRT with linac	concurrent chemoradiotherapy	OS and DFS	0.67 (0.45–0.98), P = 0.041	0.69 (0.457–1.044), P = 0.073	HR = 0.48(0.28–0.83), P = 0.009
				69	–			–	–	–
Sun et al. (17)	June 2009 to September 2014	Phase II	60 (38–78)	51	3DCRT with linac	concurrent chemoradiotherapy	DFS	0.94 (0.58–1.52), P = 0.400	1.33 (0.71–2.49), P = 0.38	0.75 (0.36–1.58), NA
				50	–			–	–	–
Hui et al. (18)	January 2009 to December 2017	Phase III	NA	184	3D-CRT/sIMRT	sequential chemoradiotherapy	DFS	0.85 (0.65–1.10), 1-sided P = 0.10	1.01 (0.68–1.51), P = 0.94	0.71 (0.51–0.97), P = 0.03
				180	–			–	–	–
Le Pechoux et al. (19)	August 2007 to July 2018	phase III	61 (36–85)	252	3D-CRT	prior (neo)-adjuvant CT	DFS	0.85 (0.67–1.07), P = 0.16	NA	NA
				249	–			–	–	–

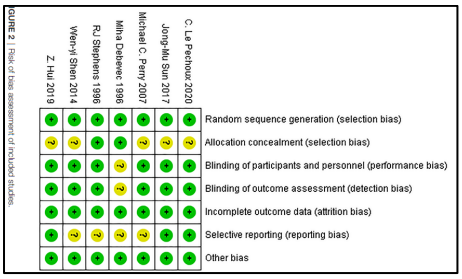
NA, not available.

TABLE 2 | The detail of radiotherapy and chemotherapy of included studies.

Trial	Radiotherapy dose				Prescription Technique	Clinical target volume	Chemotherapy
	Total dose (Gy)	Fractions	Durations (weeks)	Gy/day			
Debevec et al. (13)	30	10 or 12	2	2.5 or 3.0	Linac	isolateral hilum and mediastinum	No chemotherapy
Stephens et al. (14)	40	15	3	2.7	megavoltage X-ray and Cobalt	NA	No chemotherapy
Perry et al. (15)	50	25	5	2.0	NA	the mediastinum, supraclavicular fossae, and ipsilateral hilum	Paclitaxel and carboplatin
Shen et al. (16)	50.4	28	6	1.8	3DCRT with linac	ipsilateral mediastinum, hilum and subcarinal lymph node area	paclitaxel and cisplatin
JongMu Sun et al. (17)	50	25	5	2.0	3DCRT with linac	mediastinal lymphatic stations and the immediately adjacent lymph node stations	Adjuvant paclitaxel and carboplatin
Hui et al. (18)	50	25	6	2.0	3D-CRT/sIMRT	Ipsilateral hilum, subcarinal region and ipsilateral mediastinum	platinum based chemotherapy
Le Pechoux et al. (19)	54	27–30	6	1.8–2.0	3D-CRT	NA	prior (neo)-adjuvant CT was allowed

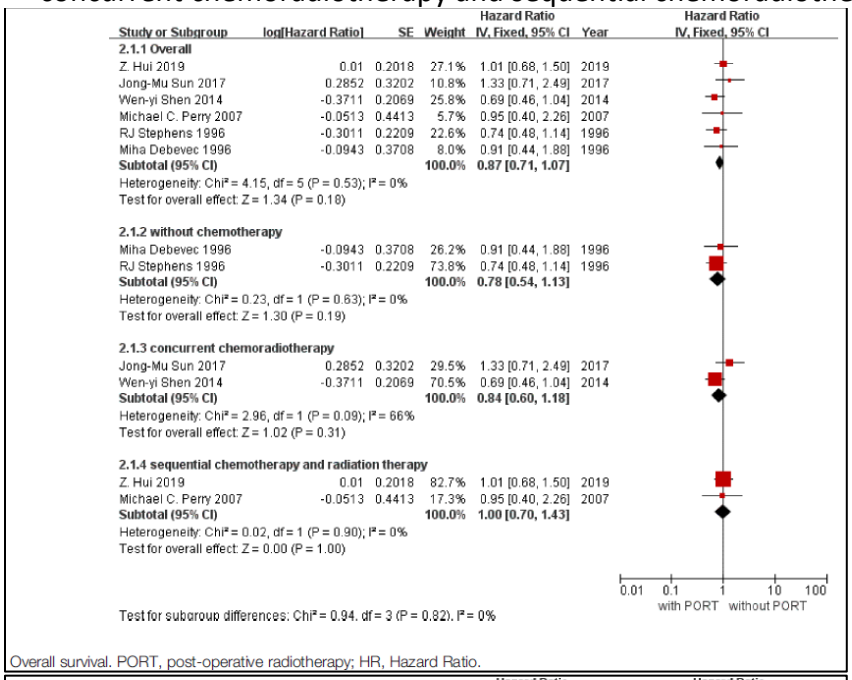
NA, not available.

Qualität der Studien:

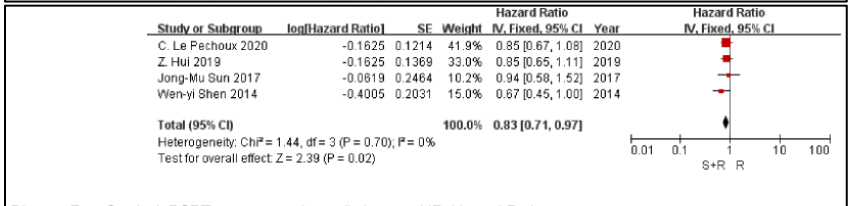


Studienergebnisse:

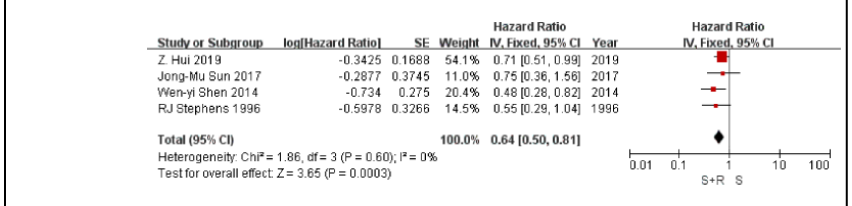
- Analyses show no benefit of PORT on OS (HR, 0.87; 95% CI, 0.71 to 1.07; p = 0.18)
- Significantly different effect of PORT on DFS (HR, 0.83; 95% CI, 0.71 to 0.97; p = 0.02) and LRFS (HR, 0.64; 95% CI, 0.50 to 0.81; p = 0.0003).
- There is not enough evidence of a difference in the effect on survival by the utility of chemotherapy along with PORT though subgroup analysis of no chemotherapy group, concurrent chemoradiotherapy and sequential chemoradiotherapy group.



Overall survival. PORT, post-operative radiotherapy; HR, Hazard Ratio.



Disease Free Survival. PORT, post-operative radiotherapy; HR, Hazard Ratio.



Local-regional recurrence-free survival. PORT, post-operative radiotherapy; HR, Hazard Ratio.

Fazit der Autoren

Our findings illustrate that in the postoperative treatment for patients with stage III-N2 NSCLC, PORT contributes to a significantly increased DFS and LR and may not associate with an improved OS, indicating a cautious selection.

Zhang C et al., 2021 [12].

Short-term outcome of neoadjuvant immunotherapy and chemotherapy in non–small cell lung cancer: A systematic review and meta-analysis

Fragestellung

The aim of the present study was to evaluate the superiority of neoadjuvant immunotherapy compared with standard neoadjuvant chemotherapy in resectable NSCLC in terms of short-term clinical outcomes and surgical outcomes.

Methodik

Population:

- Patients whose tumor was pathologically confirmed as stage I-III NSCLC

Intervention:

- neoadjuvant immunotherapy

Komparator:

- standard neoadjuvant chemotherapy

Endpunkte:

- objective response rate (ORR) of neoadjuvant treatment before surgery and at least 1 of the following clinical outcomes: MPR (viable tumor cells<10%), pathologic complete response (pCR), and complete reports of adverse events (optional for NeoIO, as most of those trials had not been officially published).

Recherche/Suchzeitraum:

- Systematische Recherche bis März 2020 (PubMed, Embase, the Cochrane Central Register of Controlled Trials, the ClinicalTrials.gov database, and Web of Science)

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- n= 10 Phase-II Studien (Immunotherapy–based neoadjuvant treatment; N=405)
- n= 11 Phase-II Studien (Chemotherapy-based neoadjuvant treatment; N=1395)

Charakteristika der Population:

- All included NeoCT trials used cisplatin- or carboplatin-based chemotherapy as neoadjuvant regimens.
- Specifically, the included NeoIO trials included 6 PD-1/PD-L1–based single-agent trials and 5 immunotherapy combination cohorts; the NEOSTARtrial contained both single-agent and dual-agent immunotherapy cohorts.

TABLE 1. Summary of included neoadjuvant immunotherapy and chemotherapy trials

Trial	N	Males, n (%)	Age, y, median (range)/ mean ± SD	Histology (SQC), n (%)	Stage (TNM)	Stage III proportion, n (%)	Neoadjuvant regimen	Treatment cycles	Primary endpoint
Immunotherapy–based neoadjuvant treatment									
Checkmate159[8]	21	10 (47.6)	67 (55-84)	6 (28.6)	I-IIIA (7th)	7 (33.3)	Nivolumab	2	Safety/ outcome
LCMC3[13]	101	47 (46.5)	65 (37-83)	35 (34.7)	IB-IIIB (8th)	46 (45.5)	Atezolizumab	2	MPR
TOP1501*	30	16 (53.3)	72 (47-81)	17 (56.7)	IB-IIIA (7th)	8 (26.7)	Pembrolizumab	2	Safety/ outcome
MK3457-233[15]	13	6 (46.2)	66 (NR)	6 (46.2)	I-IIB (8th)	0	Pembrolizumab	2	Safety
Sintilimab[16]	40	33 (82.5)	62 (47-70)	33 (82.5)	I-IIIB (8th)	18 (45.0)	Sintilimab	2	Safety
NEOSTAR (single)†	23	15 (65.2)	66.1 ± 8.5	10 (43.5)	I-IIIA (7th)	5 (21.7)	Nivolumab	3	MPR
NEOSTAR (comb)†	21	13 (61.9)	65.0 ± 8.3	7 (33.3)	I-IIIA (7th)	4 (19.0)	Nivolumab + ipilimumab	3	MPR
MAC[9]	30	15 (50.0)	67 (62-74)	12 (40.0)	II-IIIA (7th)	23 (76.7)	Atezolizumab + paclitaxel/ carboplatin	4	MPR
NADIM[14]	46	34 (73.9)	63 (41-77)	NR	IIIA (7th)	46 (100.0)	Nivolumab + paclitaxel/ carboplatin	3	2-y PFS
SAKK16/14†	67	35 (52.2)	61 (41-74)	22 (32.8)	IIIA (7th)	67 (100.0)	Durvalumab + docetaxel/ cisplatin	5	1-y EFS
NCT03366766†	13	8 (61.5)	69 (49-80)	9 (69.2)	IB-IIIA (7th)	7 (53.8)	Nivolumab + histology-based chemotherapy	3	MPR
IO-based regimen	405	232 (57.3)	—	157 (38.8)	—	231 (57.0)	—	2-5	—
Chemotherapy-based neoadjuvant treatment									
JCOG9209[17]	31	20 (64.5)	59 (32-74)	7 (22.6)	IIIA	31 (100.0)	Cisplatin/vindesine	3	NR
Chen et al. (2013)[24]	169	132 (78.1)	61 (34-75)	79 (46.7)	I-IIIA	66 (39.1)	Mitomycin/cisplatin/ vindesine	4	OS/PFS
CHEST[23]	129	100 (77.5)	60.6 (37.6-76.3)	48 (37.2)	IA-IIIA	6 (4.7)	Gemcitabine/cisplatin	3	PFS
CSLC0501[27]	97	79 (81.4)	58 (26-75)	NR	IB-IIIA	29 (29.9)	Docetaxel/carboplatin	3	3-y DFS
MRCLU22/NVALT2/ EORTC08012[18]	258	186 (72.1)	62 (37-77)	131 (50.8)	IA-IIIB	21 (8.1)	MVP/MIC/NP/paclitaxel/ carboplatin/gemcitabine/ cisplatin/docetaxel/ carboplatin	3	OS
NACTH III[22]	199	175 (87.9)	65 (35-80)	107 (53.8)	IA-IIB	0	Paclitaxel/carboplatin	3	DFS
SAKK16/00[25]	115	77 (67.0)	59 (30-74)	36 (31.3)	IIIA	115 (100.0)	Cisplatin/docetaxel	3	EFS
GLCCG[21]	260	215 (82.7)	59 (35-69)	148 (56.9)	IIIA-B	260 (100.0)	Cisplatin/etoposide	3	PFS
GINEST (GC)[19]	12	5 (41.7)	61.5 (42-83)	5 (41.7)	IA-II	0	Gemcitabine/cisplatin	3	pCR
GINEST (GP)[19]	35	20 (57.1)	63 (33-79)	17 (48.6)	IA-II	0	Gemcitabine/paclitaxel	3	pCR
GINEST (GCb)[19]	40	21 (52.5)	63.5 (36-82)	12 (30.0)	IA-II	0	Gemcitabine/carboplatin	3	pCR
Zhao et al. (2016)[26]	10	9 (90.0)	58 (36-63)	3 (30.0)	IIIA	10 (100.0)	Vinorelbine/cisplatin	2	RR/CBR/ TRR
JCOG0204[20]	40	NR	NR	10 (25.0)	IB-II	0	Cisplatin/docetaxel	2	1-y DFS
Chemotherapy-based regimen	1395	1039 (74.5)	—	603 (43.2)	—	538 (38.6)	—	2-4	—

SD, Stable disease; *SQC*, squamous cell carcinoma; *MPR*, major pathologic response; *PFS*, progression-free survival; *EFS*, event-free survival; *NR*, not reported; *OS*, overall survival; *DFS*, disease-free survival; *MVP*, Mitomycin/Vinblastine/Cisplatin; *MIC*, Mitomycin/Ifosfamide/Cisplatin; *NP*, Cisplatin/Vinorelbine; *pCR*, pathologic complete response; *RR*, response rate; *CBR*, clinical benefit rates; *TRR*, tumor regression rate. *Study reported at the 2020 AATS meeting. †Studies reported at the 2020 ASCO meeting.

Qualität der Studien:

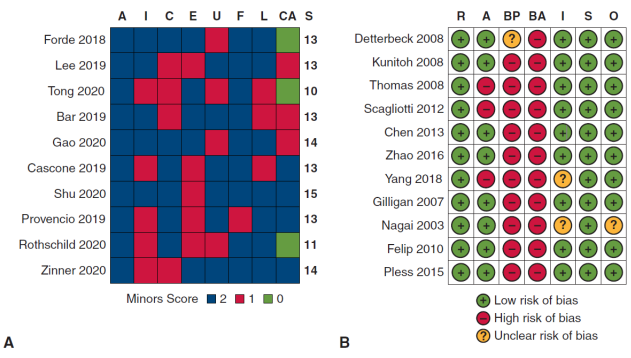


FIGURE E7. Risk of bias assessment for neoadjuvant immunotherapy and chemotherapy trials. In A: A, a clearly stated aim; I, inclusion of consecutive patients; C, prospective collection of data; E, Endpoint appropriate to the aim of study; U, unbiased assessment of the study endpoint; F, Follow-up period appropriate to the aim of the study; L, loss to follow-up <5%; CA, prospective calculation of the study size; R, random sequence generation. In B: A, allocation concealment; BP, blinding of participants and personnel; BA, blinding of outcome assessment; I, incomplete outcome data; S, selective reporting; O, other bias.

Studienergebnisse:

- Patients who received (PD-1/PD-L1 inhibitors (NeoIO) alone (13.3%; 95% confidence interval [CI], 9.0%-19.3%) had the lowest ORR compared with those who received NeoIO plus chemotherapy (CT) (62.5%; 95% CI, 54.4%-70.0%) or CT alone (41.6%; 95% CI, 36.8%-46.7%) (NeoIO vs CT, P<.001; NeoIO CT vs CT, P<.001).
- Receipt of NeoIO CT (36.2%; 95% CI, 19.2%-57.6%) was associated with an elevated pCR rate compared with receipt of NeoIO alone (10.6%; 95% CI, 6.5%-16.9%; P < .001) or standard CT (7.5%; 95% CI, 5.7%-9.8%; P < .001). Neoadjuvant CT (87.2%; 95% CI, 74.9%-94.0%) was associated with a lower R0 resection rate compared with NeoIO alone (92.7%; 95% CI, 83.4%-97.0%; P .360) or NeoIO CT (91.6%; 95% CI, 84.3%-95.7%; P .409).
- Meta-regression showed that a higher proportion of stage III patients was correlated with decreased surgical resection and R0 resection rates, whereas no impact was observed with neoadjuvant immunotherapy.

Anmerkung/Fazit der Autoren

Current data suggest that compared with neoadjuvant chemotherapy, immunotherapy-based regimens may provide superior pathological response along with a higher rate of complete resection. Immunotherapy combined with chemotherapy in neoadjuvant chemotherapy may be a more favorable clinical option. Further randomized controlled trials are warranted to provide long-term results of neoadjuvant immunotherapy for localized NSCLC and help guide clinical practice.

Pang L-L et al., 2022 [6].

Investigation of the optimal platinum-based regimen in the postoperative adjuvant chemotherapy setting for early-stage resected non-small lung

Fragestellung

Hence, we conducted this systematic review and network meta-analysis (NMA) aiming to compare the efficacy and safety of different platinum adjuvant chemotherapy regimens.

Methodik

Population:

- Patients with completely **resected NSCLC (squamous and non-squamous) at stage IB–IIIA**

Intervention/ Komparator:

- postoperative platinum chemotherapy regimen with observation-controlled group or those concerning two platinum chemotherapy regimens head-to-head comparison; given that vinorelbine, etoposide, pemetrexed, docetaxel, paclitaxel, gemcitabine, vindesine are currently commonly used in the routine clinical practice, the counterpart of the platinum doublet including these above-mentioned drugs were considered eligible; and a platinum triplet must be a platinum doublet combined with anti-angiogenesis drug

Endpunkte:

- relapse-free survival (RFS), OS, 2-year, 3-year, 5-year RFS rate and OS

Recherche/Suchzeitraum:

- Systematische Recherche bis März 2021 (PubMed, EMBASE, and The Cochrane Library, Web of Science and Scopus)

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- n= 20 RCTs (N=5483)

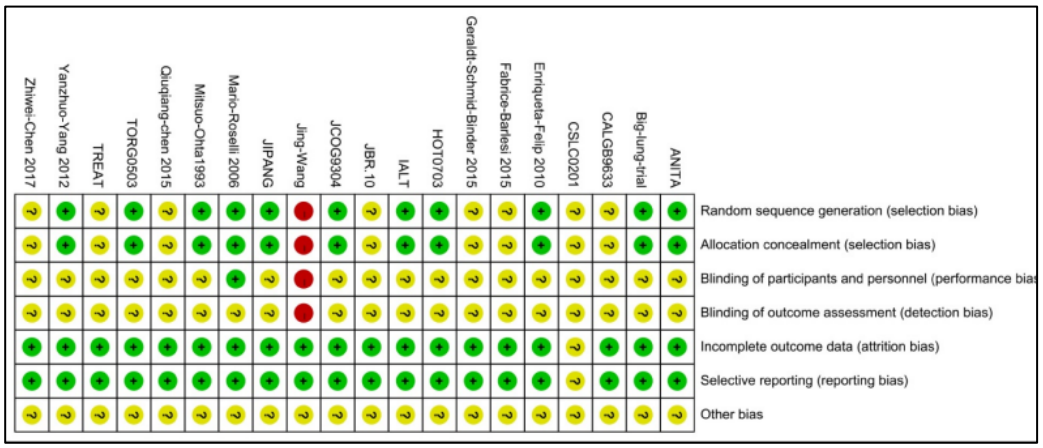
Charakteristika der Population:

- 11 RCTs compared the postoperative platinum chemotherapy regimen with the observation-controlled group
- 9 RCTs comparing two platinum chemotherapy regimens head-to- head.

Trail	Publication year	Country of region	Chemotherapy regimes	Sample size	Median follow-up (months)	Phase	Radiotherapy	Patients characteristics (Pathology; stage, PS)	Age	Sex
ANITA[37]	2006	Multicentre	Cisplatin 100 mg/m^2 + vinorelbine 30 mg/m^2 vs observation	840 (407 vs 433)	76	III	Not mandatory.	NSCLC; stage IB–IIIA	59 (32–75) vs 59 (18–75)	85% vs 87%
Big-lung-trial[36]	2003	UK	Cisplatin 80 mg/m^2 + vinorelbine 30 mg/m^2 vs observation	66 (37 vs 29)	58.8	-	Not mandatory	NSCLC; stage I–III	/	/
CALGB 9633[10]	2004	North Carolina	Carboplatin (AUC-6) +paclitaxel 200 mg/m^2 vs observation	344 (173 vs 171)	74	III	Not mentioned	NSCLC; T2 with pathologically negative lymph nodes	61 (34–78) vs 62 (40–81) (range)	65% vs 63%
CSLC0201[28]	2016	China	Carboplatin +docetaxel vs observation	82 (43 vs 39)	132	-	Not mentioned	NSCLC; stage IB–IIIA	/	/
NATCH[39]	2010	Multi Centre	Carboplatin (AUC-6.0) +paclitaxel 200 mg/m^2 vs observation	423 (211 vs 212)	51	III	Postoperative radiotherapy was allowed in patients with pathologic N2 disease.	NSCLC; stage IA with tumour size more than 2 cm, IB, II or T3N1	64 (33–81) vs 64 (36–89) (range)	86% vs 88%
Barlesi *et al*[31]	2015	France	Cisplatin 75 mg/m^2 + gemcitabine 1250 mg/m^2 vs cisplatin 75 mg/m^2 + docetaxel 75 mg/m^2	136 (67 vs 69)	20.2	-	Not mandatory.	NSCLC; stage IB–III	57 (44–74) vs 57 (36–71)	75% vs 74%
HOT0703[22]	2020	Japan	Cisplatin 40 mg/m^2 + gemcitabine 1000 mg/m^2 vs carboplatin (AUC-5) + gemcitabine 1000 mg/m^2	102 (51 vs 51)	69.6	II	Not mentioned	NSCLC; stage IB–IIIA	63 (40-72) vs 64 (36–74) (range)	67% vs 63%
IALT[32]	2004	France	Cisplatin 100 mg/m^2 + vinorelbine 30 mg/m^2 vs observation	500 (248 vs 262)	49.2	-	Not allowed.	NSCLC; stage I, II or III	/	/
JBR10[35]	2005;2010	North American	Cisplatin + vinorelbine vs observation	482 (240 vs 242)	111.6	III	Not mentioned	NSCLC; stage IB (T2N0) or II (T1-2N1)	61 (35–82) vs 60.5 (34–78)	64% vs 66%
JCOG9304[23]	2003	Japan	Cisplatin 80 mg/m^2 + vindesine 3 mg/m^2 vs observation	159 (59 vs 60)	-	-	Not mentioned	NSCLC;N2	62 (41–75) vs62 (43–74)	68% vs 62%
Jing Wang *et al*[29]	2012	China	Cisplation 80 mg/m^2 + vinorelbine 30 mg/m^2 vs observation	451 (225 vs 226)	46	-	Not mentioned	NSCLC; stage I, II and IIIA	55 (38–83) vs 58 (38–82)	71% vs 75%
JIPANG[24]	2020	Japan	Cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 vs cisplatin 80 mg/m^2 + vinorelbine 25 mg/m^2	804 (402 vs 402)	45.2	III	Not allowed	Non-squamous NSCLC; N2 stage II or IIIA	65 (58–69) vs 64 (57–67)	60% vs 58%
Roselli *et al*[34]	2006	Italy	Cisplatin 100 mg/m^2 + etoposide 120 mg/m^2 vs observation	140 (70 vs 70)	40.31	-	Not mentioned	NSCLC; stage IB disease (pT2N0)	64.7±9.9 vs 62.9±9.2	91% vs 76%
JLCSSG[25]	1993	Japan	Cisplatin 80 mg/m^2 + vindesine 3 mg/m^2 vs observation	181 (90 vs 91)	31.2	-	Not mentioned	NSCLC; stage III	56.3±9.1 vs 58.9±8.4	77%S. 87%
Chen *et al*[11]	2015	China	Cisplatin 75 mg/m^2 + docetaxel 75 mg/m^2 vs cisplatin 75 mg/m^2 + gemcitabine 1250 mg/m^2	92 (45 vs 47)	22	-	Not mentioned	NSCLC; stage II–III	55 (32–67) vs 56 (31–67) (range)	84% vs 87%
Schmid-Bindert *et al*[38]	2015	Germany, France, and Spain	Cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 vs carboplatin (AUC-5) + pemetrexed 500 mg/m^2	112 (63 vs 59)	-	II	Not-mentioned	NSCLC; stage IB, IIA or IIB	61 (44–75) vs 59 (43–69)	78% vs 70%
TORG0503[26]	2019	Japan	Cisplatin 80 mg/m^2 + docetaxel 60 mg/m^2 vs carboplatin AUC-6+Paclitaxel 200 mg/m2	111 (58 vs 53)	-	II	Not mentioned	NSCLC; stage IB, II and IIIA	63 (33–70) vs 59 (34–70)	60% vs 66%
Trail	**Publication year**	**Country of region**	**Chemotherapy regimes**	**Sample size**	**Median follow-up (months)**	**Phase**	**Radiotherapy**	**Patients characteristics (Pathology; stage, PS)**	**Age**	**Sex**
TREAT[33]	2015	German	Cisplatin 50 mg/m^2 + vinorelbine 25 mg/m^2 vs cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2	132 (67 vs 65)	36 m	II	Not allowed	NSCLC; stages IB, IIA, IIB,	58 (40–73) vs 60 (38–74)	72%vs 77%
Yanzhuo Yang *et al*[30]	2012	China	Carboplatin (AUC=5–6) + docetaxel 75 mg/m^2+ endostar 15 mg vs carboplatin+docetaxel	76 (38 vs 38)	22	-	Not mentioned	NSCLC; stage IB-III	55.6 (36–74) vs 60.2 (45–77)	31% vs 27%
Chen *et al*[27]	2017	China	Cisplatin 75 mg/m^2 + vinorelbine 25 mg/m^2 + endostar 7.5 mg/m^2 vs cisplatin+vinorelbine	250 (125 vs 125)	60	III	Not mentioned	NSCLC; stage IB to IIIA	58 (33–75) vs 55.5 (37–71)	66% vs 67%

AUC, area under the curve; NSCLC, non-small cell lung cancer; PS, performance status.

Qualität der Studien:



Studienergebnisse:

- The chemotherapy group had a significant RFS and OS advantage compared with the observation group (HR 0.67; 95% CI 0.56 to 0.81, p<0.0001; HR 0.80; 95% CI, 0.73 to 0.88, p<0.0001, respectively).
- Compared with the observation arm, only the 'cisplatin_vinorelbine' regimen had a significant RFS and OS advantage (HR 0.63; 95% CI 0.43 to 0.87; HR 0.74; 95% CI 0.63 to 0.87, respectively) while the remaining chemotherapy regimens had no significant difference of efficacy compared with the observation group.
- In terms of the safety of adjuvant chemotherapy, the incidence of haematological toxicities and nausea/vomiting was not significantly higher in the 'cisplatin_vinorelbine' arm than in other chemotherapy group.

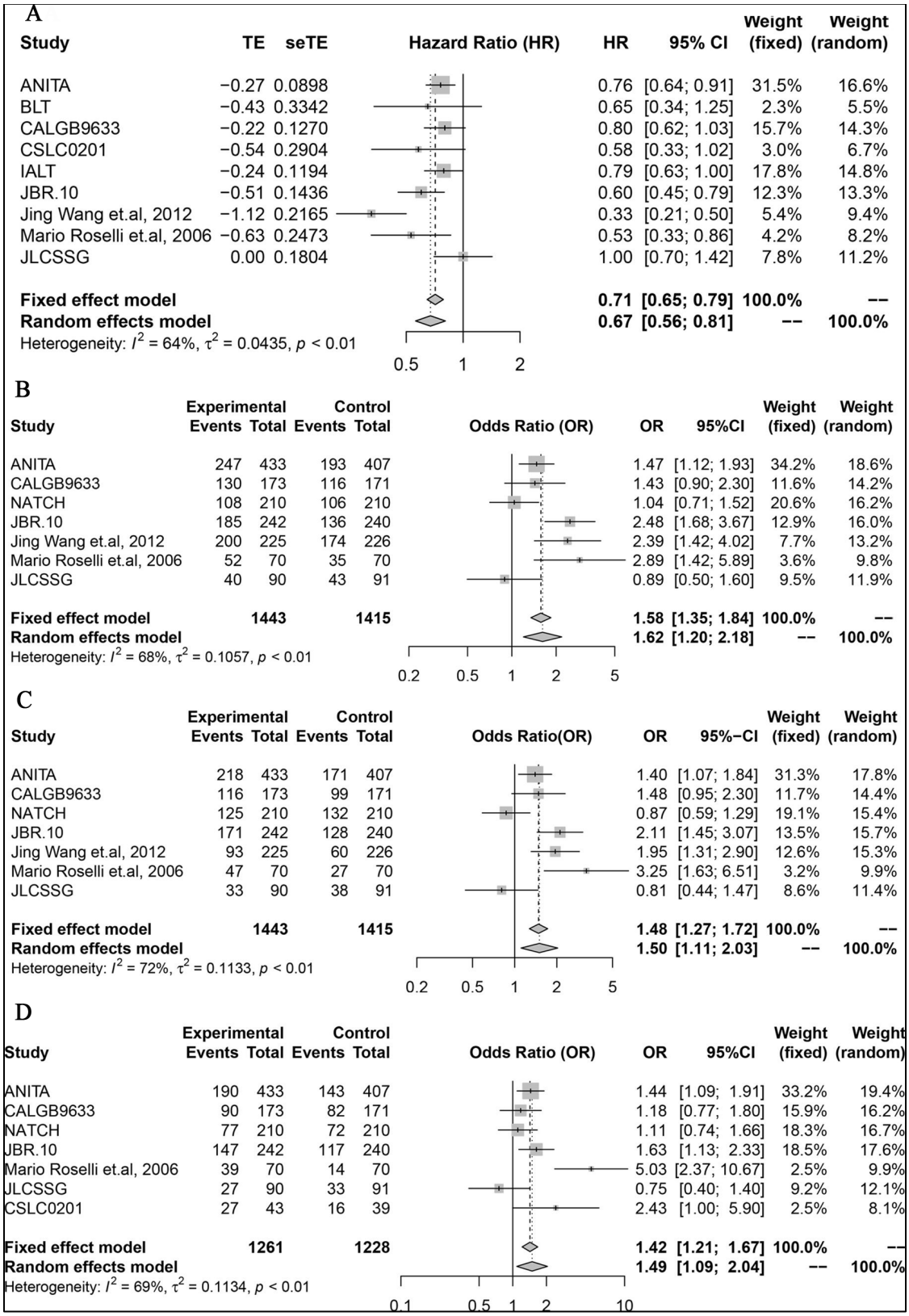


Figure 2 *(A) The efficacy of platinum-based postoperative adjuvant chemotherapy in improving the RFS compared with the observation group. (B) A 2-year RFS rate of the chemotherapy arm in comparison with the observation arm. (C) A 3-year RFS rate of the chemotherapy arm in comparison with the observation arm. (D) A 5-year RFS rate of the chemotherapy arm in comparison with the observation arm. RFS, relapse-free survival.*

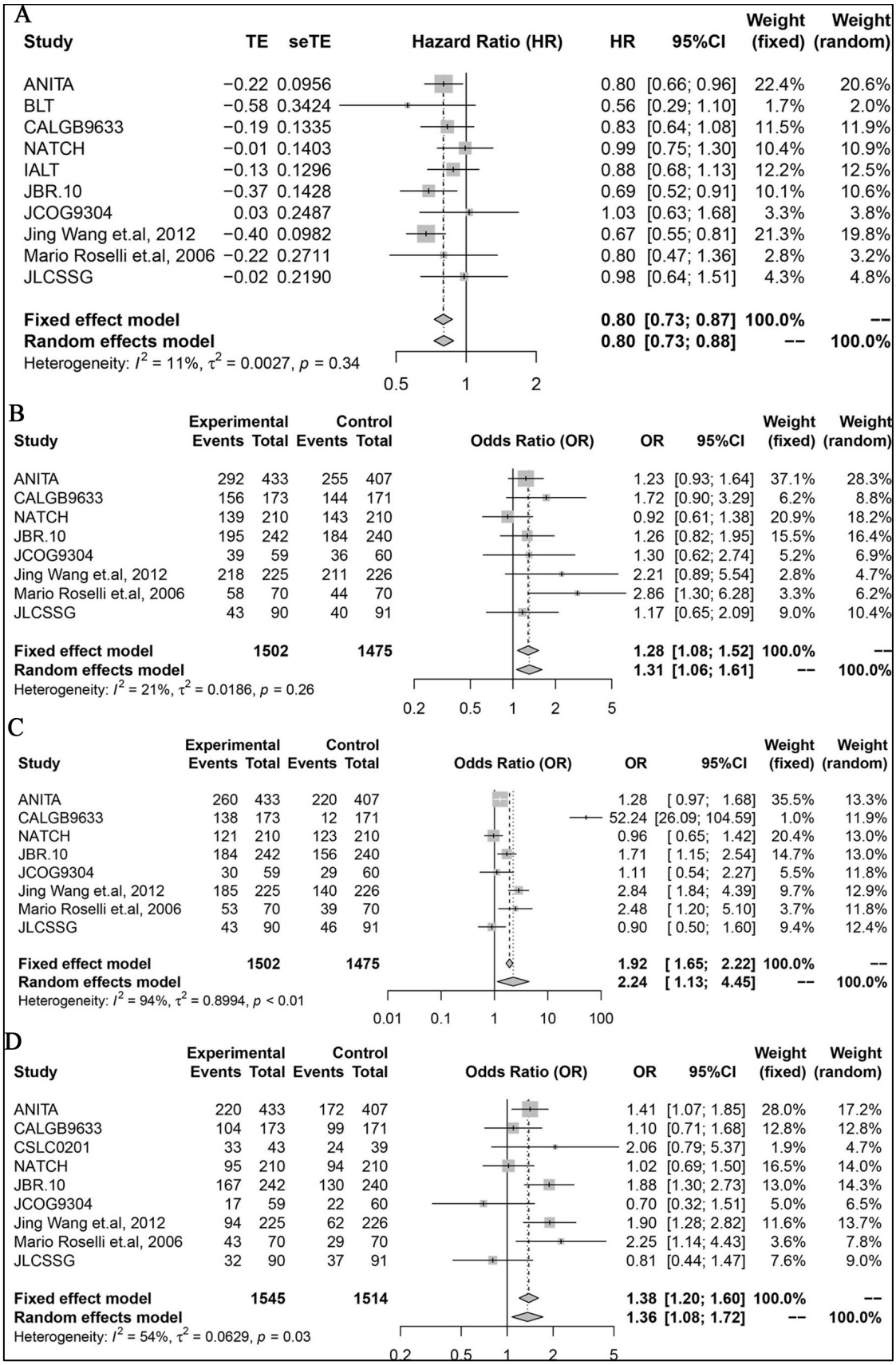
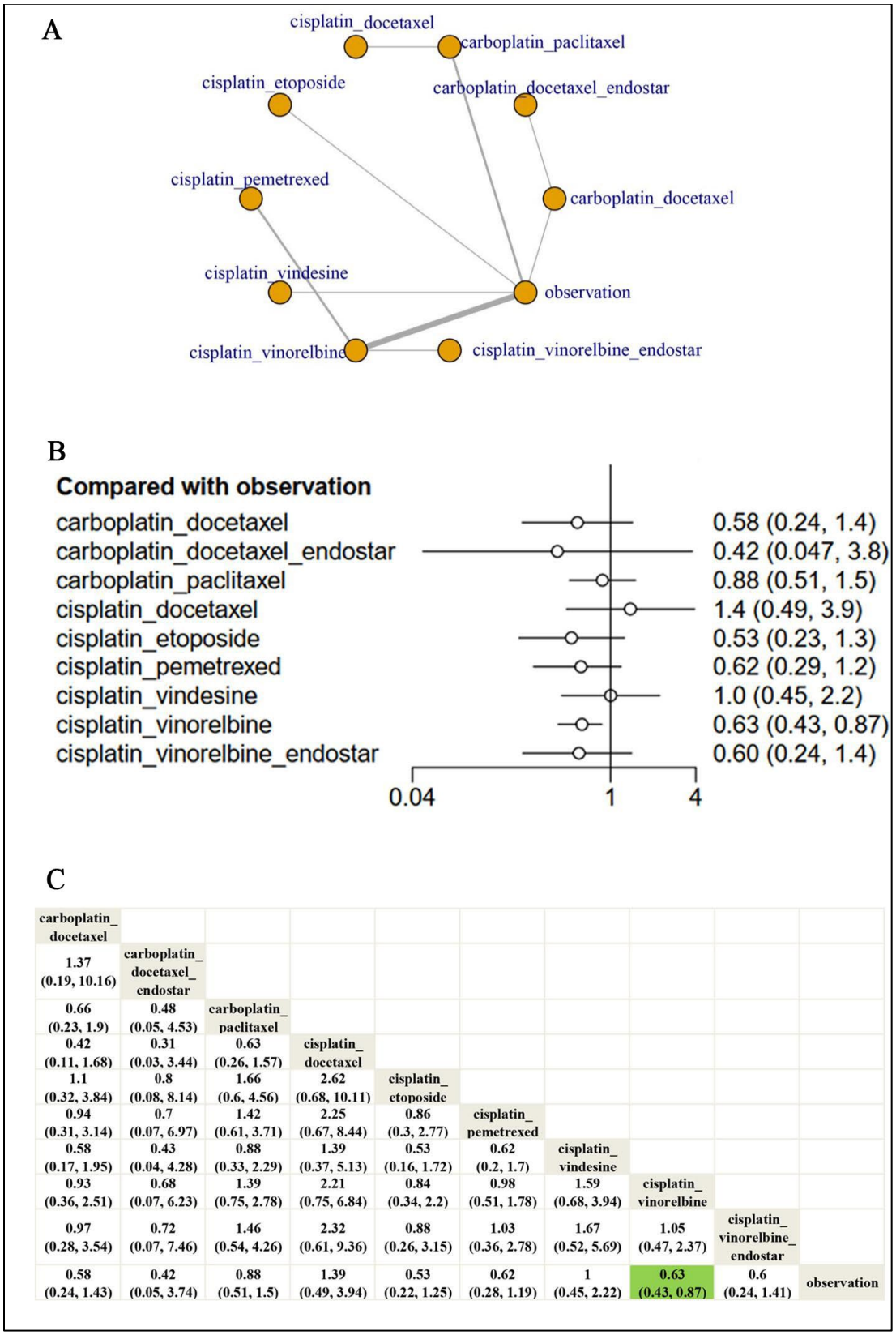


Figure 4 *(A) The efficacy of platinum-based postoperative adjuvant chemotherapy in improving the OS compared with the observation group. (B) A 2-year OS rate of the chemotherapy arm compared with the observation arm. (C) A 3-ear OS rate of the chemotherapy arm compared with the observation arm. (D) A 5-year OS rate of the chemotherapy arm compared with the observation arm. OS, overall survival.*



carboplatin_ docetaxel									
1.37 (0.19, 10.16)	carboplatin_ docetaxel_ endostar								
0.66 (0.23, 1.9)	0.48 (0.05, 4.53)	carboplatin_ paclitaxel							
0.42 (0.11, 1.68)	0.31 (0.03, 3.44)	0.63 (0.26, 1.57)	cisplatin_ docetaxel						
1.1 (0.32, 3.84)	0.8 (0.08, 8.14)	1.66 (0.6, 4.56)	2.62 (0.68, 10.11)	cisplatin_ etoposide					
0.94 (0.31, 3.14)	0.7 (0.07, 6.97)	1.42 (0.61, 3.71)	2.25 (0.67, 8.44)	0.86 (0.3, 2.77)	cisplatin_ pemetrexed				
0.58 (0.17, 1.95)	0.43 (0.04, 4.28)	0.88 (0.33, 2.29)	1.39 (0.37, 5.13)	0.53 (0.16, 1.72)	0.62 (0.2, 1.7)	cisplatin_ vindesine			
0.93 (0.36, 2.51)	0.68 (0.07, 6.23)	1.39 (0.75, 2.78)	2.21 (0.75, 6.84)	0.84 (0.34, 2.2)	0.98 (0.51, 1.78)	1.59 (0.68, 3.94)	cisplatin_ vinorelbine		
0.97 (0.28, 3.54)	0.72 (0.07, 7.46)	1.46 (0.54, 4.26)	2.32 (0.61, 9.36)	0.88 (0.26, 3.15)	1.03 (0.36, 2.78)	1.67 (0.52, 5.69)	1.05 (0.47, 2.37)	cisplatin_ vinorelbine_ endostar	
0.58 (0.24, 1.43)	0.42 (0.05, 3.74)	0.88 (0.51, 1.5)	1.39 (0.49, 3.94)	0.53 (0.22, 1.25)	0.62 (0.28, 1.19)	1 (0.45, 2.22)	0.63 (0.43, 0.87)	0.6 (0.24, 1.41)	observation

Figure 5 *(A) Network evidence of the comparisons for the best adjuvant chemotherapy concerning OS. (B) Forest plots of the comparisons for the different cytotoxicity chemotherapy regimens concerning OS. (C) The league table of the comparisons for the different cytotoxicity chemotherapy regimens concerning OS. OS, overall survival; SUCRA, surface under the cumulative ranking curve.*

Anmerkung/Fazit der Autoren

In conclusion, this study summarised the adjuvant cytotoxicity chemotherapy regimens for patients with early-stage resected NSCLC. Research on adjuvant cytotoxicity chemotherapy might be an out-of-date topic but numerous NSCLC patients could obtain benefit from the optimal cytotoxicity chemotherapy regimen. 'Cisplatin_vinorelbine' had a significant survival advantage with a relatively good safety profile in the adjuvant setting while the 'cisplatin_pemetrexed' arm was not superior to the other therapeutic methods in improving survival.

Wang L et al., 2023 [10].

Effect of postoperative radiotherapy on survival in patients with completely resected and pathologically confirmed stage N2 non-small-cell lung cancer: a systematic review and meta-analysis.

Fragestellung

An updated meta-analysis was conducted in this study to investigate the efficacy of PORT and prognosis in patients with completely resected and pathologically confirmed stage N2 NSCLC.

Methodik

Population:

- patients aged ⩾18 years with completely resected and pathologically confirmed stage N2 NSCLC

Intervention/Komparator:

- PORT in the study group and nonPORT in the control group, regardless of whether postoperative adjuvant chemotherapy was combined in both groups

Endpunkte:

- OS, DFS, LRFS, or distant metastasis-free survival (DMFS)

Recherche/Suchzeitraum:

- Databases were searched up to 2 March 2022

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool / NOS

Ergebnisse

Anzahl eingeschlossener Studien:

- 20 studies (6340 patients)

Charakteristika der Population/Studien:

- participants were predominantly males, multiple or multisite lymph node metastases were common, and the radiotherapy dose range was 30–66 Gy and 1.8–3.0 Gy/d.

Qualität der Studien:

- most studies were considered at low risk of bias, four studies were unclear on the risk of allocation concealment, one study was unclear on the risk of blinding of participants and personnel and blinding of outcome assessors, and four studies were unclear on the risk of selective outcome reporting. For non-RCT studies, the NOS quality scores ranged from 7 to 9, and all studies were rated as of 'high quality'.

Studienergebnisse:

- The PORT significantly increased OS [hazard ratio (HR) = 0.77, 95% CI: 0.71–0.84, $p < 0.001$), LRFS (HR = 0.63, 95% CI: 0.52–0.76, $p < 0.001$), and DFS (HR = 0.72, 95% CI: 0.63–0.82, $p < 0.001$) while it showed no significant difference in improving DMFS (HR = 0.86, 95% CI: 0.71–1.05, $p = 0.14$).
- Subgroup analyses
  - significantly improved OS in patients was observed in the retrospective study group (HR = 0.75, 95% CI: 0.69–0.82, $p < 0.05$) compared with the RCT study group (HR = 0.87, 95% CI: 0.71–1.07, $p > 0.05$)
  - Compared with the subgroup without adjuvant chemotherapy, significantly improved OS in patients was observed in the sequential postoperative chemoradiotherapy group (HR = 0.79, 95% CI: 0.70–0.90, $p < 0.05$) and postoperative concurrent chemoradiotherapy group (HR = 0.73, 95% CI: 0.60–0.90, $p < 0.05$) or a subgroup with both sequential and concurrent chemoradiotherapy (HR = 0.75, 95% CI: 0.62–0.90, $p < 0.05$).

Anmerkung/Fazit der Autoren

The results of this study suggest that PORT may provide better local recurrence control and survival benefit in the postoperative treatment of patients with completely resected stage N2 NSCLC, and may be included in the postoperative treatment options. Nevertheless, this conclusion needs to be further confirmed by more prospective studies based on modern precision radiotherapy techniques in the future, and longterm survival needs to be observed in future follow-ups.

3.3 Leitlinien

Leitlinienprogramm Onkologie Leitlinie, 2024 [3,4]

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

S3-Leitlinie Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms, Langversion 3.0

Zielsetzung/Fragestellung

- Unterstützung von Ärzten, betroffenen Patienten und Bürgern mit einem erhöhten Risiko für ein Lungenkarzinom bei medizinischen Entscheidungendurch evidenzbasierte und formal konsentierte Empfehlungen
- Schaffung einer Grundlage für inhaltlich gezielte ärztliche Aus-, Fort- und Weiterbildungsmaßnahmen
- flächendeckende Umsetzung einer multidisziplinären, qualitätsgesicherten und sektorübergreifenden Versorgung des Lungenkarzinoms
- Optimierung der Diagnosekette und der stadiengerechten Therapie sowohl bei der Ersterkrankung als auch beim Rezidiv bzw. bei einer Metastasierung

Durch die Umsetzung dieser Ziele soll mittel- und langfristig die Mortalität der Patienten mit Lungenkarzinomen gesenkt und die Lebensqualität erhöht werden

Methodik

Grundlage der Leitlinie

Update - Aktualisierung der S3-Leitlinie Lungenkarzinom 2019-2022

- Repräsentatives Gremium zutreffend;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz dargelegt;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Jährliche Überprüfung der Aktualität. Gültig bis max. 2027 bzw. bis zur nächsten Aktualisierung

Recherche/Suchzeitraum:

- Zu den unter Kapitel 3 aufgeführten Schlüsselfragen wurden systematische Recherchen durchgeführt. Da die Bearbeitung des Kapitels im Rahmen der Version 3 nicht abgeschlossen werden konnte, sondern dies erst im Rahmen der Aktualisierung zur Version 4 (2024) erfolgt, werden die Suchstrategien, Suchergebnisse sowie die Bewertung der eingeschlossenen Publikationen im Report zur Version 4 dokumentiert.
- Für zusätzlich berücksichtigte Arzneimittelstudien zu den Therapieempfehlungen in den Stadien SCLC und NSCLC wurde auf die Recherchen und Bewertungen zurückgeriffen, die im Rahmen der Frühen Nutzenbewertung gemäß § 35a SGB V (Arzneimittelmarktneuordnungsgesetz – AMNOG) zur Verfügung standen (siehe Kapitel 11.1). Die Bewertungen erfolgten hier auf der Grundlage der GRADE-Systematik (siehe https://pubmed.ncbi.nlm.nih.gov/21208779/ bzw. auch https://www.ebm-netzwerk.de/de/serviceressourcen/ebm-glossar) durch das OL-Office (Gregor Wenzel und Halina Kirsch). Diese Bewertung ist in den entsprechenden Evidenztabellen abgebildet.

LoE

- entsprechend der Vorgaben des Oxford Centre for Evidence-Based Medicine

GoR

- Hinsichtlich der Stärke der aktualisierten Empfehlung (gekennzeichnet mit „2022“) werden in der Leitlinie drei Empfehlungsgrade unterschieden (A/B/0), die sich auch in der Formulierung der Empfehlungen widerspiegeln. Für die Empfehlungen, die nicht im Rahmen der Aktualsierung bearbeitet wurden (gekennzeichnet mit „2010“ gelten weiterhin die Empfehlungsgraduierung der Version aus 2010. Diese sieht vier Empfehlungsgrade (A/B/C/D) vor

Tabelle 7: Schema der Empfehlungsgraduierung für Empfehlungen 2018 und 2022

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

Tabelle 8: Konsensusstärke

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

Empfehlungen

8 Therapie des nicht-kleinzelligen Lungenkarzinoms
8.3 Stadium I/II

(Methodikeranmerkung: entprechend der Indikation werden hier ausschließlich Empfehlungen des Stadium II dargestellt)

8.3.2 Therapie bei funktionell operablen Patienten

(Methodikeranmerkung: Empfehlungen, die sich allein auf die Resektion beziehen, werden vorliegend nicht dargestellt und können der LL entnommen werden)

8.14	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **A**	Patienten mit NSCLC im Stadium I / II soll bei adäquater Lungenfunktion und fehlenden Kontraindikationen eine radikale Resektion angeboten werden, deren Ziel die R0-Tumorentfernung ist.	
Level of Evidence **2a**	[528], [595], [596], [597], [598], [599], [600], [601], [602], [593], [603], [604]	
	Starker Konsens	

8.15	Evidenzbasierte Empfehlung	modifiziert 2024
Empfehlungsgrad **A**	Beim NSCLC im Stadium I/II soll bei ausreichender kardiopulmonaler Funktion die radikale Resektion als Lobektomie durchgeführt werden. Bei Tumoren ≤ 2cm im äußeren Drittel des Parenchymmantels und zytologisch oder histologisch gesichertem N0-Status ist eine anatomische Segmentresektion der Lobektomie hinsichtlich Kuration ebenbürtig, sofern am Lungenparenchym ein Resektionsabstand erzielt werden kann, der größer ist als der Tumordurchmesser.	
Level of Evidence **1b**	[595], [596], [376], [528], [598], [605], [601], [606], [607], [608], [609]	
	Starker Konsens	

8.16	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **B**	Beim NSCLC im Stadium I und II werden nach minimal-invasiver VATS- oder RATS-Lobektomie im Vergleich zur konventionellen offenen Lobektomie - bei gleichwertigem onkologischem Ergebnis - weniger postoperative Komplikationen und weniger postoperative Schmerzen beobachtet, woraus eine verbesserte Lebensqualität und ein kürzerer Krankenhausaufenthalt resultiert. Deswegen sollte die minimalinvasive Lobektomie der konventionellen offenen Lobektomie beim NSCLC im Stadium I und II vorgezogen werden.	
Level of Evidence **2a**	[610], [611], [612], [613], [614], [615], [616]	
	Starker Konsens	

8.17	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **A**	Bei Patienten, die einer kurativen Resektion zugeführt werden, soll eine systematische Lymphknotendissektion erfolgen, um ein genaues Staging zu ermöglichen und um möglicherweise die Prognose zu verbessern.	
Level of Evidence **1b**	[617], [618], [619], [620], [621], [622], [623]	
	Starker Konsens	

8.18	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **A**	Bei Patienten mit Brustwandinfiltration ist eine R0-Situation entscheidend und es soll eine en bloc Resektion angestrebt werden.	
Level of Evidence **3**	[528], [624], [625], [626], [627], [628], [629]	
	Starker Konsens	

8.19	Konsensbasierte Empfehlung	geprüft 2024
EK	Bei einer Pleurainvasion ohne tiefere Brustwandinfiltration kann eine extrapleurale Lyse erfolgen.	
	Starker Konsens	

8.20	Konsensbasierte Empfehlung	geprüft 2024
EK	Bei tieferer Brustwandinfiltration soll eine Vollwandresektion durchgeführt werden.	
	Starker Konsens	

8.21	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **B**	Nach R1-Resektion sollten im Thorax-Onkologischen Tumorboard die weiteren Therapiemöglichkeiten (z.B. Nachresektion oder Strahlentherapie) besprochen werden.	
Level of Evidence **3b**	[630]	
	Starker Konsens	

8.3.3 Präoperative Systemtherapie

8.22	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **B**	Beim NSCLC im Stadium I führte eine präoperative Chemotherapie in randomisierten Studien bislang weder zu einer Verlängerung der rezidivfreien noch der Gesamtüberlebenszeit und wird deshalb außerhalb von Studien nicht empfohlen.	
Level of Evidence **1**	[649], [650], [651], [652], [653]	
	Starker Konsens	

8.23	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **B**	Beim NSCLC im Stadium II sollte interdisziplinär diskutiert werden, ob eine systemische, anti-neoplastische Induktionstherapie, gefolgt von Resektion, als alternative Therapieoption durchgeführt wird. Entscheidungskriterien sind Expression von PD-L1, Risiken R1/R2-Resektion, Komorbiditäten, Compliance-Einschätzung und Patientenwunsch.	
Level of Evidence **3**	[649], [650], [654], [651], [652], [653], [655]	
	Konsens	

8.24	Evidenzbasierte Empfehlung	neu 2024
Empfehlungsgrad **B**	NSCLC Patienten mit resektablen Tumoren im Stadium II und ≥1% PD-L1-Expression (ohne EGFR und ALK Alteration) und Empfehlung einer Induktionstherapie, sollte eine kombinierte Immunchemotherapie angeboten werden.	
Level of Evidence **1b**	[655], [656], [657], [658]	
	Starker Konsens	

8.3.4 Postoperative Systemtherapie

8.25	Evidenzbasierte Empfehlung	modifiziert 2024
Empfehlungsgrad **A**	Nach R0-Resektion und systematischer Lymphknotendissektion soll Patienten mit NSCLC im Stadium II in gutem Allgemeinzustand (ECOG 0/1) eine adjuvante Chemotherapie angeboten werden, wenn keine neoadjuvante Therapie durchgeführt wurde.	
Level of Evidence **1a**	[660], [661], [662], [663], [664]	
	Starker Konsens	

8.26	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **B**	Die adjuvante Chemotherapie sollte nach Abschluss der Wundheilung innerhalb von 60 Tagen nach der Resektion beginnen.	
Level of Evidence	[665], [666], [667]	
	Starker Konsens	

8.27	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **A**	In der adjuvanten Chemotherapie soll bei Patienten mit NSCLC im Stadium II in gutem Allgemeinzustand (ECOG 0/1) die Gabe einer cisplatinhaltigen Kombination über 4 Zyklen erfolgen.	
Level of Evidence **1a**	[668], [663], [664], [660]	
	Starker Konsens	

8.28	Evidenzbasierte Empfehlung	modifiziert 2024
Empfehlungsgrad **A**	Patienten mit NSCLC im Stadium II und einer aktivierenden EGFR-Mutation (nur Exon 19 Deletion, Exon 21 L858R) soll nach kompletter Resektion und adjuvanter Chemotherapie eine adjuvante Therapie mit Osimertinib über 3 Jahre angeboten werden.	

8.28	Evidenzbasierte Empfehlung	modifiziert 2024
Level of Evidence **1b**	[669], [670]	
	Konsens	

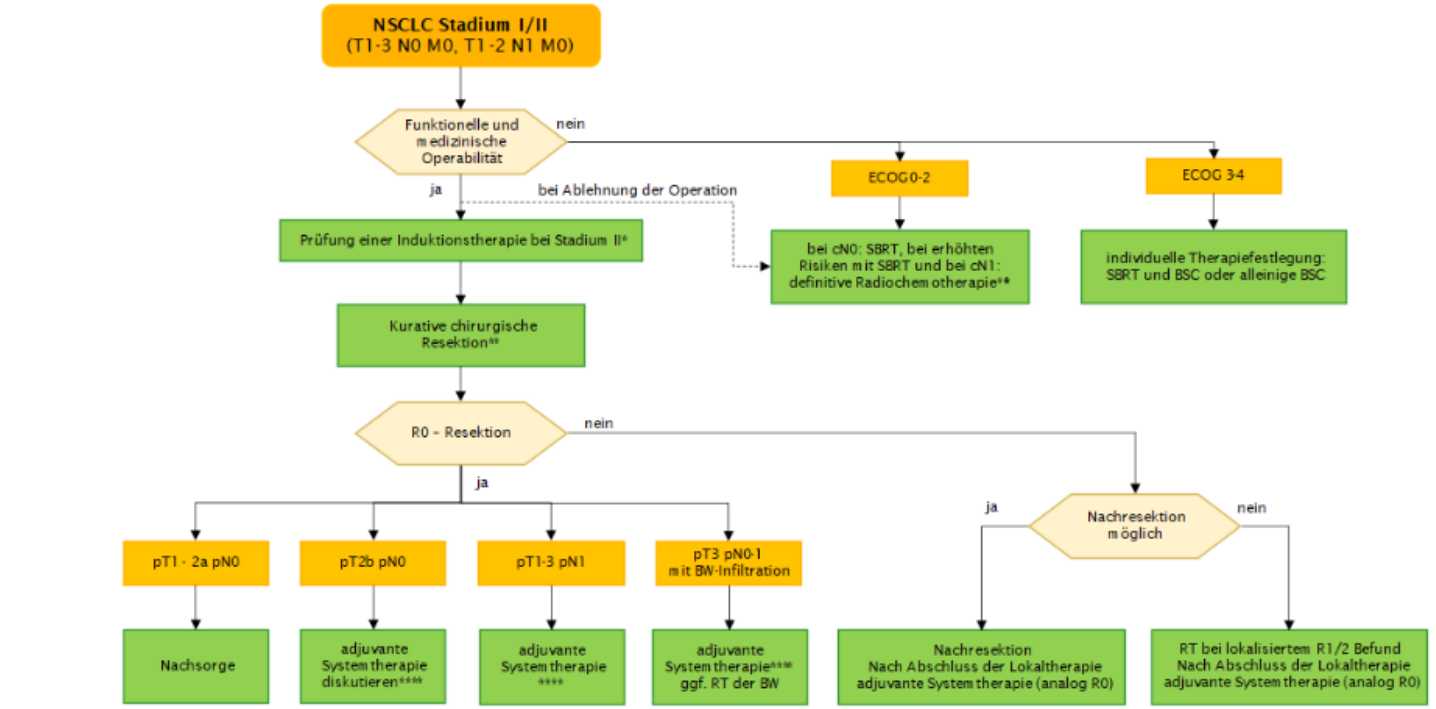
8.29	Evidenzbasierte Empfehlung	modifiziert 2024
Empfehlungsgrad **A**	Patienten mit NSCLC im Stadium II mit einer PD-L1 Expression ≥ 50 % (ohne EGFR oder ALK Alteration) soll, nach primärer R0-Resektion und durchgeführter adjuvanter Chemotherapie, eine adjuvante Therapie mit Atezolizumab über 1 Jahr angeboten werden.	
Level of Evidence **1**	[671], [672]	
	Starker Konsens	

8.30	Evidenzbasierte Empfehlung	neu 2024
Empfehlungsgrad **B**	Patienten mit NSCLC im Stadium II (ohne EGFR oder ALK Alteration) sollte, nach primärer R0-Resektion und durchgeführter adjuvanter Chemotherapie, unabhängig vom PD-L1 Status eine adjuvante Therapie mit Pembrolizumab über 1 Jahr angeboten werden.	
Level of Evidence **1**	[673]	

8.3.5 Postoperative Radiotherapie

8.31	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **A**	Patienten mit NSCLC im Stadium I und II soll nach R0-Resektion eine adjuvante Strahlentherapie nicht angeboten werden.	
Level of Evidence **1a**	[690], [680], [691], [692], [693], [694], [695], [696]	
	Starker Konsens	

8.3.6 Flowchart Stadium I/II



BW-Infiltration: Brustwand-Infiltration; SBRT: Stereotactic body radiation therapy (stereotaktische Radiotherapie), RT: Radiotherapie, BSC: Best Supportive Care
Operabilität und Resektabilität wird präoperativ seitens Thoraxchirurgie gemeinsam mit Pneumologie beurteilt.
* bei ≥1% PD -L1-Expression (ohne EGFR und ALK-Alteration) und interdisziplinärer TB-Empfehlung einer Induktionstherapie: kombinierte Immunchemotherapie
** (ggf. erweiterte) anatomische Lungenresektion + systematische Lymphknotendissektion, bei geeignetem Situs: minimalinvasiv
*** SBRT (BED10 > 100 Gy) mit lokalisationsabhängigem Dosisregime, bei ultrazentralem Tumorsitz mit Beteiligung des proximalen Bronchialbaumes vorzugsweise an spezialisierten Zentren
**** wenn keine neoadjuvante Therapie adjuvante Cisplatin-basierte Chemotherapie; bei EGF-R Mut (Exon 19/21) zusätzlich TKI (derzeit ist Osimertinib zugelassen)oder adjuvante Immuntherapie im Rahmen der Zulassung

Abbildung 12: Flowchart zur Therapie des nicht-kleinzelligen Lungenkarzinoms im Stadium I/II

8.5.2 Inzidentelles Stadium IIIA(N2) beim NSCLC – Stadium IIIA1 und IIIA2 nach Robinson-Einteilung – Multimodale Therapiekonzepte

8.44	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **A**	Beim NSCLC im Stadium III mit inzidentellem N2-Status (IIIA1 bzw. IIIA2) soll nach kompletter Resektion (R0) und systematischer Lymphknotendissektion, bei fehlender Kontraindikation, eine adjuvante Kombinationschemotherapie erfolgen. Die Chemotherapie soll nach Abschluss der Wundheilung innerhalb von 60 Tagen nach Resektion erfolgen.	
Level of Evidence **1a**	[778], [779], [780], [781], [782], [689], [783], [663], [708], [677], [680], [681], [666], [784]	
	Starker Konsens	

8.45	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **A**	Die adjuvante Chemotherapie beim NSCLC im Stadium IIIA1 und IIIA2 soll bei fehlender Kontraindikation als eine cisplatinhaltige Kombination über 4 Zyklen erfolgen. Nur bei Kontraindikation gegen Cisplatin soll der Einsatz von Carboplatin erwogen werden.	
Level of Evidence **1b**	[703], [781], [782], [788], [789], [790], [791], [792], [793], [794], [795], [796], [797], [798], [799], [800], [801], [677], [680], [681], [666], [688], [802], [768], [803], [784]	
	Starker Konsens	

8.46	Konsensbasierte Empfehlung	geprüft 2024
EK	Bei Patienten mit NSCLC im Stadium IIIA1 und IIIA2 mit klinisch relevanter Komorbidität aufgrund der vorangegangenen Resektion oder vorbestehender Erkrankungen sollte die Durchführung einer adjuvanten Kombinationschemotherapie individuell geprüft und in einem interdisziplinär ausgerichteten Team mit entsprechender Erfahrung erfolgen.	
	Starker Konsens	

8.47	Evidenzbasierte Empfehlung	modifiziert 2024
Empfehlungsgrad **A**	Patienten mit NSCLC im Stadium IIIA1 und IIIA2 und einer aktivierenden EGFR-Mutation (nur Exon 19 Deletion, Exon 21 L858R) soll nach kompletter Resektion und adjuvanter Chemotherapie eine adjuvante Therapie mit Osimertinib über 3 Jahre angeboten werden.	
Level of Evidence **1b**	[669], [670]	
	Starker Konsens	

8.48	Evidenzbasierte Empfehlung	modifiziert 2024
Empfehlungsgrad **A**	Patienten mit NSCLC im Stadium IIIA mit einer PD-L1 Expression ≥ 50 % (ohne EGFR oder ALK Alteration) soll, nach primärer R0-Resektion und durchgeführter adjuvanter Chemotherapie, eine adjuvante Therapie mit Atezolizumab über 1 Jahr angeboten werden.	
Level of Evidence **1**	[671], [672]	
	Starker Konsens	

8.49	Evidenzbasierte Empfehlung	neu 2024
Empfehlungsgrad **B**	Patienten mit NSCLC im Stadium IIIA (ohne EGFR oder ALK Alteration) sollte, nach primärer R0-Resektion und durchgeführter adjuvanter Chemotherapie, unabhängig vom PD-L1 Status eine adjuvante Therapie mit Pembrolizumab über 1 Jahr angeboten werden.	
Level of Evidence **1**	[673]	

8.50	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **A**	Für Patienten mit inkompletter Resektion soll primär die Möglichkeit einer Nachresektion geprüft werden. Sofern keine R0-Resektion sinnvoll zu erzielen ist, soll innerhalb eines multimodalen Gesamtkonzeptes nach Indikationsstellung im Thorax-Onkologischen Tumorboard eine postoperative Strahlentherapie angeboten werden.	
Level of Evidence **2a**	[703], [821], [822], [823], [824], [825], [826], [827], [828], [829], [614], [352], [619], [693], [807], [830]	
	Starker Konsens	

8.51	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **B**	Für Patienten mit R0 Resektion und mediastinalem Lymphknotenbefall im NSCLC-Stadium IIIA1 bzw. IIIA2 sollte zusätzlich zur adjuvanten Chemotherapie die Indikation zur postoperativen Mediastinalbestrahlung individuell geprüft aber nicht routinemäßig gestellt werden.	
Level of Evidence **1a**	[832], [833], [834], [835], [836], [837], [838]	
	Starker Konsens	

8.5.3 Stadium IIIA3 nach Robinson-Einteilung beim NSCLC – Multimodale Therapiekonzepte

8.52	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **A**	Patienten mit NSCLC im Stadium IIIA3 und technischer und funktioneller Operabilität sollen multimodal behandelt werden. Derzeitige multimodale Optionen sind die definitive Radiochemotherapie +/- Durvalumab und die Operation nach neoadjuvanter Therapie.	
Level of Evidence **1a**	[841], [842], [780], [843], [844], [845], [846], [847], [848], [695], [795], [804], [827], [849], [850], [851], [852], [853], [854], [855], [856], [857], [858], [358], [768], [830], [859], [860]	
	Konsens	

8.53	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **B**	Wird bei Patienten mit NSCLC Stadium IIIA3 im Rahmen einer Induktion eine Phase alleiniger Chemotherapie eingesetzt, sollte präferentiell eine Kombination aus Cisplatin und einem Taxan eingesetzt werden.	
Level of Evidence **1b**	[703], [795], [804], [862], [863], [864], [865]	
	Konsens	

8.54	Evidenzbasierte Empfehlung	neu 2024
Empfehlungsgrad **0**	Bei NSCLC Patienten mit resektablen Tumoren im Stadium IIIA3 und ≥1% PD-L1-Expression kann im Rahmen einer Induktion eine kombinierte Immunchemotherapie eingesetzt werden.	
Level of Evidence **1b**	[655], [656]	
	Starker Konsens	

8.55	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **B**	Bei alleiniger Induktionschemotherapie sollte nach Operation und R0-Resektion eines NSCLC im Stadium IIIA3 eine Evaluation im Thorax-Onkologischen Tumorboard und bei erhöhtem lokoregionärem Rezidivrisiko eine mediastinale Radiotherapie erfolgen. Die Dosis sollte 50-54 Gy in 5-6 Wochen betragen.	
Level of Evidence **2b**	[804], [868], [869], [870], [871], [836], [833], [872], [873], [874], [875], [876], [877], [822], [709], [878], [879]	
	Starker Konsens	

8.5.4 Stadium IIIA beim NSCLC ohne N2 (T4N0 und T4N1) – Multimodale Therapiekonzepte

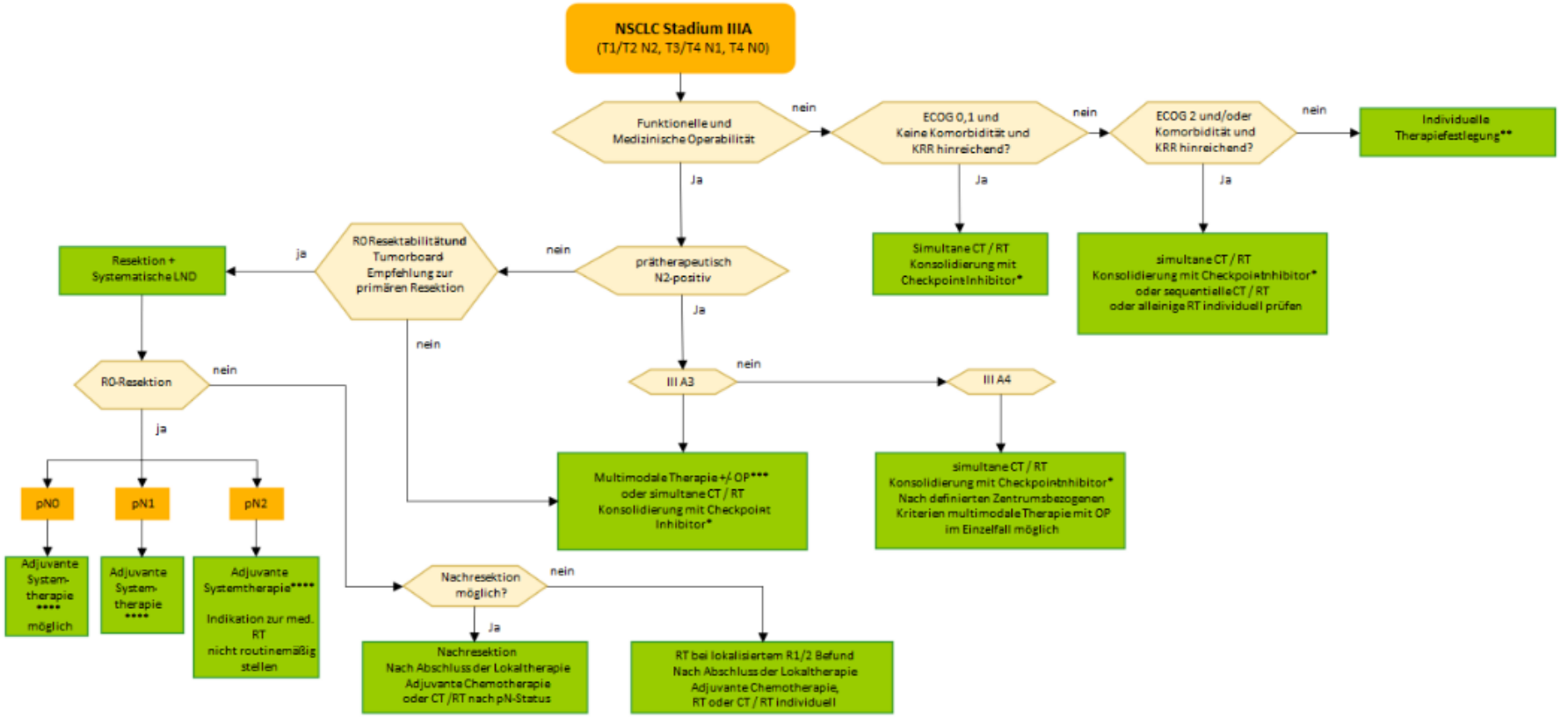
8.56	Konsensbasiertes Statement	geprüft 2024
EK	In den Subgruppen NSCLC T4N0 und T4N1 (jeweils Stadium IIIA) ist nach interdisziplinärer Evaluation im Thorax-Onkologischen Tumorboard die primäre Operation bzw. die Integration der Operation in das Gesamtbehandlungskonzept bei technischer und funktioneller Operabilität möglich. Dies sollte gegen die Vorteile eines neoadjuvanten Vorgehens (siehe Empfehlungen 8.52 und 8.53) abgewogen werden.	
	Starker Konsens	

8.58	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad 0	Für selektierte Patienten mit NSCLC im Stadium IIIA4 / IIIB kann nach interdisziplinärer Evaluation im Thorax-Onkologischen Tumorboard ein multimodaler Behandlungsansatz unter Integration der Operation erfolgen, sofern eine R0 Resektion sehr wahrscheinlich ist.	
Level of Evidence 1b	[726], [897], [699], [898], [847], [848], [892], [796], [893], [854], [899], [703], [900], [804], [768], [901], [902], [822]	
	Starker Konsens	

8.59	Evidenzbasierte Empfehlung	neu 2024
Empfehlungsgrad 0	Bei NSCLC Patienten mit resektablen Tumoren im Stadium IIIB, nur T3N2, und ≥1% PD-L1-Expression kann im Rahmen einer Induktion eine kombinierte Immunchemotherapie angeboten werden.	
Level of Evidence 1b	[655], [656]	
	Starker Konsens	

8.5.7 Algorithmen Stadium III

Algorithmus IIIA prätherapeutisch



* derzeit ist Durvalumab bei PDL1 Expression von ≥1% zugelassen
** derzeit ist Cemiplimab Monotherapie bei PDL1 ≥ 50% oder Chemotherapie+Cemiplimab bei PD-L1 ≥ 1 % zugelassen
*** Beschreibung siehe im ausführlichen Text, auch ESPATUE ohne OP möglich, bei ≥ 1% PD-L1-Expression (ohne EGFR und ALK-Alteration) und interdisziplinärer TB Empfehlung einer Induktionstherapie: kombinierte Immunchemotherapie
**** adjuvante Cisplatin basierte Chemotherapie bei EGF-R Mut (Exon 19/21) zusätzlich TKI (derzeit ist Osimertinib zugelassen) oder adjuvante Immuntherapie im Rahmen der Zulassung

Abbildung 14: Flowchart NSCLC Stadium IIIA

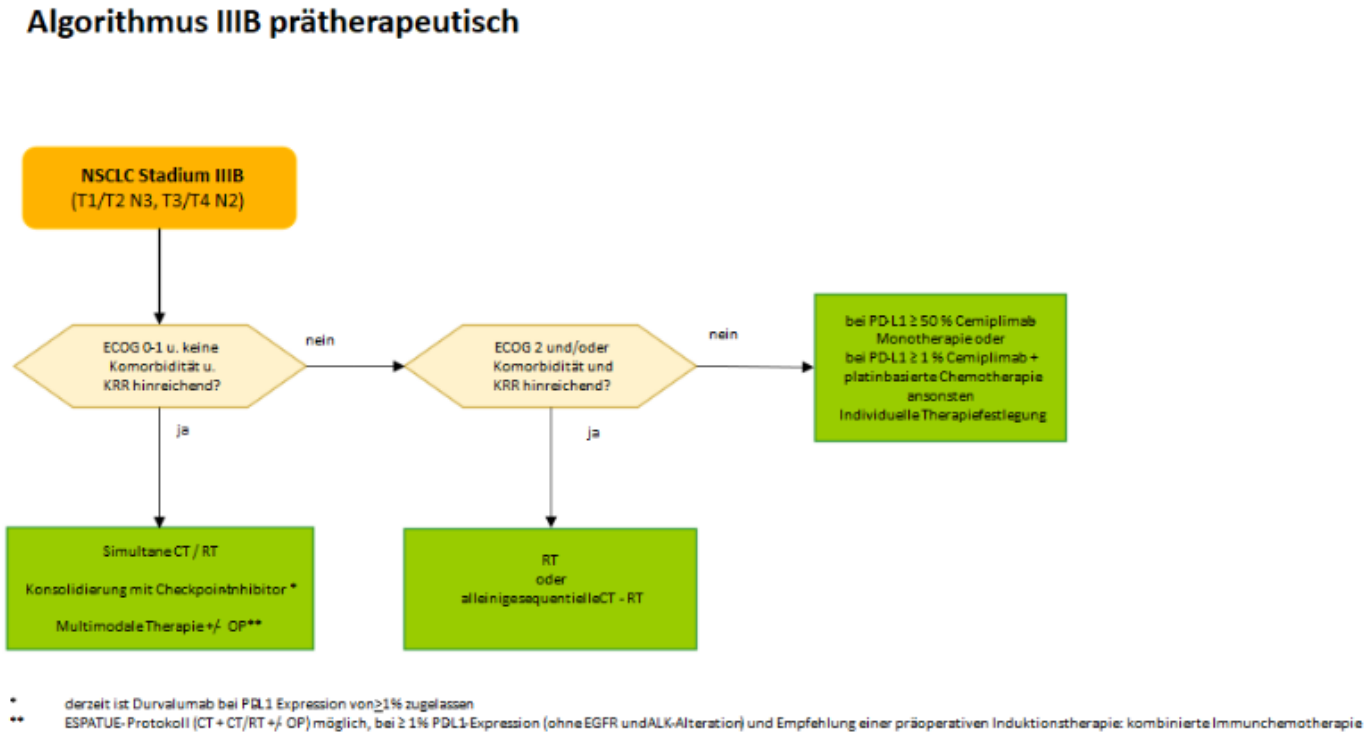


Abbildung 15: Flowchart zur Therapie des nicht-kleinzelligen Lungenkarzinoms im Stadium IIIB

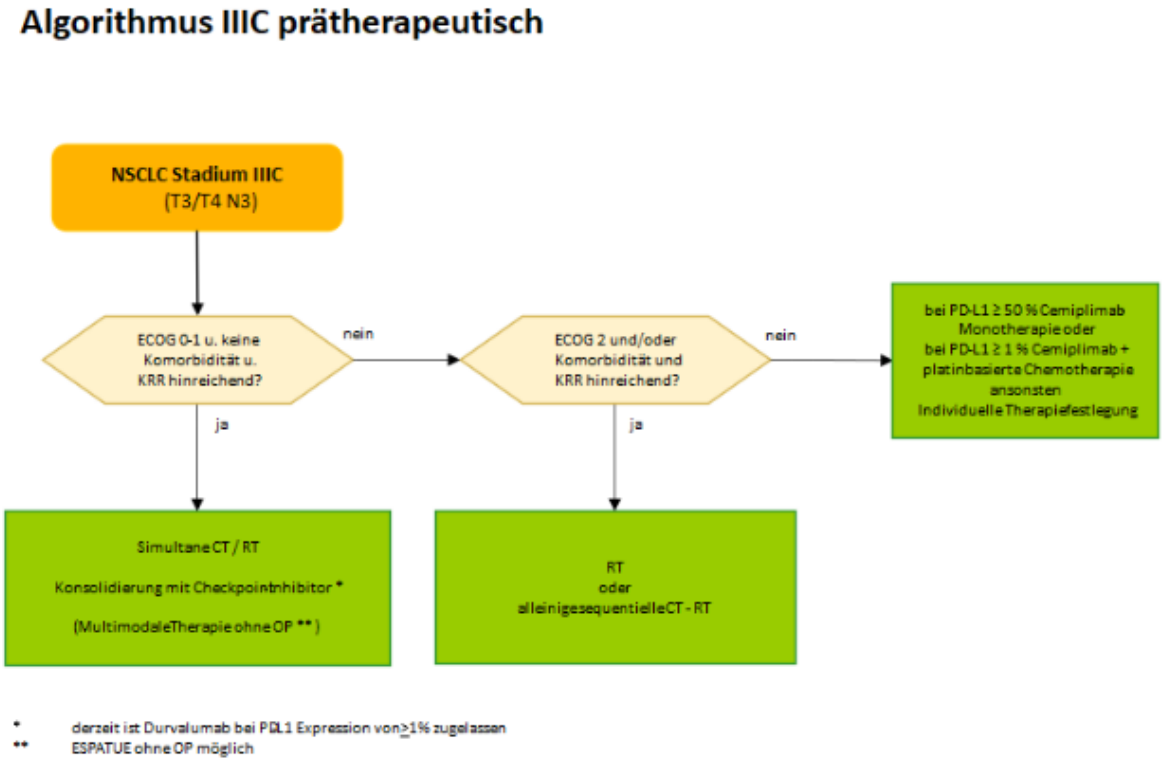


Abbildung 16: Flowchart NSCLC Stadium IIIC

Singh N et al., 2023 [9].

American Society of Clinical Oncology (ASCO)

Management of Stage III Non–Small-Cell Lung Cancer: ASCO Guideline Rapid Recommendation Update.

Zielsetzung/Fragestellung

To provide evidence-based recommendations to practicing clinicians on management of patients with stage III non–small-cell lung cancer (NSCLC).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium und Patientenvertretung dargelegt;
- Interessenkonflikte und Angaben zur Finanzierung dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz zutreffend;
- Formale Konsensusprozesse dargelegt; externes Begutachtungsverfahren:
- "[…] reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine
- Committee (EBMC)";
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität: laufende Aktualisierung geplant, Änderungseinträge und Gültigkeitsdauer jedoch unklar: "ASCO's formal updating process select existing guidelines are developed as living guidelines. The living guideline model requires constant updating of the literature and ongoing expert review and approval to provide current, user-friendly, high-quality, and evidence-based recommendations"

Recherche/Suchzeitraum:

- Original LL → **Daly ME et al., 2022 [1]**: PubMed (January 1990-August 2021) and Cochrane Library (January 2010-August 2021) of SRs and phase II and III randomized clinical trials (RCTs)
- Update: Three randomized control trials (RCTs) were published in 2022 prompted this amendment to the 2021 guideline.

LoE/GoR:

- The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process

Table 1. Definitions for Quality of Evidence Grades[7]

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- Strength of recommendations: The Expert Panel provides a rating of the strength of each recommendation. This assessment reflects the extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. Recommendations may fall into two categories; strong and weak. Factors determining the strength of a recommendation include balance between benefits and harms, certainty of evidence, confidence in values & preferences, and resource use. Recommendations may be made for or against the use of an intervention.

Recommendations

Surgery

- Recommendation 2.1. For patients with stage IIIA (N2) NSCLC, induction therapy followed by surgery (with or without adjuvant therapy) may be offered if all of the following conditions are met: (1) A complete resection (R0) of the primary tumor and involved lymph nodes is deemed possible; (2) N3 lymph nodes are deemed to be not involved by multidisciplinary consensus; (3) Perioperative (90-day) mortality is expected to be low (≤ 5%) (Type: Evidence based; balance of benefit and harm; Evidence quality: moderate; Strength of recommendation: weak)
- Recommendation 2.2. For selected patients with T4N0 disease (by size or extension), surgical resection may be offered if medically and surgically feasible following multidisciplinary review (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: weak).

Neoadjuvant therapy.

- Recommendation 3.1. Patients who are planned for a multimodality approach incorporating surgery as defined in Recommendation 2.1 should receive systemic neoadjuvant therapy (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).
- Recommendation 3.2. Patients with N2 disease who are planned for surgical resection should receive neoadjuvant chemotherapy or neoadjuvant concurrent chemoradiation (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).
- Recommendation 3.3. For patients with resectable superior sulcus disease, neoadjuvant concurrent chemoradiation should be administered (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).
- Recommendation from Update: Patients with stage III NSCLC who are planned for surgical resection should receive neoadjuvant chemoimmunotherapy, neoadjuvant chemotherapy, or neoadjuvant concurrent chemoradiation (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Adjuvant therapy.

- Recommendation 4.1. Patients with resected stage III NSCLC who did not receive neoadjuvant systemic therapy should be offered adjuvant platinum-based chemotherapy (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).
- Recommendation 4.2. Patients with resected stage III NSCLC with EGFR exon 19 deletion or exon 21 L858R mutation may be offered adjuvant osimertinib after platinum-based chemotherapy (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

- Recommendation 4.3. For patients with completely resected NSCLC with mediastinal N2 involvement without extracapsular extension who have received neoadjuvant or adjuvant platinum-based chemotherapy, postoperative radiation therapy should not be routinely offered (Type: Evidence based; balance of benefit and harm; Evidence quality: moderate; Strength of recommendation: weak).
- Recommendations from Update: For recommendations regarding the use of adjuvant atezolizumab after complete resection of stage IB-IIIA NSCLC, please refer to the IMPOWER-010 trial discussed in the rapid update on guidelines for adjuvant treatment after complete resection of stage I-III NSCLC.

Referenzen der Empfehlungen

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Lung cancer: diagnosis and management

Leitlinienorganisation/Fragestellung

This guideline covers diagnosing and managing non-small-cell and small-cell lung cancer. It aims to improve outcomes for patients by ensuring that the most effective tests and treatments are used, and that people have access to suitable palliative care and follow-up.

Methodik

Grundlage der Leitlinie

- Update (This guideline replaces CG121, and is the basis of QS17); Last updated: 14 March 2023
- 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:

- The sources for the 2019 and 2022 versions are the same:
  - Cochrane Database of Systematic Reviews – CDSR
  - Cochrane Central Register of Controlled Trials – CENTRAL
  - Database of Abstracts of Reviews of Effects – DARE
  - Health Technology Assessment Database – HTA
  - EMBASE (Ovid)
  - MEDLINE (Ovid)
  - MEDLINE In-Process (Ovid)
- The searches were conducted between October 2017 and April 2018 for 9 review questions (RQ).
- Searches were re-run in May 2018

LoE/ GoR

- RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Other study were quality assessed using the ROBINS-I too
- Systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups (High, Moderate, Low)
- A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses

Sonstige methodische Hinweise (Updates)

- March 2023: We added the NICE technology appraisal guidance on mobocertinib to the systemic anti-cancer therapy treatment pathways for advanced non-small-cell lung cancer.
- September 2022: We added the NICE technology appraisal guidance on tepotinib to the systemic anti-cancer therapy treatment pathways for advanced non-small-cell lung cancer.
- August 2022: We have changed how the information on systemic anti-cancer therapy for advanced non-small-cell lung cancer is presented.

- In March 2019: We reviewed the evidence and made new recommendations on mediastinal lymph node assessment, brain imaging, prophylactic cranial irradiation, radical radiotherapy and operable stage IIIA disease. These recommendations are marked [2019].

Update-Kennzeichnung:

These recommendations are marked [2005, amended 2019] or [2011, amended 2019].

Recommendations marked [2005] or [2011] last had an evidence review in 2005 or 2011. In some cases, minor changes have been made to the wording to bring the language and style up to date, without changing the meaning.

Empfehlungen

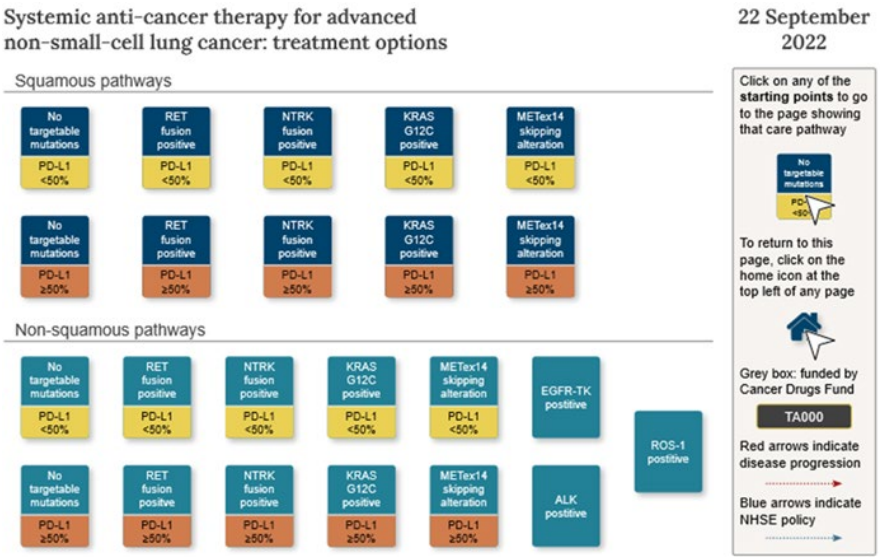
1.7 Combination treatment for non-small-cell lung cancer

- 1.7.2 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]
- 1.7.3 Offer postoperative chemotherapy to people with good performance status (WHO 0 or 1) and T1a–4, N1–2, M0 NSCLC. [2011]
- 1.7.4 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]
- 1.7.5 Offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy. [2011]
- 1.7.6 For people with stage I–II NSCLC that are suitable for surgery, do not offer neo-adjuvant treatment outside a clinical trial. [2011, amended 2019]
- 1.7.7 Ensure eligible people have the benefit of detailed discussion of the risks and benefits of adjuvant chemotherapy. [2011]
- 1.7.8 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]
- 1.7.9 For people with operable stage IIIA–N2 NSCLC who can have surgery and are well enough for multimodality therapy, consider chemoradiotherapy with surgery. [2019]
- 1.7.10 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]
- 1.7.11 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]
- 1.7.12 Multidisciplinary teams that provide chemoradiotherapy with surgery should have expertise in the combined therapy and in all of the individual components. [2019]
- 1.7.13 Centres performing lung resections for lung cancer should validate their data for the Royal College of Physicians Lung Cancer Clinical Outcomes publication and the National Lung Cancer Audit. [2019]

1.8 Systemic anti-cancer therapy (SACT) for advanced non-small-cell lung cancer
Treatment pathways

We have produced treatment pathways bringing together NICE recommended treatment options from this guideline and relevant technology appraisal guidance on advanced non-

small-cell lung cancer (squamous and non-squamous). The treatment pathways cover the recommended treatment options at each decision point.
https://www.nice.org.uk/guidance/ng122/resources/treatment-pathways-11189888173



Methodikernmerkung: „Treatment pathways" hier nicht weiter aufgeführt, da keine konkrete Angabe zu Tumorstadium, keine Unterscheidung bzgl. neo- bzw. adjuvanter Behandlung sowie Fokus auf Tumorprogress.

Passiglia F et al., 2020 [7]

Italian Association of Medical Oncologyg (AIOM)

Diagnosis and treatment of early and locally advanced non-small-cell lung cancer: The 2019 AIOM (Italian Association of Medical Oncology) clinical practice guidelines.

Leitlinienorganisation/Fragestellung

Evidence-based guideline for the management of lung tumors.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium, Patientenvertretung nicht angegeben;
- Interessenkonflikte dargelegt, finanzielle Unabhängigkeit nicht erwähnt;
- Systematische Suche, Auswahl und Bewertung der Evidenz zutreffend;
- Formale Konsensusprozesse und externes Begutachtungsverfahren nicht erwähnt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist über die Hintergrundinformationen dargestellt;
- Regelmäßige Überprüfung der Aktualität: keine Angabe zu Gültigkeit bzw. Aktualisierung

Recherche/Suchzeitraum:

- Medline (PubMed), Embase-databases and Cochrane-Library, up to September 2019.

LoE/GoR

- GRADE
- The global quality of evidence was defined as follow:

  - High (high grade of confidence in the study results): high probability that the estimated effect is similar to the true effect.
  - Moderate (moderate grade of confidence in the study results): moderate probability that the estimated effect is similar to the true effect, but limited possibility that it is substantially different.
  - Low (low grade of confidence in the study results): limited probability that the estimated effect is similar to the true effect, with high possibility that it is substantially different
  - Very low (very low grade of confidence in the study results): very limited probability that the estimated effect is similar to the true effect, with very high possibility that it is substantially different.
- The strength of clinical recommendations is graduated on four levels according to their clinical relevance, considering the benefit/risk outcomes ratio, the quality of evidence and other additional variables (equity, acceptability, feasibility, and patients' preference):
  - Strong for: The intervention should be considered as the treatment of choice (benefits are higher than risks)
  - Conditional for: The intervention may be considered as treatment of choice (not sure that benefits are higher than risks)
  - Conditional against: The intervention should not be considered as treatment of choice, except for selected cases after discussion with the patient (not sure that benefits are higher than risks)

Recommendations

Clinical Recommendations for the Diagnosis and Treatment of Early and Locally Advanced NSCLC.

Global quality of evidence GRADE	Clinical recommendation	Strenght of recommendation
Moderate	For patients with resectable NSCLC and abnormal mediastinal lymph-nodes at CT/PET scan, invasive sampling by endosonography should be considered as treatment of choice (compared to mediastinoscopy).	Conditional for
Moderate	For patients with stage I NSCLC, video-assisted thoracoscopic surgery (VATS) should be considered as treatment of choice	Conditional for
High	For patients with surgically resected, stage I-IIIA NSCLC, cisplatin-doublets adjuvant chemotherapy should be considered as a treatment of choice	Strong for
High	For patients with surgically resected, stage I-II NSCLC, post-operative radiotherapy must not be considered as a treatment option	Strong against
High	For patients with unresectable stage III NSCLC and ECOG-PS 0–1, definitive concurrent chemoradiation should be considered as treatment of choice	Strong for
High	For patients with unresectable stage III NSCLC, a cisplatin-based combination regimen should be considered as treatment of choice in association to definitive radiotherapy	Strong for
Low	For patients with unresectable stage III NSCLC, with partial response or stable disease (RECIST v1.1) after definitive chemoradiation, and tumor PD-L1 ≥ 1 %, consolidation treatment with durvalumab for 12 months should be considered as treatment of choice	Strong for

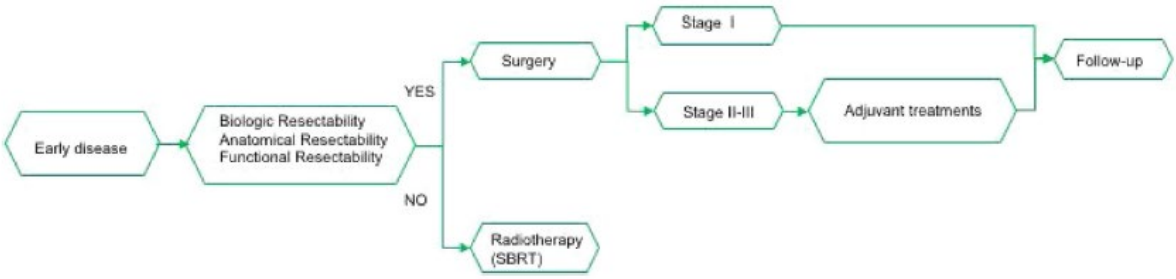


Fig. 2. Treatment of Early Stage NSCLC.

Fig. 3. Treatment of Locally Advanced NSCLC.

Hintergrund

5. Treatment of early disease
5.3. Adjuvant treatments

Post-operative platinum-based chemotherapy is recommended for all patients with stage II and III surgically resected disease, with performance status (ECOG PS) of 0–1 and without significant comorbidities (Table 1). Two meta-analysis demonstrated that post-operative platinum-based chemotherapy led to more than 10 % reduction in the risk of death, resulting in about 5 % absolute 5-years OS and diseasefree survival (DFS) improvement. Incidence of severe toxicities was about 65 %, with grade 3–4 neutropenia reported in 37 % of cases (Pignon et al., 2008; Burdett et al., 2015). Although the optimal interval between surgery and adjuvant treatment, emerging from randomized studies, is actually considered 6–8 weeks, a recent analysis of the National Cancer Database showed a comparable outcome in patients treated after a longer interval (Salazar et al., 2017). Data coming from the LACE meta-analysis suggested that adjuvant chemotherapy efficacy and tolerability are the same in the small subgroup of>70 years old patients, while prospective data on patients> 75 years old are lacking (Pignon et al., 2008). The majority of studies investigating carboplatin-based adjuvant regimens failed to show any survival benefit (Strauss et al., 2008; Ou et al., 2010; Felip et al., 2010), while direct comparison with cisplatin-doublets are currently lacking. Based on the results of the JBR.10 and ANITA trials (Douillard et al., 2006; Butts et al., 2010), cisplatin-vinorelbine is currently considered as the best regimen for adjuvant setting. Third generation agents, with at least comparable efficacy, such as gemcitabine, may be considered as an alternative valid option. Even if platinum-pemetrexed showed equal efficacy and better tolerability profile in phase II-III studies (Kreuter et al., 2016; Kenmotsu et al., 2019), it is not currently reimbursed and recommended as adjuvant therapy in Italy. In the decision process for adjuvant chemotherapy, several factors, including, age, pre- and post-operative morbidities, should be considered and discussed within a multidisciplinary team (Fig. 2). Several studies investigated the role of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in the adjuvant setting showing conflicting results, with a potential benefit likely limited to EGFR-mutated NSCLC (Kelly et al., 2015; Goss et al., 2013; Yue et al., 2018; Zhong et al., 2018; Li et al., 2014). The high heterogeneity of included populations, comparator arms, and treatment regimens, among these studies, along with the absence of OS data, do not allow to draw any definitive conclusion about the efficacy of these agents. Waiting for the ongoing prospective randomized trials investigating the efficacy of third-generation TKIs in biomarker-selected NSCLC patients, the use of EGFR-TKIs is not currently recommended in the adjuvant setting. Several studies and meta-analyses clearly demonstrated that postoperative radiotherapy (PORT) in patients with stage I-II NSCLC, is associated with higher risk of death [HR 1.18 (95 % CI 1.07–1.31)], disease recurrence [HR 1.10 (IC 95 % 0.99–1.21)], and local recurrence [HR 1.12 (IC 95 % 1.01–1.24), with absolute 5 % decrease in survival rate at 2 years (PORT Meta-analysis Trialists Group, 1998; Burdett et al., 2016). Therefore, it cannot be recommended as part of adjuvant strategies (Table 1).

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6. Treatment of locally advanced disease

6.1.2. Neoadjuvant treatments

Several studies and meta-analyses (Lim et al., 2009; NSCLC Metaanalysis Collaborative Group, 2014) suggested that the estimated benefit from neoadjuvant chemotherapy is comparable to that expected with adjuvant chemotherapy (5 % absolute 5 years OS increase), thus it may be considered as a feasible and ethical approach for patients with stage IIIA-IIIB (N2) NSCLC, and should be always evaluated in the context of multidisciplinary teams.

The phase III, randomized, Lung Intergroup trial 0139 (Albain et al., 2009) compared concurrent definitive chemoradiation versus concurrent induction chemoradiation followed by surgery in stage III (N2) NSCLC patients, showing no survival differences between the two treatment arms. A significant increase of median OS in favor of trimodal strategy has been observed in the subgroup of patients undergoing lobectomy (OS: 34 months versus 22 months), while median OS was significantly lower (19 months) with pneumonectomy. Another study compared sequential chemoradiation versus chemotherapy alone as induction treatment in stage III (N2) NSCLC, showing no significant OS differences between the two arms (Pless et al., 2014). These data suggest that

concurrent chemoradiation may be an effective induction strategy in selected patients with stage IIIA-IIIB (N2) NSCLC, and should be evaluated in the context of an experienced multidisciplinary team.

An Italian 2019 survey revealed as in patients with stage III, nonbulky, multi-station N2 disease, 66 % of thoracic specialists declare to prefer a neoadjuvant approach (with chemo or chemoradiation), rather than a definitive concomitant chemoradiation treatment (Bruni et al., 2018).

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6.1.3. Adjuvant treatments

Several studies included in the LACE meta-analysis (Pignon et al.,2008) demonstrated a 4.2 % absolute 5 years survival rate improvement for the subgroup of patients with stage IIIA-IIIB (N1 or single station N2) NSCLC who received adjuvant chemotherapy after surgical resection, suggesting cisplatin-doublets as the best regimen.

Although the results of the PORT meta-analysis (PORT Meta-analysis Trialists Group, 2000) showed a not clear survival benefit in patients with stage III, N2 pathological disease undergoing radiotherapy after radical surgery, more recent meta-analyses demonstrated that PORT is associated to a reduction in risk of loco-regional and systemic recurrences (Billiet et al., 2014; Li et al., 2016; Liu et al., 2019), with a significant increase in OS in the subgroup of patients with extensive pN2 involvement (HR = 0.85; 95 % CI: 0.79-0.92) (Liu et al., 2019). Waiting for the final results of the prospective LungArt trial, PORT may be considered as an effective treatment for surgically resected patients with extensive N2 pathological involvement or R1 disease, and should be evaluated in the context of an experienced multidisciplinary team.

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American Society of Clinical Oncology (ASCO)
Adjuvant systemic therapy and adjuvant radiation therapy for stage I-IIIA completely resected non-small-cell lung cancer: ASCO Guideline Rapid Recommendation Update.

Zielsetzung/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)?
In 2017, ASCO with Ontario Health—Cancer Care Ontario published a guideline on adjuvant therapy in resected stage I-III NSCLCs. Two RCTs were published in 2020 and 2021 and prompted this amendment to the 2017 guideline.

Methodik

Grundlage der Leitlinie

Update: Amendment to the 2017 guideline

- Repräsentatives Gremium, keine Patientenvertretung angegeben;
- Interessenkonflikte dargelegt, Angaben zur Finazierung fehlen;
- Systematische Suche, Auswahl und Bewertung der Evidenz zutreffend;
- Formale Konsensusprozesse dargelegt; externes Begutachtungsverfahren: "[…] independently reviewed and approved by the EBMC";
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität: laufende Aktualisierung geplant, Änderungseinträge und Gültigkeit jedoch unklar: "ASCO's formal updating process select existing guidelines are developed as living guidelines. The living guideline model requires constant updating of the literature and ongoing expert review and approval to provide current, user-friendly, high-quality, and evidence-based recommendations"

Recherche/Suchzeitraum:

- Update-Recherche: targeted electronic literature search to identify RCTs of osimertinib and atezolizumab in this patient population was conducted, keine Angabe bzgl. Suchzeitraum

LoE/GoR

Table 1. Definitions for Quality of Evidence Grades[7]

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- Strength of recommendations: The Expert Panel provides a rating of the strength of each recommendation. This assessment reflects the extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. Recommendations may fall into two categories; strong and weak. Factors determining the strength of a recommendation include balance between benefits and harms, certainty of evidence, confidence in values & preferences, and resource use. Recommendations may be made for or against the use of an intervention.

- Certainty of evidence: The quality of evidence used to inform a given recommendation is assessed to evaluate its validity, reliability, and consistency. The quality of evidence is rated for each outcome across studies. Factors assessed when rating the quality of evidence include study design, consistency of results, directness of evidence, precision, publication bias, magnitude of effect, confounding, and dose-response gradient. This assessment considers the individual study quality ratings, the overall risk of bias, and the overall validity and reliability of the total body of evidence. The summary rating is an indication of the Expert Panel's confidence that an estimate of the effect is adequate to support a particular recommendation. The certainty of the evidence is defined as one of four grades: high, moderate, low, or very low. Definitions are available in Table 1.

Recommendations

2021 UPDATED RECOMMENDATION

- Recommendation 1.3
  Stages IIA, IIB, and IIIA: Adjuvant cisplatin-based chemotherapy is recommended for all patients. Adjuvant osimertinib is recommended after chemotherapy for patients with tumorswith sensitizing EGFR mutations, regardless of the PD-L1status. Adjuvant atezolizumab is recommended for all patients with PD-L1 ≥ 1% after cisplatin-based chemotherapy except for patients with sensitizing EGFR mutations (Type: evidence based and panel consensus; Evidence quality: high; Strength of recommendation: strong).

Note: the guideline recommendations are based on the 7th edition staging system used in the studies as opposed to the current 8th edition staging system for lung cancer.[5]

Referenzen zu den Empfehlungen

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5.AJCC 8th Edition for Lung cancer. AJCC Cancer Staging Manual (ed 8) New York, NY: Springer, 2017

2016 RECOMMENDATION (*Guideline 2017-unverändert*)

- 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[2]).
- 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[4]; Strength of recommendation: Moderate).

Referenzen zu den Empfehlungen

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2023) am 27.11.2023

#	Suchfrage
1	[mh "Carcinoma, Non-Small-Cell Lung"] OR [mh ^"Lung Neoplasms"]
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 lesion* OR malignan*):ti,ab,kw
4	#2 AND #3
5	nsclc*:ti,ab,kw
6	#1 OR #4 OR #5
7	#6 with Cochrane Library publication date from Nov 2018 to present

Systematic Reviews in PubMed am 27.11.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	**"Carcinoma, Non-Small-Cell Lung"[majr]**
2	"nonsmall cell lung"[tiab:~0] OR "non small cell lung"[tiab:~0]
3	#2 AND ((((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab])
4	#1 OR (#3)
5	(#4) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR

#	Suchfrage
	scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
6	((#5) AND ("2018/11/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 27.11.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	"Carcinoma, Non-Small-Cell Lung"[mh]
2	Lung Neoplasms/therapy
3	"nonsmall cell lung"[tiab:~0] OR "non small cell lung"[tiab:~0] OR Lung[ti]
4	(#3) AND ((((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab])
5	#1 OR #2 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
7	(((#6) AND ("2018/11/01"[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]))
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 27.11.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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4. **Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften).** Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms; S3-Leitlinie; Langversion 3.0 [online]. AWMF-Registernummer 020-007OL. Berlin (GER): Leitlinienprogramm Onkologie; 2024. [Zugriff: 25.03.2024]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Lungenkarzinom/Version_3/LL_Lungenkarzinom_Langversion_3.0.pdf.
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[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46.https://doi.org/10.1016/j.jclinepi.2016.01.021

Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO