

**Behandlungs- und Versorgungspraxis des kleinzelligen und des nicht-
kleinzelligen Bronchialkarzinoms Stadium III: Welche Gemeinsamkeiten
und Unterschiede bestehen in der klinischen Praxis?**

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Vorwort

Diese Dissertation ist das Ergebnis einer intensiven und lehrreichen Zeit, in der ich von vielen Seiten Unterstützung erfahren durfte.

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Inhaltsverzeichnis

Abkürzungsverzeichnis

Zusammenfassung	1
Einleitung	1
Methoden und Ergebnisse	4
Diskussion	7
Zusammenfassung	13
Referenzen.....	14
Thesen	18
Publikationsteil.....	19
Publikation 1: Survey of treatment and care practices in small-cell lung cancer among German radiation oncologists.....	20
Publikation 2: Treatment patterns in stage III non-small-cell lung cancer patients: a population-based study using German cancer registry data.....	34
Erklärungen	

Abkürzungsverzeichnis

CRT	Chemoradiotherapie
CT	Computertomografie
ES-SCLC	extensive disease small-cell lung cancer
F-FDG-PET	F-Fluor-Desoxyglucose-Positronen-Emissions-Tomographie
HR	Hazard Ratio
IMRT	intensitätsmodulierte Strahlentherapie
KI	Konfidenzintervall
LS-SCLC	limited disease small-cell lung cancer
NSCLC	nicht-kleinzelliges Bronchialkarzinom
OS	medianes Gesamtüberleben
PCI	prophylaktische kraniale Bestrahlung
PD-L1	programmierter Zelltod-Ligand 1
PET-CT	Positronen-Emissions-Tomographie
PFS	progressionsfreies Überleben
RCT	randomisiert-kontrollierte Studie
RT	Thoraxbestrahlung
SCLC	kleinzelliges Bronchialkarzinom

Zusammenfassung

Behandlungs- und Versorgungspraxis des kleinzelligen und des nicht-kleinzelligen Bronchialkarzinoms Stadium III: Welche Gemeinsamkeiten und Unterschiede bestehen in der klinischen Praxis?

Einleitung

Lungenkrebs ist eine der häufigsten bösartigen Krebserkrankungen in Deutschland, wobei das nicht-kleinzellige Karzinom (NSCLC) ca. 85% und das kleinzellige Karzinom (SCLC) etwa 15 % aller Fälle ausmacht [1]. In den letzten 30 Jahren verhalten sich die Neuerkrankungs- sowie Sterberaten bei Frauen und Männern gegensätzlich. Steigt sie bei Frauen kontinuierlich an, nimmt sie bei den Männern im Laufe der Jahre ab. Als Ursache für diese Entwicklung sieht man am ehesten eine Umstellung der Rauchgewohnheiten bei beiden Geschlechtern. Tabakkonsum ist der Hauptrisikofaktor einer Lungenkrebserkrankung. Als weitere exogene, jedoch untergeordnete Faktoren zählen kanzerogene Stoffe wie Asbest oder polyzyklische aromatische Kohlenwasserstoffe und Luftschadstoffe wie Feinstaub oder Dieselabgase. Auch endogene Faktoren in Form einer genetischen Prädisposition oder Lungenvorerkrankungen spielen eine Rolle. [1]

Das kleinzellige Bronchialkarzinom zeichnet sich durch sein aggressives Wachstum und eine frühe Entwicklung von Metastasen aus. Es wird in die Stadien der „very limited“, „limited“ und „extensive disease“ unterteilt, wobei Letztere durch ein Auftreten von Metastasen charakterisiert ist. Die Therapie des SCLC weist in Deutschland, aber auch weltweit, große Unterschiede auf. Obwohl sich die Standardtherapie, bestehend aus Chemotherapie und Bestrahlung, als wirksam erwiesen hat, gibt es bis heute große Differenzen in der Behandlungs- und Versorgungspraxis. [23] Die große Bedeutung der Chemotherapie zeigt sich sowohl im Stadium der „limited“ als auch der „extensive disease“. Mehrere Studien haben den Überlebensvorteil einer Chemotherapie im Vergleich zu einer alleinigen Operation nachgewiesen [2].

Darüber hinaus besteht nach wie vor eine Konfliktlage bei einem Einsatz der prophylaktischen kranialen Bestrahlung (PCI). Es wird beispielsweise diskutiert, welchen Einfluss die PCI auf Patienten hat, bei denen eine Hirnmetastasen-Freiheit nach einer Chemoradi-

otherapie (CRT) radiologisch nachgewiesen wurde [3]. Zudem ist unklar, welche Dosierung und Fraktionierung zu applizieren ist. Darüber hinaus gibt es Diskrepanzen hinsichtlich der Einschlusskriterien und der Frage, welche Patientengruppe am meisten von dieser Therapieform profitiert [4]. Frühere Studien untersuchten auch, in welchem Umfang und in welchen Abständen Kontrolluntersuchungen als Nachsorge durchgeführt werden sollten, insbesondere bei Patienten, bei denen keine prophylaktische Schädelbestrahlung durchgeführt wurde [3].

Neue Behandlungsmethoden, wie die Antikörpertherapie mit dem programmierten Zelltod-Liganden 1 (PD-L1) Atezolizumab, rücken stärker in den Fokus und konnten sich in den letzten Jahren teilweise in der Praxis etablieren [5].

Das nicht-kleinzellige Bronchialkarzinom (NSCLC) wird in vier Stadien unterteilt. Das Stadium III des NSCLC beschreibt eine heterogene Gruppe von Patienten, bei denen der Tumor lokal fortgeschritten ist. Aufgrund dieser Heterogenität unterteilt man das Stadium in die Subgruppen A-C, wobei die Tumorausbreitung und ein mögliches Vorhandensein von Metastasen in ipsilateralen oder kontralateralen Lymphknoten diese definiert [6, 7]. Die 5-Jahren-Überlebensrate im Stadium III wird bei Frauen auf 27 % und bei Männern auf 20 % geschätzt [8].

Die optimale Behandlung für NSCLC-Patienten im Stadium III ist nach wie vor ein Diskussionsthema. Während die aktuellen Leitlinien für die Mehrzahl der Patienten im Stadium III eine gleichzeitige Chemoradiotherapie (CRT) als Standardbehandlung empfehlen, können Faktoren, wie beispielsweise das Unterstadium des Tumors, die Resektabilität, oder das Patientenprofil (Lungenfunktion, Begleiterkrankungen und Alter) die Behandlungsstrategie und damit das Überleben beeinflussen [9]. Um den idealen Behandlungsplan für einen Patienten mit nicht-kleinzelligem Lungenkrebs festzulegen, ist es daher unerlässlich, den Tumor genau zu beurteilen.

Die Behandlung von fortgeschrittenem Lungenkrebs hat sich in den letzten zehn Jahren erheblich verändert, vor allem aufgrund von Fortschritten bei den Diagnose- und Behandlungsstrategien. Hierzu zählen vor allem der F-Fluor-Desoxyglucose-Positronen-Emissions-Tomographie (F-FDG-PET/CT) und der intensitätsmodulierten Strahlentherapie (IMRT). Änderungen bei den Chemotherapieschemata, die Einführung der Immuntherapie und das Aufkommen gezielter Therapien für bestimmte genetische Mutationen sind ebenfalls zu erwähnen. [10-17] Diese Fortschritte könnten zu einer Verbesserung des Überlebens von NSCLC-Patienten geführt haben.

In Anbetracht dieser Entwicklungen bestand das Ziel unserer Studie darin, die Behandlungsmuster in einer Kohorte von Patienten mit NSCLC im Stadium III über verschiedene Zeiträume zu beschreiben. Zudem wollten wir untersuchen, ob Patienten, die jüngst diagnostiziert und behandelt wurden, ein verbessertes Gesamtüberleben aufweisen.

Methoden und Ergebnisse

Um die Versorgungspraxis beim kleinzelligen Bronchialkarzinom zu untersuchen, erstellten wir eine anonyme Umfrage mit 34 Items, die per E-Mail an etwa 1300 Strahlentherapeuten in ganz Deutschland verschickt wurde (Tabelle 3). Der Befragungszeitraum erstreckte sich von August 2020 bis Januar 2021. Insgesamt erhielten wir 74 Rückmeldungen.

Unser Projekt wurde auf ethische Unbedenklichkeit geprüft und von der Ethikkommission der Medizinischen Fakultät der Martin-Luther-Universität Halle-Wittenberg genehmigt (Referenznummer 2020-139).

Um regionale Unterschiede zu identifizieren, unterteilten wir die 16 Bundesländer in 4 Gruppen (Nord, West, Ost, Süd). Zusätzlich wurden die Teilnehmer nach ihrem Alter, der Berufserfahrung und der Anzahl der jährlich betreuten Patienten mit SCLC befragt. Ein Schwerpunkt der Fragen lag auf dem Einsatz der konsolidierenden Thoraxbestrahlung (RT) und der PCI. Bewertet wurden u. a. Fraktionierung und Dosierung, Planungstechniken, Definition des Zielvolumens und patientenspezifische Einschlusskriterien. Zudem wurde der Einsatz einer Antikörpertherapie durch Atezolizumab beleuchtet.

Als Ergebnisse konnten wir festhalten, dass beim LS-SCLC die Therapieplanung überwiegend anhand Computertomographie (CT) Thorax/Abdomen/Becken (88 %), PET-CT (86 %) und Lungenfunktionstests (88 %) durchgeführt wird. Neunundneunzig Prozent der Befragten führten die Bestrahlung gleichzeitig mit der Chemotherapie durch, vorzugsweise beginnend im Zyklus eins oder zwei (71 %) der Chemotherapie. Das häufigste Dosis- und Fraktionierungsschema für die RT war 60-66 Gy in 30-33 Fraktionen (einmal täglich: 62 % aller Befragten). Für die RT beim ES-SCLC wurde am häufigsten 30 Gy in 10 Fraktionen (einmal täglich: 33 % aller Befragten) angegeben. Nur 25 % verwendeten eine simultane Chemosensibilisierung bei einer konsolidierenden Bestrahlung. Die Einschlusskriterien für die PCI waren bei LS-SCLC und ES-SCLC ähnlich, wobei der Karnofsky-Index (78 % und 75 %) den wichtigsten Entscheidungsfaktor darstellte. Die Befragten verwendeten in beiden Stadien am häufigsten ein Bestrahlungsschema von 30 Gy in 15 Fraktionen (68 % LS-SCLC, 60 % ES-SCLC). Eine Immuntherapie wurde beim LS-SCLC von 45 % der Befragten regelmäßig oder gelegentlich eingesetzt, wobei eine eingeschränkte Lungenfunktion (37 %), kardiale Begleiterkrankungen (30 %) und Lebe-

rinsuffizienz (30 %) die am häufigsten genannten Ausschlusskriterien für diese Therapieform waren. Siebenundachtzig Prozent der Strahlentherapeuten gaben an, Atezolizumab bei Patienten mit ES-SCLC zu verwenden.

Zur Beurteilung versorgungswissenschaftlicher Fragestellungen beim NSCLC im Stadium III führten wir eine retrospektive Studie basierend auf Daten des deutschen Krebsregisters durch. Diese umfasste insgesamt 14.606 NSCLC-Patienten im Stadium III, die zwischen 2007 und 2018 diagnostiziert wurden. Drei Zeiträume wurden entsprechend der Verfügbarkeit moderner Diagnose- und Behandlungsstrategien definiert (2007-2010 Periode geringer Verfügbarkeit, 2011-2014 Übergangsperiode, 2015-2018 moderne Periode). Die Patienten wurden nach der Behandlung kategorisiert, die sie in diesen Zeiträumen erhielten (nur Operation, Operation + Strahlentherapie, Operation + Chemotherapie, nur Strahlentherapie, nur Chemotherapie, Strahlentherapie + Chemotherapie, und Operation + Strahlentherapie + Chemotherapie). Kaplan-Meier-Kurven und multivariate Cox-Proportional-Hazard-Modelle wurden verwendet, um den Zusammenhang zwischen der Diagnose während einer bestimmten Ära und dem Überleben zu untersuchen.

Von den 14.606 NSCLC-Patienten im Stadium III wiesen 44,7 % Stadium IIIA, 39,0 % Stadium IIIB und 16,3 % Stadium IIIC auf. Bezogen auf die drei Zeitabschnitte ergab sich kein Unterschied in der Verteilung. Die drei häufigsten Behandlungsmodalitäten, die die Patienten über die drei Zeiträume hinweg erhielten, waren Strahlentherapie + Chemotherapie, nur Strahlentherapie und nur Chemotherapie.

Unsere gesamte Stichprobe wies ein medianes Gesamtüberleben (OS) von 18 Monaten auf (95% KI 17,0-19,0). Die beobachtete 3-Jahres-Überlebensrate betrug 30,5 % (95 % KI 29,7-31,3), wobei diese von 26,2 % (95 % KI 24,9-27,6) im Zeitraum 2007-2010 auf 37,1 % (95 % KI 35,4-39,0) im Zeitraum 2015-2018 anstieg. Diese Entwicklung spiegelte sich auch im OS wider, welches von 16 Monaten (95 % KI 15,0-17,0) im Zeitraum 2007-2010 auf 22 Monate (95 % KI 21,0-23,0) im Zeitraum 2015-2018 stieg.

Zudem wurde deutlich, dass Patienten, bei denen ein NSCLC zwischen 2015-2018 diagnostiziert wurde, unabhängig von der Behandlung stets ein besseres Gesamtüberleben aufwiesen als Patienten, welche die Diagnose zwischen 2007-2010 erhielten.

Unsere Cox-Proportional-Hazard-Modelle unterstrichen diese Verbesserung der Überlebensrate. Patienten, die in der Übergangszeit und in der modernen Periode diagnostiziert wurden, wiesen durchweg ein geringeres Risiko für die Gesamtmortalität auf als Patienten

ten, die in der Periode 2007-2010 diagnostiziert wurden. Dies galt insbesondere für Patienten, die in den Unterstadien IIIA [2015-2018: IIIA HR 0,60, 95 % KI (0,49-0,75)] und IIIC [2015-2018: IIIC HR 0,69, 95 % KI (0,56-0,85)] eine Strahlen- und Chemotherapie erhielten.

Diskussion

Unsere Umfrage zeigte, dass weiterhin Unterschiede in der Versorgungspraxis des SCLC in deutschen Strahlentherapiezentren bestehen. Dies betraf Dosierungsschemata, Indikationen für eine Bestrahlung oder auch den Einsatz der Antikörpertherapie.

LS-SCLC

In der Behandlung des LS-SCLC variierten die Behandlungsschemata in der Chemoradiotherapie, wobei in der Umfrage 66 Gy in 30 bis 33 Fraktionen (einmal täglich) und 45 Gy in 30 Fraktionen (zweimal täglich) am häufigsten genannt wurden.

In der randomisierten CONVERT-Studie von Faivre-Finn et al. [18] wurden diese beiden Schemata im Hinblick auf das Gesamtüberleben verglichen. Das mediane OS betrug 30 Monate (95 % Konfidenzintervall [KI] 24-34) in der Gruppe mit zweimal täglicher Gabe gegenüber 25 Monaten (21-31) in der Gruppe mit einmal täglicher Gabe [18]. Ebenso zeigte sich ein nicht signifikanter Vorteil beim 2-Jahres-OS (56 % gegenüber 51 %) für die zweimal täglich verabreichte Therapie. Die Studie ergab, dass es nur geringe Unterschiede zwischen den beiden Schemata im Hinblick auf das OS gab [18]. Die Hyperfraktionierung erwies sich in Bezug auf Dauer und Compliance als sinnvoller Ansatz zur Behandlung des SCLC, ist aber in der klinischen Routine nicht das bevorzugte Schema.

In der norwegischen THORA-Studie [19] wurde eine hochdosierte Thoraxbestrahlung von 60 Gy in 40 Fraktionen mit einer Standarddosis von 45 Gy in 30 Fraktionen verglichen, wobei beide Patientengruppen zweimal täglich bestrahlt wurden. Beim 2-Jahres-OS zeigte sich ein signifikanter Vorteil auf Seiten der Hochdosis-Bestrahlung (74 % gegenüber 48 %). Eine erhöhte Toxizität wurde in der 60-Gy-Gruppe nicht beobachtet. Nach Ansicht der Autoren sollte dieses Behandlungsschema daher als Alternative in Betracht gezogen werden [19].

Yin et al. [20] untersuchten 2019 in einer Metaanalyse das OS und die Inzidenz von Hirnmetastasen bei Patienten mit PCI im Vergleich zu Patienten ohne PCI. Es zeigte sich, dass der Einsatz einer PCI zu einer signifikant geringeren Inzidenz von Hirnmetastasen und einem leicht verlängerten OS führte. Hierbei sei zu erwähnen, dass Patienten, die nach einer CRT eine kraniale Bildgebung erhielten und keine Hirnmetastasen aufwiesen, keinen OS-Vorteil durch die PCI hatten (Hazard Ratio [HR] = 0,94; 95% KI 0,74-1,18). Im Gegensatz dazu zeigten Patienten ohne Bildgebung einen signifikanten Vorteil (HR = 0,70; 95% KI 0,57-0,85) [20].

Levy et al. [21] nutzten die Daten der CONVERT-Studie [18], um herauszufinden, ob es beim LS-SCLC einen Zusammenhang zwischen dem Auftreten von Hirnmetastasen und dem Anwendungsschema der Thoraxbestrahlung gibt. In der Studie entwickelten 8 % der zuvor einmal täglich und 9 % der zuvor zweimal täglich bestrahlten Patienten Hirnmetastasen; somit konnte kein Zusammenhang festgestellt werden [21].

In der Umfrage gab ein Drittel der Befragten an, Atezolizumab regelmäßig bei Patienten mit LS-SCLC einzusetzen. In einer im Mai 2019 begonnenen randomisierten Phase-II/III-Studie von Higgins et al. [22] wird die Kombination von Chemotherapie und Atezolizumab bei Patienten mit LS-SCLC untersucht, wobei progressionsfreies Überleben (PFS) und OS die primären Endpunkte darstellen. Für Atezolizumab wird eine Hazard Ratio von 0,62 für das PFS und 0,71 für das OS bei einem Signifikanzniveau von 0,025 erwartet [22].

Zusammenfassend verglichen wir unsere Umfrageergebnisse und die oben genannten Studien mit den aktuellen nationalen Leitlinien [23] für die Behandlung des LS-SCLC. Die Leitlinie empfiehlt eine kombinierte Chemotherapie mit Cisplatin und Etoposid, die über vier bis sechs Zyklen angewendet werden sollte. Neunundneunzig Prozent der von uns Befragten verwendeten Cisplatin/Etoposid. Nach der Leitlinie [23] sollte bei allen Patienten mit bestrahlungsfähiger Tumorausdehnung eine Strahlentherapie durchgeführt werden. Diese sollte zeitgleich mit der Chemotherapie erfolgen und frühzeitig begonnen werden. Unserer Umfrage zufolge begannen 71 % der Strahlentherapeuten die Strahlentherapie im ersten oder zweiten Zyklus, 27 % im dritten oder vierten Zyklus der Chemotherapie. In der CONVERT-Studie [18] konnte kein signifikanter Unterschied zwischen dem Einsatz eines konventionellen Behandlungsschemas mit 60-66 Gy in 30 Fraktionen (einmal täglich) und einem hyperfraktionierten Schema mit 45 Gy in 30 Fraktionen (zweimal täglich) nachgewiesen werden. In der deutschen Leitlinie [23] werden daher beide Schemata empfohlen, was sich auch in unserer Umfrage widerspiegelte. Zweiundsechzig Prozent der Befragten behandelten mit 60-66 Gy in 30 Fraktionen (einmal täglich) und 21% mit 45 Gy in 30 Fraktionen (zweimal täglich).

Die Leitlinie [23] empfiehlt die PCI bei allen Patienten in Remission mit einem Behandlungsschema von 25 oder 30 Gy in 2,0 bzw. 2,5 Einzeldosen, was von 99 % unserer Befragten bestätigt wurde.

Für die Durchführung einer Antikörpertherapie wurden in der aktuellen Leitlinie [23] keine Empfehlungen ausgesprochen.

ES-SCLC

Zur Beurteilung der Wirksamkeit einer PCI bei Patienten mit ES-SLCL führten Takahashi et al. [3] eine randomisierte Studie durch und verglichen das OS zwischen der PCI-Gruppe und der Kontrollgruppe, wobei vor Studienbeginn Hirnmetastasen mittels MRT ausgeschlossen wurden. Die Patienten erhielten im Verlauf Kontroll-MRTs in dreimonatigen Abständen für ein Jahr und anschließend nach 18 und 24 Monaten. Die Studie ergab ein Hirnmetastasierungs-Risiko nach 12 Monaten von 32,9 % in der PCI- und von 59 % in der Kontrollgruppe. Die Überlebenszeit betrug 11,6 Monate in der PCI- und 13,7 Monate in der Kontrollgruppe. Die Autoren kamen zu dem Schluss, dass eine PCI bei Patienten ohne Hirnmetastasen-Nachweis nicht notwendig ist, sofern regelmäßige MRT-Kontrollen, wie oben erwähnt, durchgeführt werden. Asymptomatische Metastasen sollten mit Strahlen- und Chemotherapie behandelt werden. [3]

Chen et al. [24] untersuchten den Effekt einer frühen gegenüber einer späten PCI. Die frühe PCI wurde definiert als ein Intervall zwischen dem Beginn der Chemotherapie und dem Beginn der Bestrahlung von weniger als 6 Monaten und die späte PCI als ein Intervall von mehr als 6 Monaten. Primärer Endpunkt war die Inzidenz von Hirnmetastasen, die in der frühen PCI-Gruppe signifikant niedriger war als in der späten PCI-Gruppe (HR, 0,45; 95% KI 0,23-0,89; $p = 0,024$) [24].

Laut unserer Umfrage fand eine Immuntherapie durch Atezolizumab bei Patienten mit ES-SCLC in 33 % regelmäßig und in 44 % gelegentlich Anwendung.

In der IMPower133-RCT [5] wurde die Kombination von Atezolizumab und Carboplatin plus Etoposid untersucht. Endpunkte waren das OS und das PFS. Im Vergleich zur Placebogruppe hatte die Atezolizumab-Gruppe ein signifikant verlängertes OS (12,3 vs. 10,3 Monate; HR 0,70; 95% KI 0,54 bis 0,91; $p = 0,007$) und ein verlängertes PFS (5,2 vs. 4,3 Monate). Bezogen auf individuelle Ausgangsmerkmale profitierten Patienten unter 65 Jahre (OS 12,1 Monate Atezolizumab vs. 11,5 Monate Placebo) und über 65 Jahre (12,5 vs. 9,6 Monate). Bei Patienten mit Hirnmetastasen zeigte sich ein Vorteil in der Placebogruppe (8,5 vs. 9,7 Monate). [5] Aufgrund der kleinen Population sind jedoch weitere Studien notwendig, um Standards in der Behandlung von Patienten mit Hirnmetastasen und Immuntherapie zu etablieren. Hinsichtlich der Nebenwirkungen, hauptsächlich in Form von Neutropenie, Anämie, Thrombozytopenie, Alopezie und Übelkeit, zeigte die Kombination von Etoposid und Atezolizumab keinen Unterschied zur alleinigen Chemotherapie (Grad 1 oder 2 36,9 vs. 34,7%, Grad 3 oder 4 56,6 vs. 56,1%, Grad 5 jeweils 1,5%) [5].

Wir verglichen unsere Umfrageergebnisse mit den aktuellen nationalen Leitlinien [21]. Zur Dosierung und Fraktionierung der Strahlentherapie beim ES-SCLC fanden sich keine Empfehlungen [21], was sich in unsere Umfrage anhand sehr heterogener Ergebnisse widerspiegelte. Die Leitlinie empfiehlt ausdrücklich die Kombination von Chemotherapie und Immuntherapie [21]. Zusätzlich zu den oben genannten Studien haben Meta-Analysen gezeigt, dass Patienten unabhängig von Alter oder Leistungsstatus von einer PD-L1-Checkpoint-Inhibitor-Therapie profitieren [21]. Aufgrund der Variabilität beim Einsatz der Strahlentherapie sind genauere Empfehlungen erforderlich.

Eine Einschränkung der Umfrage war die geringe Zahl der Teilnehmer. Mit 74 beantworteten Fragebögen zählten wir eine Rücklaufquote von weniger als 1 %.

Da unsere Umfrage anonym durchgeführt wurde, liegen uns keine Daten über die Art der Einrichtung vor, aus der die Antworten stammen. Daher können wir keine Rückschlüsse darauf ziehen, ob es Unterschiede in der Versorgung zwischen Universitätskliniken, außeruniversitären Krankenhäusern und dem ambulanten Bereich gab.

NSCLC

In unserer zweiten Studie untersuchten wir die Behandlungsmodalitäten und das Gesamtüberleben von NSCLC-Patienten im Stadium III in Deutschland zwischen 2007 und 2018. Unsere Ergebnisse zeigten eine Verbesserung des Gesamtüberlebens im Laufe der Zeit. Zu dieser Entwicklung könnten unter anderem Fortschritte in der Entwicklung von Diagnoseinstrumenten wie dem FDG-PET und Behandlungsmethoden wie dem IMRT beigetragen haben.

Eine aktuelle Kohortenstudie der jungen DEGRO-Studiengruppe [13] untersuchte die Auswirkungen der Strahlentherapieplanung auf das Gesamtüberleben und stellte fest, dass bei NSCLC-Patienten im Stadium III, die zwischen 2010 und 2013 diagnostiziert wurden, der Einsatz von PET/CT zu besseren Ergebnissen führte (HR = 0,80, KI 0,56-1,16). Eine ähnliche Entwicklung konnten Nestle et al. [15] feststellen. Sie verdeutlichten, dass eine FDG-PET-basierte Reduktion des Zielvolumens das Risiko einer lokoregionalen Progression im Vergleich zur konventionellen (CT-)Planung verringerte [HR 0,57, 95% KI 0,30-1,06] [15]. Die zunehmende Anwendung der IMRT bei gleichzeitiger Chemoradiotherapie zeigte ebenfalls eine Verbesserung des Überlebens, da durch eine präzise und gezielte Verabreichung das Risiko lebensbedrohlicher Toxizität minimiert wird [25].

Die verbesserten Überlebensraten in der Periode von 2015-2018 beziehen sich auf verschiedene Aspekte, wobei die Anwendung der IMRT, eine Weiterentwicklung der Chemotherapieschemata und die Einführung der Immuntherapie hervorzuheben sind.

In der aktuellen nationalen S3-Leitlinie [23] wird das Einrichten eines interdisziplinären Tumorboards empfohlen, um den Umfang der erforderlichen Diagnostik festzulegen, das Tumorstadium exakt einzustufen und fundierte Entscheidungen über die bestmögliche Behandlung eines jeden einzelnen Patienten zu treffen. Als bevorzugte Therapiemethode für Patienten mit NSCLC im Stadium III, einschließlich derer mit inoperablen Tumoren, sollte eine gleichzeitige CRT angewendet werden. Darüber hinaus wird für ausgewählte Patienten mit einer PD-L1-Expression von 1 % oder mehr die Kombination von Immuntherapie und CRT empfohlen. [23]

In Anbetracht der Tatsache, dass die Diagnosen in unserer Studie über einen Zeitraum von 12 Jahren (2007-2018) gestellt wurden, ist der Trend zur bimodalen Behandlungsmodalität von Strahlentherapie + Chemotherapie als bevorzugte Therapie für NSCLC im Stadium III offensichtlich. Diese Patientengruppe wies zusammen mit denjenigen, die mit Operation + Strahlentherapie behandelt wurden, die größte Verbesserung der Überlebensrate auf.

In unserer Studie wurde deutlich, dass erhebliche Unterschiede in den Behandlungsmodalitäten der verschiedenen Unterstadien des NSCLC vorherrschen. Die meisten Patienten, bei denen die Diagnose im Stadium IIIA gestellt wurde, erhielten entweder eine alleinige Operation oder eine Kombination aus Operation und Chemotherapie. Patienten im Stadium IIIB und IIIC wurden in etwa 75 % der Fälle durch Strahlentherapie + Chemotherapie oder Strahlentherapie allein behandelt. Diese Ergebnisse entsprachen den in den Leitlinien [23] empfohlenen Therapiekonzepten.

In allen Unterstadien konnte eine Verbesserung der Gesamtüberlebenszeit erzielt werden. Dies deutet darauf hin, dass die Fortschritte in den diagnostischen und therapeutischen Strategien einem breiten Spektrum von Patienten zugutekommen.

Die Verbesserung der Überlebensrate ist nicht auf eine mögliche Stadienverschiebung zurückzuführen, da sich der Anteil der diagnostizierten Unterstadien über die Zeiträume hinweg konstant hielt.

In unserer Studie konnten wir nicht feststellen, ob das Ausbleiben einer Operation auf die Inoperabilität des Tumors oder die Untauglichkeit des Patienten zurückzuführen war.

Außerdem enthielt unser Datensatz keine Informationen über die Bestrahlungsdosis, Einzelheiten zum chirurgischen Eingriff, die Art der Chemotherapie und die Behandlungsabsicht (kurativ/palliativ).

Vorteil unserer Studie war der große Datensatz, der sechs deutsche, bevölkerungsbasierte Register über 12 Jahre umfasste und eine Bevölkerung von etwa 22,4 Millionen Menschen (~ 27 % der gesamten deutschen Bevölkerung) repräsentierte.

Zusammenfassung

Unsere Umfrage zur Behandlungs- und Versorgungspraxis bei SCLC zeigte, dass sich deutschlandweit in vielen Bereichen die gleichen Standards etabliert haben; wobei in bestimmten Behandlungsmethoden weiterhin große Unterschiede bestehen. Bei der Dosierung, Fraktionierung und den Einschlusskriterien für RT und PCI gibt es nach wie vor keinen klaren Konsens, obwohl in einigen veröffentlichten Studien Überlebensvorteile für bestimmte Schemata festgestellt wurden. Die Umfrage zeigte auch, dass die Häufigkeit der Anwendung der Immuntherapie mit Atezolizumab variiert. Um diese Therapieform in beiden Stadien weiter zu etablieren, sind weitere Ergebnisse erforderlich.

Zur Beurteilung, inwiefern sich das Behandlungsmuster des NSCLC im Stadium III über die letzten Jahre entwickelt, bietet unsere Arbeit einen wichtigen Überblick. Basierend auf der Studie kann nachvollzogen werden, wie sich das Gesamtüberleben durch Veränderungen in Behandlungsmodalitäten, Diagnoseinstrumenten und anderen Faktoren verbessert. Es wird von entscheidender Bedeutung sein, weitere Forschungen durchzuführen, um das Zusammenspiel dieser Variablen vollständig zu verstehen. So kann die Behandlung eines einzelnen Patienten deutlich verbessert werden.

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Thesen

1. Es sind weitere Studien notwendig, um die Behandlungs- und Versorgungsmethoden beim NSCLC und SCLC besser zu standardisieren.
2. Es können neue Therapieverfahren durch weitere Studien etabliert werden.
3. National sowie international bestehen weiterhin Unterschiede in der Versorgungspraxis beim SCLC.
4. Die am häufigsten verwendeten Schemata für die Thoraxbestrahlung bei ES-SCLC sind 30 Gy in 10 Fraktionen und 45-50 Gy in 25 Fraktionen.
5. Eine Antikörpertherapie durch Atezolizumab verbessert das Gesamtüberleben beim SCLC und NSCLC.
6. Der Einsatz durch Atezolizumab führt nicht zu vermehrten Nebenwirkungen wie Neutropenie, Anämie, Thrombozytopenie oder Alopezie.
7. Die Anwendung einer prophylaktischen Schädelbestrahlung beim LS-SCLC führt zu einem Überlebensvorteil bei Patienten, bei denen vor Therapiebeginn keine Bildgebung durchgeführt wurde.
8. Bei Patienten mit ES-SCLC und radiologischer Hirnmetastasenfreiheit ist keine prophylaktische Schädelbestrahlung notwendig, solange ein Follow-Up mit regelmäßigen Kontrollen stattfindet.
9. Der Einsatz von Behandlungs- und Therapiemethoden wie dem F-FDG-PET/CT und der intensitätsmodulierten Strahlentherapie (IMRT) führen zu einem Überlebensvorteil bei NSCLC-Patienten.
10. Das Gesamtüberleben bei Patienten mit NSCLC steigt von 2007 bis 2018 an.

Publikationsteil

Publikation 1:

„Survey of treatment and care practices in small-cell lung cancer among German radiation oncologists“

Gnüchtel, J., Vordermark, D. & Medenwald, D. Survey of treatment and care practices in small-cell lung cancer among German radiation oncologists. *Strahlenther Onkol* 199, 631–644 (2023). <https://doi.org/10.1007/s00066-022-02019-9>

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Anteil an der Publikation: Autorenschaft

Publikation 2:

„Treatment patterns in stage III non-small-cell lung cancer patients: a population-based study using German cancer registry data“

Bedir, A., Mehrotra, S., Gnüchtel, J. et al. Treatment patterns in stage III non-small-cell lung cancer patients: a population-based study using German cancer registry data. *J Cancer Res Clin Oncol* 149, 15489–15497 (2023). <https://doi.org/10.1007/s00432-023-05289-7>

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Survey of treatment and care practices in small-cell lung cancer among German radiation oncologists

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Abstract

Background The management of small-cell lung cancer shows differences, particularly with regard to the use of radio- (RT), chemo-, and immunotherapy. We performed a survey among German radiation oncologists to assess the management of small-cell lung cancer (SCLC).

Methods A 34-question online survey was created and sent out by e-mail to radiation oncologists throughout Germany. The survey period extended from August 2020 to January 2021. The questions addressed indications for RT, planning techniques, dosing/fractionation, target volume definition for consolidative thoracic irradiation, and the use of prophylactic cranial irradiation (PCI). At the same time, we surveyed the use of atezolizumab. The survey addressed the treatment practice for limited-stage SCLC (LS-SCLC) and extensive-stage SCLC (ES-SCLC).

Results We received 74 responses. In LS-SCLC, treatment is planned predominantly based on diagnostic information from computed tomography (CT) of the thorax/abdomen/pelvis (88%), PET-CT (86%), and pulmonary function testing (88%). In LS-SCLC, 99% of respondents perform radiation concurrently with chemotherapy, preferably starting with cycle one or two (71%) of chemotherapy. The most common dose and fractionation schedule was 60–66 Gy in 30–33 fractions (once daily: 62% of all respondents). In ES-SCLC, 30 Gy in 10 fractions (once daily: 33% of all respondents) was the most commonly used regimen in consolidative thoracic irradiation. Only 25% use chemosensitization with RT. The inclusion criteria for PCI were similar for limited and extensive disease, with Karnofsky index (78% and 75%) being the most important decision factor. Respondents use a schedule of 30 Gy in 15 fractions most frequently in both stages (68% limited stage [LS], 60% extensive stage [ES]). Immunotherapy was used regularly or occasionally in LS-SCLC by 45% of respondents, with reduced lung function (37%), cardiac comorbidities (30%), and hepatic insufficiency (30%) being the most commonly mentioned exclusion criteria for this form of therapy. In ES-SCLC, atezolizumab use was reported in 78% of all questionnaires. Half of the respondents (49%) administer it simultaneously with cranial irradiation.

Conclusion Our survey showed variability in the management of SCLC. Results from future studies might help to clarify open questions regarding the optimal treatment paradigms. In addition, new treatment modalities, such as immunotherapy, might change practices in the near future.

Keywords Radiotherapy · Chemotherapy · Immunotherapy · Prophylactic cranial irradiation · Atezolizumab

Abbreviations

BID	<i>Bis in die</i> (twice a day)
CI	Confidence interval
CRT	Chemoradiotherapy
CTV	Clinical target volume
ECOG	Eastern Cooperative Oncology Group
ES	Extensive stage
ES-SCLC	Extensive disease small-cell lung cancer
FDG	Fluorodeoxyglucose
GTV	Macroscopic tumor volume
HR	Hazard ratio
LC	Limited stage

Availability of data and materials The data generated and analyzed during the current survey are available at <https://de.surveymonkey.com/results/SM-TBRG58529>

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LRC	Locoregional control
LS-SCLC	Limited stage small-cell lung cancer
MTV	Metabolic tumor volume
NSCLC	Non-small-cell lung cancer
PCI	Prophylactic cranial irradiation
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
OR	Odds ratio
OS	Overall survival
RCT	Randomized controlled trial
RT	Radiotherapy
SCLC	Small-cell lung cancer
SUV _{max}	Maximum standardized uptake value
TRAE	Treatment-related adverse events

Introduction

Lung cancer is one of the most common malignant cancers in Germany, with small-cell carcinoma accounting for approximately 16% of all cases [1]. It is characterized by aggressive growth and early development of metastases.

Although standard therapy consisting of chemotherapy and radiation has been shown to be effective, there continues to be wide variation in treatment and care practices.

The importance of chemotherapy is reflected by both limited and extensive disease stages. Several studies demonstrated the survival benefit of using chemotherapy compared to surgery alone [2].

In addition, there remains a conflict regarding the use of prophylactic cranial irradiation (PCI). For example, what is the benefit of PCI for patients who have been radiologically proven to be free of brain metastases after chemoradiotherapy (CRT) [3]? In addition, which dosage and fractionation is most effective? Furthermore, there are discrepancies regarding the inclusion criteria and which patient population benefits most from this form of therapy [4]. Previous studies also investigated to which extent and at what intervals control examinations should be performed as follow-up, especially in patients in whom no prophylactic cranial irradiation was performed [3].

New treatment methods, such as antibody therapy with the programmed cell death ligand 1 (PD-L1) atezolizumab, are coming more into focus and have already been able to establish themselves in practice to some extent [5].

Based on the CASPIAN trial [6], another PDL1-ligand, durvalumab, was approved for treatment of SCLC in 2021 [7], but this was only after our survey was performed. Therefore, with regard to checkpoint inhibitors, our survey included only atezolizumab, which was already approved in 2019 [8].

Methods

We compiled a survey of 34 items, which we sent out by e-mail to about 1300 radiation oncologists throughout Germany (Table 3). The survey period extended from August 2020 to January 2021 and we received a total of 74 responses.

The questions were initially related to demographic data. To identify the location of the participants' practices, we divided the states into four groups: region north: Bremen, Hamburg, Mecklenburg-Western Pomerania, Lower Saxony, and Schleswig-Holstein; region west: Hesse, North Rhine-Westphalia, Rhineland-Palatinate, and Saarland; region east: Berlin, Brandenburg, Saxony, Saxony-Anhalt, and Thuringia; region south: Baden-Württemberg and Bavaria.

In addition, we asked for the physician's approximate age, years of professional experience, and the number of patients with SCLC cared for annually. The survey was conducted anonymously, and we were only able to obtain a more detailed analysis based on these demographic data. Our project was evaluated for ethical clearance and received approval from the ethics committee of the Medical Faculty, Martin Luther University Halle-Wittenberg (reference number 2020-139).

The main part of the survey was related to management of LS-SCLC and ES-SCLC. The radiation oncologists were asked to select the answers that most closely matched their standard of care in each case.

The primary focus of the questions was use of consolidative thoracic irradiation and prophylactic cranial irradiation. We evaluated fractionation and dosing, planning techniques, definition of the target volume, and patient-specific inclusion criteria, among other factors.

We also considered the use of antibody therapy with atezolizumab.

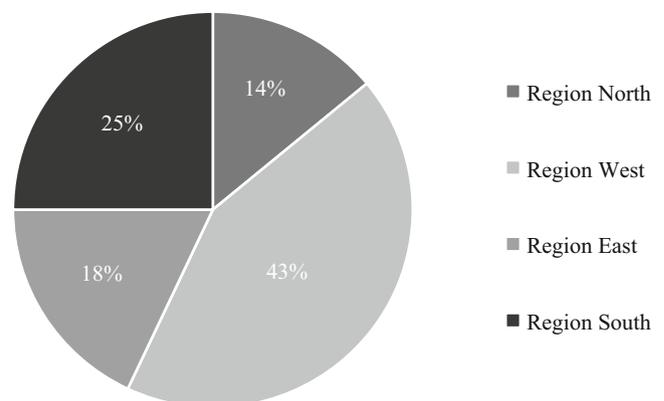


Fig. 1 Regional distribution of respondents

Table 1 Positional control and frequency of image guidance in radiotherapy of limited-stage small-cell lung cancer

Positional control	Responses, n (%)
Kilovoltage orthogonal	17 (23.6)
Megavoltage orthogonal	11 (15.3)
Kilovoltage cone-beam CT	47 (65.3)
Megavoltage CT/cone-beam CT	24 (33.3)
Other	4 (5.6)
Interval of image guidance	
Daily	37 (50.7)
Weekly	20 (27.4)
Other	16 (21.9)

Results

Demographics

We received responses from all four of the regional subgroups, with region west being the most represented at 43%, followed by region south at 25%, and region east and region north at 18 and 14%, respectively (Fig. 1).

Participant age varied widely, from 20–29 years to >60 years, although every age group was represented. In addition, differences in professional experience were evident. The number of lung cancer patients treated by a radiation oncologist per year ranged from 5 to 300, 42 physicians (58%) reported that their proportion of SCLC patients was 11 to 20%.

LS-SCLC

We asked radiation oncologists which diagnostic methods they generally use for treatment planning. With more than 85% each, CT of the thorax/abdomen/pelvis (88%), PET-CT (86%), a planning CT with dosimetric limits (85%), and pulmonary function testing (88%) were reported most frequently. Seventy-five percent also mentioned using EBUS or mediastinoscopy as a diagnostic tool. Cranial magnetic resonance imaging was reported as another important method.

Table 2 Overview of responses regarding factors affecting the decision to use PCI in limited and extensive stages

Variable	Responses, n (%)	
	LS-SCLC	ES-SCLC
Clinical and radiological response	7 (9.6)	5 (6.9)
Extent of primary tumor	9 (12.3)	11 (15.3)
Karnofsky index or performance status	57 (78.0)	54 (75.0)
Significant weight loss (>10–15%)	7 (9.6)	8 (11.1)
Toxicity of radiochemotherapy	26 (35.6)	21 (29.2)
Use of extrathoracic consolidative irradiation	–	6 (8.3)
Use of consolidative irradiation of intrathoracic manifestation	–	18 (25.0)
Basic cognitive ability	32 (43.8)	34 (47.2)
No metastases in repeated cranial imaging	26 (35.6)	26 (36.1)
Age	3 (4.2)	1 (1.4)
Compliance	1 (1.4)	–
Comorbidities	1 (1.4)	1 (1.4)

n number, LS-SCLC limited stage small-cell lung cancer, ES-SCLC extensive stage small-cell lung cancer

Management of radiotherapy in LS-SCLC

Reportedly, the most commonly used schedule for thoracic irradiation was 60 to 66 Gy in 30 to 33 fractions once a day (62%). In 22%, 45 Gy in 30 fractions BID (twice a day) was used (Fig. 2).

Ninety-nine percent of the radiation oncologists reported to apply radiation simultaneously with chemotherapy; 1% sequentially due to poor tolerability. The initiation of RT was most frequently indicated in the first or second cycle of chemotherapy (71%), much less frequently in the third or fourth cycle (27%).

Concerning the clinical target volume at the beginning of the second cycle in patients with T2N2M0 LS-SCLC, 33% defined it as macroscopic tumor volume including contigu-

Fig. 2 Dosage and fractionation in simultaneous radiochemotherapy for limited-stage small-cell lung cancer

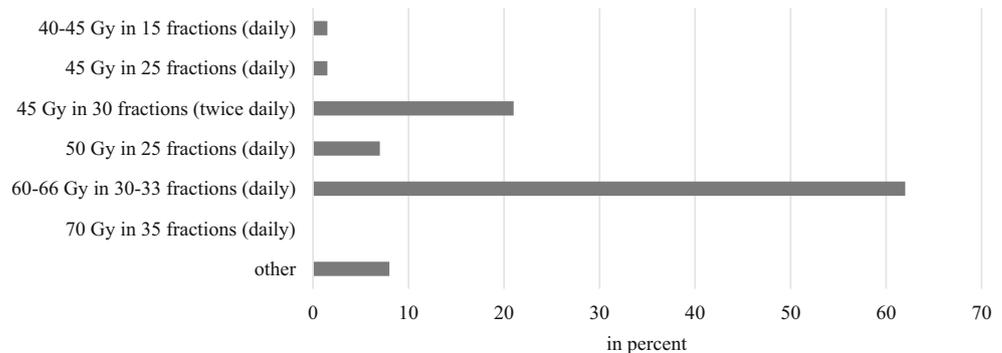


Fig. 3 Use of prophylactic cranial irradiation in relation to radiologic or symptomatic response after radiochemotherapy in limited-stage small-cell lung cancer (*LS-SCLC*) and extensive-stage small-cell lung cancer (*ES-SCLC*)

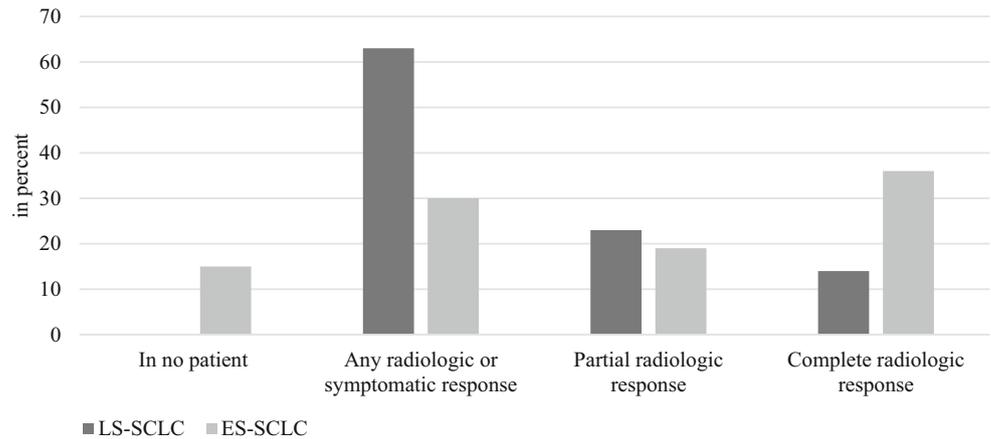
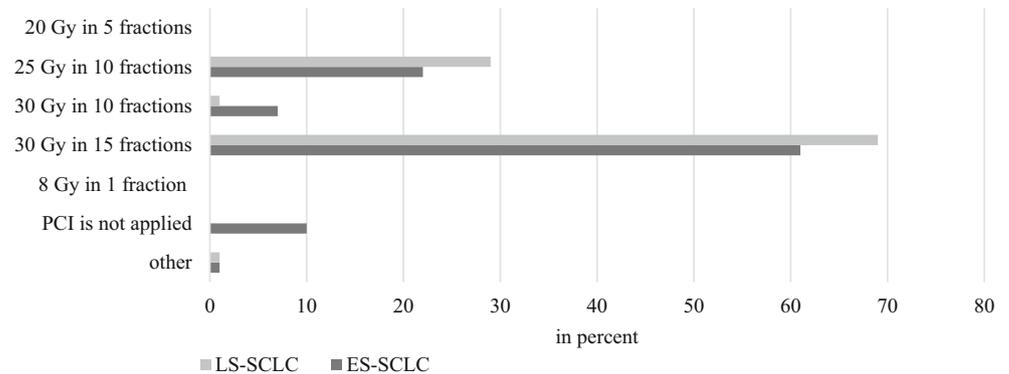


Fig. 4 Dosage and fractionation in prophylactic cranial irradiation for limited-stage small-cell lung cancer (*LS-SCLC*) and extensive-stage small-cell lung cancer (*ES-SCLC*)



ous lymph node stations and an additional margin. Tumor volume with additional margins to consider microscopic involvement (30%) was mentioned to a similar extent.

If tumor volume decreases after the first chemotherapy cycle, 41% of the respondents would leave the target volume unchanged according to the planning CT and 21% would expand it to the pretherapeutic volume. A compromise between both would be chosen by 38%.

For positional control in radiotherapy, 65% would use kilovoltage cone-beam CT, 33% would use megavoltage cone-beam CT. Most participants indicated daily use of im-

age guidance (51%). Twelve percent reported daily application for the first few days and once a week during further treatment (Table 1).

PCI in LS-SCLC

In the majority of cases (63%), PCI would be used in patients with any radiologic or symptomatic response to chemoradiotherapy; in 14% it would only be used in patients with complete radiologic response (Fig. 3).

Among these factors, the Karnofsky index (78%) was the most important in deciding whether to offer cranial irradiation. In addition, cognitive ability (44%) was also an important consideration. Patient age over 70 years would influence the decision in only 4% (Table 2).

A dose of 30 Gy in 15 fractions (68%) was the most common schedule for PCI, followed by 25 Gy in 10 fractions (29%; Fig. 4).

Antibody therapy with atezolizumab in LS-SCLC

Less than half (45%) of the respondents would use antibody therapy with atezolizumab in the limited disease stage (Fig. 5).

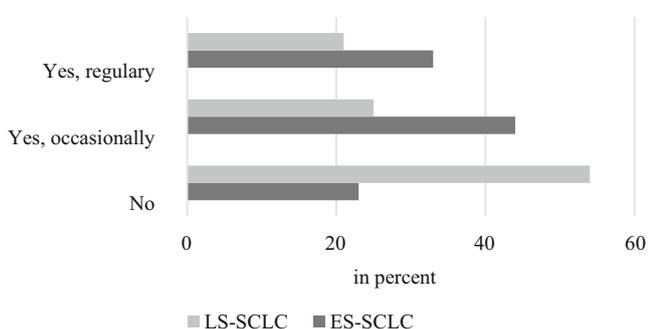


Fig. 5 Frequency of use of antibody therapy with atezolizumab in limited-stage small-cell lung cancer (*LS-SCLC*) and extensive-stage small-cell lung cancer (*ES-SCLC*)

Exclusion criteria for this therapy were mainly reduced lung function (37%), cardiac comorbidities (30%), or liver insufficiency (30%). A cut-off age was not specified.

Special situations in LS-SCLC

The radiation oncologists were asked whether a patient with contralateral supraclavicular lymph node involvement would be irradiated. Nearly 1/3 (30%) indicated that this patient had extensive disease by definition, and that irradiation would not be used in this case. Fifteen percent would use irradiation routinely, more than half (55%) only when dosimetrically safe to do so.

For a patient in a clinical T1/2a N0 LS-SCLC stage, the majority (51%) indicated radiotherapy to be a primary intervention simultaneous with chemotherapy. Otherwise, it would be used as adjuvant treatment postoperatively and with a pN2 situation (25%) or regardless of pathologic status (14%).

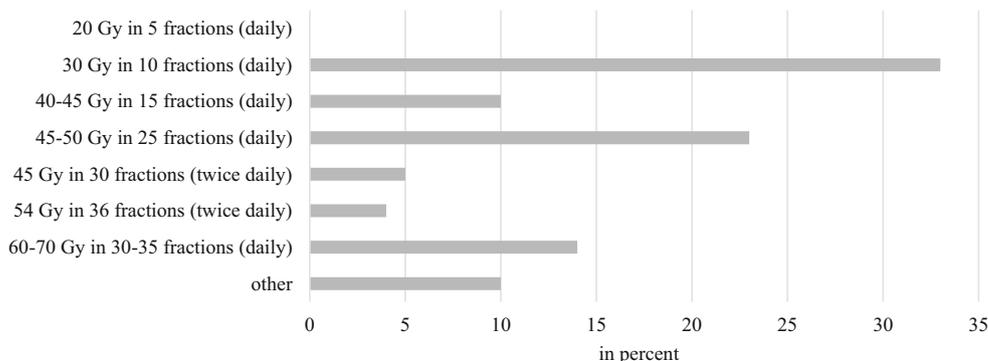
ES-SCLC

Management of radiotherapy in ES-SCLC

All participants reported offering radiation to all symptomatic patients with ES-SCLC. When asked whether thoracic radiotherapy was relevant after chemotherapy, the majority (56%) reported that it would be used for any response, and insofar as the thoracic tumor burden was the greatest. Thirty percent would use it when there was a complete radiologic response to chemotherapy outside the thorax and a complete or partial response within the thorax. The most commonly used schedules were 30 Gy in 10 fractions once a day (33%) and 45–50 Gy in 25 fractions once a day (23%; Fig. 6). Furthermore, 25% indicated a simultaneous chemosensitization with consolidative radiation.

Tumor remnants plus prechemotherapy-involved parenchymal foci and lymph node stations were most commonly used to define the clinical target volume in ES-SCLC (42%). Slightly less frequently (33%), only the tumor remnants would represent the target volume.

Fig. 6 Dosage and fractionation in simultaneous radiochemotherapy for extensive-stage small-cell lung cancer



Consolidative radiotherapy outside the thorax would be given by 65% of the participants, with the majority (61%) assuming a limited tumor before and after chemotherapy. Oligometastasis defines tumor limitation in this context.

PCI in ES-SCLC

Most of the respondents answered that they would perform PCI if there was a complete (35%) or partial (19%) radiologic response to chemotherapy. Fifteen percent of radiation oncologists reported that cranial irradiation would not be used at all in patients with ES-SCLC (Fig. 3).

Similar to the decision factors in LS-SCLC regarding whether to use PCI, the clinical performance according to ECOG or Karnofsky index (75%) and cognitive ability (47%) were the most frequently mentioned parameters in extensive disease. Confirmation of the absence of brain metastases on cranial control imaging (36%) was indicated as another important factor (Table 2).

A schedule with 30 Gy in 15 fractions (60%) was most common (Fig. 4).

Antibody therapy with atezolizumab in ES-SCLC

Thirty-three percent of respondents reported regular use of atezolizumab in patients with ES-SCLC, while 45% would use it occasionally. Nearly one fifth (22%) would not use this therapeutic modality (Fig. 5). About half of the respondents (49%) mentioned that simultaneous use with PCI would not be an issue. Otherwise, minimum intervals of 1 day (14%) or 1 week (29%) were indicated.

Discussion

The survey showed that differences in SCLC care practices are relevant in German radiotherapy centers. This refers to application regimens in radiation, indications for radiation, or even the use of antibody therapy.

LS-LSCS

A large consensus existed in terms of overall treatment planning, with wide application of PET-CT for target volume definition alongside conventional CT. For staging and disease recurrence, FDG-PET-CT plays a major role due to its high sensitivity and specificity. Detection of distant metastases and delineation of the primary tumor and lymph nodes allow optimal planning of radiation. For NSCLC, an international randomized multicenter trial [9] has already shown that the use of FDG-PET in treatment planning reduced CTVs. In multimodality protocols, metabolic FDG-PET parameters (i.e., maximum standardized uptake value [SUV_{max}], metabolic tumor volume [MTV]) [9] were found to significantly correlate with overall and progression-free survival, and/or local tumor control [9]. PET tracers other than FDG have been investigated in lung carcinoma. Hypoxia markers in non-small-cell lung cancer (NSCLC) predicted poor outcome and thus could be helpful in planning treatment escalation [9].

Furthermore, in simultaneous chemoradiotherapy, treatment regimens vary, with 66 Gy in 30 to 33 fractions (once daily) and 45 Gy in 30 fractions (twice daily) mentioned most frequently in the survey (Fig. 2).

In the randomized CONVERT trial by Faivre-Finn et al. [10], these two regimens were compared in terms of overall survival (OS). Median OS was 30 months (95% confidence interval [CI] 24–34) in the twice-daily group versus 25 months (21–31) in the once-daily group [10]. Similarly, there was a non-significant benefit in 2-year OS (56% vs. 51%) for the twice-daily regimen. Adverse events related to grade 3 to 4 esophagitis occurred with similar frequency (19% vs. 19%); neutropenia occurred more frequently in the 66 Gy in 30 fractions group (74% vs. 65%). The study found that there were only minor differences between the two regimens in terms of OS [10]. Hyperfractionation was found to be a reasonable approach to treat SCLC in terms of duration and compliance, but is not the preferred schedule in clinical routine.

The Norwegian THORA trial [11] compared high-dose thoracic irradiation of 60 Gy in 40 fractions with a standard dose of 45 Gy in 30 fractions, with both groups of patients receiving irradiation twice per day. The 2-year OS showed a significant advantage on the side of high-dose irradiation (74% vs. 48%). Increased toxicity was not observed in the 60 Gy group. Thus, according to the authors, this treatment regimen should be considered as an alternative [11].

According to our survey, radiotherapy was most often started in cycle one or two of chemotherapy. Murray et al. [12] compared early radiation parallel to the first cycle with late radiation parallel to the last cycle of chemotherapy. An advantage of the early group in comparison to the late group

was found in terms of progression-free survival (PFS; 15.4 vs. 11.8 months) and OS (21.2 vs. 16 months) [12].

De Ruyscher et al. [13] supported this approach in their meta-analysis. They compared OS in early (according to the study inclusion criterion, before cycle three of chemotherapy) and late radiotherapy onset, with early onset showing an absolute survival gain of 7.7% at 5 years compared with a later start. It should be mentioned that an early onset led more often to development of acute severe esophagitis (odds ratio [OR] 1.93 [1.45–2.56]) [13].

Hu et al. [14] compared hyperfractionated RT (1.5 Gy twice a day in 30 fractions) and hypofractionated RT (2.5 Gy once a day in 22 fractions) to evaluate the influence of the timing of RT in addition to efficacy. Good median OS (28.3 vs. 22.0 months) and locoregional control (LRC; 1-year LRC 82.1% vs. 60.7%, 2-year LRC 84.9% vs. 68.8%) were achieved in both groups. Using a Cox regression analysis, it was found that time from chemotherapy initiation to RT less than 43 days was associated with better LRC. Similarly, a period of less than 63 days between the start of chemotherapy and the end of RT was associated with improved OS. It was concluded that timing is more important than dose intensification [14].

PCI LS-SCLC

A meta-analysis of Yin et al. [15] published in 2019 included seven randomized controlled trials (RCT) from 1987 to 2017 to compare overall survival and the incidence of brain metastases in patients with PCI vs. without PCI. It showed that the use of PCI resulted in a significantly reduced incidence of brain metastases and slightly prolonged OS. It should be noted that patients who received cranial imaging following CRT and were free of brain metastases had no OS benefit from PCI (hazard ratio [HR]=0.94; 95% CI 0.74–1.18). In contrast, patients without imaging showed a significant benefit (HR=0.70; 95% CI 0.57–0.85) [15].

To further investigate the development of brain metastases in LS-SCLC, Levy et al. [16] used the data from the CONVERT trial [10]. The authors examined whether there was an association between the incidence of brain metastases and the application schedule of thoracic irradiation. In this trial, 82% of all patients received subsequent PCI after CRT, with 8% of previously once-daily and 9% of previously twice-daily thoracic irradiated patients developing brain metastases. Thus, the type of thoracic irradiation was found to have no effect on brain metastasis [16].

Zheng et al. [17] identified risk factors for the development of brain metastases in patients with LS-SCLC without PCI. Retrospectively, they found that high T stage, high neutrophil-to-lymphocyte ratio, early thoracic radiotherapy,

and fewer chemotherapy cycles increased the risk of developing brain metastases [17].

Atezolizumab LS-SCLC

One third of our respondents reported regular use of atezolizumab in patients with LS-SCLC, 44% occasionally. While regular use was reported in 33% of respondents from region west, it was significantly less in the east (15%) and south (11%) regions. In region north, no regular use was described.

A phase II/III randomized trial by Higgins et al. [18] initiated in May 2019 is evaluating the combination of chemotherapy and atezolizumab in patients with LS-SCLC. Primary endpoints are PFS and OS. Results are expected in 2024. Atezolizumab is expected to yield a hazard ratio of 0.62 for PFS and 0.71 for OS at a one-sided significance level of 0.025 [18].

In the following we have compared our survey results and the abovementioned studies with the current national guidelines [25] for the treatment of SCLC. The guideline recommends use of combined chemotherapy with cisplatin and etoposide, which should be used over four to six cycles. Ninety-nine percent of our respondents use cisplatin/etoposide. According to the guideline [25], radiotherapy should be used in all patients with tumor extension that can be irradiated. This should be simultaneous to chemotherapy and be started early. According to our survey, 71% of radiation oncologists start radiotherapy in cycle one or two, 27% in cycle three or four of chemotherapy. In the CONVERT study [10], no significant difference between the use of a conventional treatment regimen with 60–66 Gy in 30 fractions (once daily) and a hyperfractionated regimen with 45 Gy in 30 fractions (twice daily) could be demonstrated. Based on this, the German guideline [25] recommends both regimens. This was also evident in our survey. Sixty-two percent of the respondents treat with 60–66 Gy in 30 fractions (once daily) and 21% with 45 Gy in 30 fractions (twice daily).

The guideline recommends PCI in all patients in remission [25]. According to our survey, 63% use PCI for any response to chemotherapy, 23% for partial radiologic response, and 14% for complete radiologic response. A regimen of 25 or 30 Gy in 2.0 or 2.5 single doses, respectively, is recommended; this is confirmed by 99% of our respondents.

Regarding antibody therapy, there are no recommendations in the current guideline. This was reflected in our survey. The frequency of use of atezolizumab therapy varied widely. As mentioned above, studies [18] are currently being conducted on this topic. More precise recommendations must be based on these results.

ES-SCLC

PCI ES-SCLC

Slotman et al. [19] published an RCT in 2007 in which they evaluated the efficacy of PCI in patients with ES-SCLC and any response to chemotherapy. The risk of brain metastasis was 14.6% in the PCI group and 40.4% in the control group. The 1-year survival rate was 27.1% with PCI and 13.3% without intervention [19]. Because this trial failed to include imaging in the form of MRI before study entry and the brain metastasis status was therefore unknown, the validity of this study has been questioned.

In this regard, a Japanese RCT by Takahashi et al. [3] investigated the efficacy of PCI in patients with extensive-stage SCLC in whom brain metastases could be excluded by MRI prior to study entry and compared OS between the PCI group and the observation group. A control MRI was performed at 3-monthly intervals for 12 months and at 18 and 24 months thereafter. The study found that the risk of brain metastasis at 12 months was 32.9% in the PCI group and 59% in the observation group. The OS, however, was 11.6 months in the PCI group and 13.7 months in the observation group. The authors concluded that PCI is not necessary in patients who are free of brain metastases provided there is follow-up with regular controls every 3 months for 1 year and at 18 and 24 months thereafter. Asymptomatic metastases then should be treated with radiotherapy and chemotherapy [3].

A 2018 meta-analysis [20] also examined the role of PCI in ES-SCLC, showing an advantage of the PCI group over the non-PCI group in terms of 1-year survival (37.1% vs. 27.1%), PFS (HR = 0.83; 95% CI 0.70–0.98), and risk of brain metastasis (HR = 0.34; 95% CI 0.23–0.50). OS specifically improved in patients younger than 65 years. However, no significant OS benefit was observed overall [20].

Chen et al. [21] studied the effect of early vs. late PCI. Early PCI was defined as an interval between the initiation of chemotherapy and the initiation of radiation of less than 6 months and late PCI as an interval of more than 6 months. Primary endpoint was the incidence of brain metastases, which was significantly lower in the early PCI group than in the late PCI group (HR, 0.45; 95% CI 0.23–0.89; $p = 0.024$) [21].

Atezolizumab ES-SCLC

According to our survey, immunotherapy with atezolizumab was used regularly in 33% and occasionally in 44%, while it did not significantly feature in the clinical routine of 23% of the respondents.

In the west of Germany, 37% of radiation oncologists reported regular use of atezolizumab, slightly less in the

southern (33%) and eastern (30%) regions. As in LS-SCLC, this form of therapy was least common in the northern region (20%).

The IMPower133 RCT [5] evaluated the combination of atezolizumab and carboplatin plus etoposide in patients with ES-SCLC. Endpoints represented overall survival and progression-free survival. Compared with the placebo group, the atezolizumab group had significantly increased OS (12.3 vs. 10.3 months; HR 0.70; 95% CI 0.54 to 0.91; $p=0.007$) and prolonged PFS (5.2 vs. 4.3 months). Relative to individual baseline characteristics, the combination with immunotherapy also showed benefits. Thus, patients younger than 65 years (OS 12.1 months atezolizumab vs. 11.5 months placebo) and older than 65 years (12.5 vs. 9.6 months) benefited. This relation was similar for patients with an ECOG score of zero (16.6 vs. 12.4 months) and one (11.4 vs. 9.3 months). Patients with brain metastases showed an advantage in the placebo group (8.5 vs. 9.7 months). The study included patients with brain metastases, while no differences in OS or PFS were observed. Nevertheless, due to the small population, further studies are necessary to establish standards in the treatment of patients with brain metastases and immunotherapy. With regard to side effects, mainly in the form of neutropenia, anemia, thrombocytopenia, alopecia, and nausea, the combination of etoposide and atezolizumab showed no difference compared to chemotherapy alone (grade 1 or 2 36.9 vs. 34.7%, grade 3 or 4 56.6 vs. 56.1%, grade 5 both 1.5%) [5].

Mansfield et al. [22] also examined atezolizumab therapy in terms of a risk–benefit profile. For this purpose, adverse events from the IMPower133 trial [5] and subjective patient assessments were evaluated. Health-related quality of life improved in both groups, but the improvement was significantly more pronounced and long-lasting in the atezolizumab group [22].

Atezolizumab is approved for patients with ES-SCLC but is also used in limited disease. The extent to which there is a benefit from immunotherapy at this stage is unclear, due to the paucity of data at this point. As noted above, Higgins et al. [18] are evaluating the survival benefit and progression-free survival with atezolizumab in patients with LS-SCLC, and results are expected in 2024 [18].

There is also an issue with its use in patients with brain metastases. These were included in the IMPower trial [5], but in a small population, so results from subgroups will need to follow in the future. To evaluate different immunotherapies, Zhou et al. [23] published a meta-analysis in 2019 that compared chemotherapy alone and chemotherapy in combination with a PD-L1 antibody, CTLA-4 antibody (cytotoxic T-lymphocyte-associated protein 4), or VEGF antibody (vascular endothelial growth factor). Here, the combination with atezolizumab showed

the greatest benefit for OS (12.3 vs. 10.3 months) and no increased toxic effects compared to etoposide–platinum therapy alone (58.1% vs. 57.7%). Bevacizumab, a monoclonal antibody against VEGF, showed the best PFS but did not confer an OS advantage (8.9 vs. 9.8 months). At the same time, it was associated with the highest rate of treatment-related adverse events (TRAE) (62.1% vs. 54.7%). Similarly, the combination of etoposide–platinum plus ipilimumab showed no significant difference for OS (11 vs. 10.9 months) [23].

The CASPIAN trial [6], conducted between 2017 and 2018, evaluated the efficacy of the PDL1 ligand durvalumab in combination with platin–etoposide compared to platin–etoposide alone. It showed a significant improvement in median OS for durvalumab (13.0 vs. 10.3 months) [6]. Also examined was the combination of durvalumab plus the CTLA-4-antibody tremelimumab and platin–etoposide vs. platin–etoposide alone. There was no benefit in terms of OS (10.4 vs. 10.5 months) and thus no evidence for synergistic effects of these two immunotherapies [24].

Regarding the dosage and fractionation of radiotherapy in ES-SCLC, no recommendations are found in the current national guideline [25]. The answers in our survey were also very varied in this respect: 33% apply 30 Gy in 10 fractions, 23% 45–50 Gy in 25 fractions, and 14% 60–70 Gy in 30–35 fractions. Accordingly, a recommendation would result in more homogeneous application.

The guideline states that patients with a response to first-line chemotherapy should be offered PCI or have regular MRI checks every 3 months in the first year. A regimen of 25 or 30 Gy in 2.0 or 2.5 Gy single doses, respectively, is recommended [25]; 83% of our respondents applied it this way.

The national guideline specifically recommends combining chemotherapy with immunotherapy. In addition to the abovementioned studies, meta-analyses clearly showed that patients benefited from PD-L1 checkpoint inhibitor therapy regardless of age or performance status [25]. However, in our survey, antibody therapy was used regularly in only 33% and occasionally in 44%. Although there is a clear recommendation for combined chemotherapy and immunotherapy, its use is not yet established in many centers according to our survey. More precise recommendations are needed because of the variability in the use of radiotherapy.

A limitation of the survey is the low number of participants. With 74 questionnaires answered, we had a response rate of less than 1%. However, it should be mentioned here that we sent the survey to individual radiation oncologists. We assume that in many cases the questionnaires were answered on behalf of a clinic or medical practice. However, it is also possible that several radiotherapists from the same institution answered the questionnaire. Because our survey was anonymous, we do not have data on the type of fa-

cility from which the responses originated. Therefore, we cannot infer whether there are differences in terms of care between university hospitals, non-university hospitals, and the ambulatory setting.

Of course, a survey as a method of data collection also brings disadvantages. Due to the multiple-choice system, survey participants are bound to answers, even though we allowed an open response for several questions.

Conclusion

Our survey showed that German radiation oncologists have the same standards in many approaches, but that there are differences in certain treatment methods. Dosing, fraction-

ation, and inclusion criteria for RT and PCI continue to have no clear consensus, although survival benefits for certain regimens have been noted in some published trials. The survey also showed variable frequency of use of immunotherapy with atezolizumab. More results are needed to further establish this form of therapy in both stages. Thus, we hope that in the future, through additional trials, treatment and care practices can be better standardized and new therapeutic methods established.

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Table 3 Survey

1. Do you treat lung cancer with radiation therapy?

- Yes
 No

Demographics

2. Please tell us your approximate age.

- 20–29
 30–39
 40–49
 50–59
 >60

3. In which region do you currently practice?

- Region North (Bremen, Hamburg, Mecklenburg-Western Pomerania, Lower Saxony, Schleswig-Holstein)
 Region West (Hesse, North Rhine-Westphalia, Rhineland-Palatinate, Saarland)
 Region East (Berlin, Brandenburg, Saxony, Saxony-Anhalt, Thuringia)
 Region South (Baden-Württemberg, Bavaria)

4. For approximately how many years have you been treating lung cancer?

- <5 years
 5–10 years
 10–15 years
 15–20 years
 >20 years

5. How many newly diagnosed lung cancer patients do you treat per year? _____

6. How many of these patients reported in question 5 have a diagnosis of SCLC?

- <10%
 11–20%
 21–30%
 >30%

Limited disease of SCLC

7. What diagnostic methods do you use to plan treatment for an LS-SCLC? Please select all that apply.

- CT chest, abdomen, pelvic
 PET-CT
 EBUS/mediastinoscopy
 Pleura cytology
 X-Ray
 CT simulation in dosimetric constraints
 Pulmonary function testing (FEV1, DLCO)
 Other (please specify): _____

8. Would you irradiate a patient with contralateral supraclavicular lymph node involvement? Please select the answer that is closest to your standard of care.

- No, because by definition this patient is classified as having extensive disease according to prospective randomized trials.
 Yes, but only if it is dosimetrically safe to perform
 Yes, routinely

Table 3 (Continued)

9. How would you describe your initial radiotherapy regimen for a patient in a clinical T1/2a N0 SCLC stage? Please select the answer that is closest to your standard of care.
- As a primary treatment simultaneous to chemotherapy (without surgery)
 - As adjuvant treatment postoperatively, regardless of pathological status
 - As adjuvant treatment postoperatively, if the lymph node status is pN2
10. In most cases of LS-SCLC, simultaneous radiochemotherapy is the current standard of care. What is your current dose and fractionation preference for radiotherapy? Please select the answer that is closest to your standard of care.
- 40–45 Gy in 15 fractions (once daily)
 - 45 Gy in 25 fractions (once daily)
 - 45 Gy in 30 fractions (twice daily)
 - 50 Gy in 25 fractions (once daily)
 - 60–66 Gy in 30–33 fractions (once daily)
 - 70 Gy in 35 fractions (once daily)
 - Other (please specify): _____
11. Do your patients with LS-SCLC most often receive combined chemotherapy of a platinum derivative (cisplatin or carboplatin) and etoposide (46 cycles) simultaneously with radiotherapy? If “No,” please indicate the regimen which is used.
- Yes
 - If “No,” please specify your regimen: _____
12. During which cycle of chemotherapy do you prefer to start concurrent radiochemotherapy (CRT) in patients with LS-SCLC? Please select the answer that is closest to your standard of care.
- Cycle 1 or 2
 - Cycle 3 or 4
 - Cycle 5 or 6
 - Radiation is given after chemotherapy (not simultaneously, but sequentially)
 - The choice of cycle generally does not matter.
 - The choice of cycle does not matter as long as the total treatment time does not exceed 30 days AND platinum-based chemotherapy is given
13. When planning radiochemotherapy for a patient with T2N2M0 LS-SCLC at the start of the second cycle of chemotherapy, how is the clinical target volume (CTV) typically defined for you? Please select the answer that is closest to your standard of care.
- The macroscopic tumor volume (GTV) alone as presented in the current planning CT (no additional margin in the sense of a CTV)
 - Macroscopic tumor volume with additional margins to account for microscopic involvement
 - Macroscopic tumor volume including adjacent lymph node stations and an additional margin
 - Macroscopic tumor volume plus the ipsilateral mediastinum, the ipsilateral hilus, and an additional margin
 - Macroscopic tumor volume plus the entire mediastinum, the ipsilateral hilum, and an additional margin
14. If the tumor volume at the time of planning CT decreases after a first cycle of chemotherapy, would you expand the clinical target volume to the tumor volume that existed before chemotherapy?
- Yes, I would include the entire pretherapeutic volume.
 - No, my clinical target volume would not change, regardless.
 - I would choose something in between
15. What image-based methods do you use for positional control in radiotherapy of a LS-SCLC?
- Kilovoltage orthogonal
 - Megavoltage orthogonal
 - Kilovoltage cone beam CT
 - Megavoltage CT/Cone-Beam CT
 - Others (please specify): _____
16. At what intervals do you use an image guidance?
- Only at the beginning of treatment
 - Weekly
 - Daily
 - Other (please specify): _____
17. In which patient with LS-SCLC are you most likely to use prophylactic cranial irradiation (PCI) after radiochemotherapy?
- In no patients
 - Patients with any response to radiochemotherapy (radiologic or symptomatic)
 - Patients with a partial radiologic response to radiochemotherapy
 - Patients with a complete radiologic response

Table 3 (Continued)

18. Are there other factors that would affect your decision to offer PCI at LS-SCLC? Please select all that apply.
- Not applicable, as I do not use PCI at LS-SCLC
 - No, clinical and radiological response are the most important factors
 - Extent of primary tumor (bulky disease)
 - Karnofsky index or performance status
 - Significant weight loss (>10–15%)
 - Toxicity of radiochemotherapy
 - Basic cognitive ability
 - Repeated cranial imaging (CT, MRI) shows no metastases
 - Other (please specify): _____
19. What dose and fractionation do you use for PCI in LS-SCLC?
- 20 Gy in 5 fractions
 - 25 Gy in 10 fractions
 - 30 Gy in 10 fractions
 - 30 Gy in 15 fractions
 - 8 Gy in 1 fraction
 - Not applicable, as I do not use PCI with LS-SCLC
 - Other (please specify): _____
20. How do you plan to perform PCI? Please select the answer that is closest to your standard of care.
- Clinical only setting with or without thermoplastic mask
 - Virtual simulation with or without mask
 - Complete CT simulation with mask
 - CT simulation with mask and hippocampal avoidance
 - Not applicable, as I do not use PCI for LS-SCLC
 - Other (please specify): _____
21. Do your patients use atezolizumab in combination with platinum-based chemotherapy as part of limited disease radiochemotherapy?
- Yes, regularly
 - Yes, occasionally
 - No, not in the stage of limited disease
22. Do you have any criteria that would lead you to abstain from atezolizumab therapy? Please select all possible answers (if used in the stage of limited disease in the context of chemotherapy outside the actual radiation phase).
- Impaired lung function
 - Cardiac comorbidity (NYHA)
 - Kidney dysfunction (eGFR)
 - Liver insufficiency (Child score)
 - Current smoker
 - Regardless of smoking status
 - Brain metastases
 - No brain metastases
 - Independent of brain metastases
 - Cut-off age (if so, please enter the age): _____
- Extensive disease of SCLC*
23. Do you offer radiation therapy to relieve symptoms in patients with symptomatic ES-SCLC?
- Yes
 - No
24. Do you consider consolidative thoracic radiation relevant after palliative chemotherapy? Please select the answer that is closest to your standard of care.
- No
 - I use consolidative thoracic radiotherapy only in the context of clinical trials.
 - Yes, only if there is a complete radiologic response to chemotherapy outside the thorax and a complete or partial response inside the thorax.
 - Yes, for any response to chemotherapy when thoracic manifestation is the major tumor burden
 - Yes, for any response to chemotherapy, regardless of tumor burden
 - Other (please specify): _____
25. What dose and fractionation do you use for consolidative thoracic irradiation?
- 20 Gy in 5 fractions (once daily)
 - 30 Gy in 10 fractions (once daily)
 - 40–45 Gy in 15 fractions (once daily)
 - 45–50 Gy in 25 fractions (once daily)
 - 45 Gy in 30 fractions (twice daily)
 - 54 Gy in 36 fractions (twice daily)
 - 60–70 Gy in 30–35 fractions (once daily)
 - Not applicable, as I do not use consolidative irradiation for ES-SCLC.
 - Other (please specify): _____

Table 3 (Continued)

26. Would you use simultaneous chemosensitization with consolidative radiation?
 Yes
 No
 Not applicable, as I do not use consolidating irradiation
27. What would be your clinical target volume for consolidative irradiation of an ES-SCLC? Please select the answer that is closest to your standard of care.
 Only tumor residues as visualized on planning CT
 Tumor residues and the parenchymal foci and lymph node stations involved prior to chemotherapy
 Tumor residues and the entire mediastinum
 Not applicable, as I do not use consolidative radiotherapy.
 Other (please specify): _____
28. Do you use consolidative radiation outside the thorax in patients with ES-SCLC? Please select the answer that is closest to your standard of care.
 No
 Yes, only in the context of a clinical trial
 Yes, only if tumor was limited before and after chemotherapy (oligometastatic)
 Yes, only if the tumor was limited after chemotherapy (oligometastatic), regardless of the situation before chemotherapy
29. In which patient with ES-SCLC are you most likely to use prophylactic cranial irradiation after palliative chemotherapy? Please select the answer that is closest to your standard of care.
 In no patient
 Patients with any response (radiologic or symptomatic) to chemotherapy
 Patients with a partial radiologic response to chemotherapy
 Patients with a complete radiologic response to chemotherapy
30. Are there other factors that would affect your decision to use PCI at ES-SCLC? Please select all that apply.
 Not applicable, as I do not use PCI at ES-SCLC.
 No, clinical and radiological response are the most important factors
 Karnofsky index or performance status
 Size of primary tumor in relation to distant metastases
 Use of consolidative irradiation of intrathoracic manifestation
 Use of extrathoracic consolidative irradiation
 Significant weight loss (> 10–15%)
 Toxicity of chemotherapy
 Cognitive function at the beginning
 Repeat cranial imaging (CT, MRI) shows no metastases
 Other (please specify): _____
31. What dose and fractionation do you use for PCI in ES-SCLC?
 20 Gy in 5 fractions
 25 Gy in 10 fractions
 30 Gy in 10 fractions
 30 Gy in 15 fractions
 8 Gy in 1 fraction
 Not applicable, as I do not use PCI with ES-SCLC
 Other (please specify): _____
32. How do you plan to perform PCI? Please select the answer that is closest to your standard of care.
 Clinical only setting with or without thermoplastic mask
 Virtual simulation with or without mask
 Complete CT simulation with mask
 Complete CT simulation with mask and hippocampal avoidance
 Not applicable, as I do not use PCI for LS-SCLC
 Other (please specify): _____
33. Do you use atezolizumab in combination with platinum-based chemotherapy as part of extensive disease radiochemotherapy in your patients?
 Yes, regularly
 Yes, occasionally
 No, not in the stage of extensive disease
34. Do you see any problems with cranial irradiation of brain metastases in the context of therapy with atezolizumab?
 Radiation and simultaneous treatment with atezolizumab are generally possible
 A minimum interval of one day should be observed
 A minimum interval of one week should be observed
 A minimum interval of more than one week should be observed

SCLC small-cell lung cancer, *LS-SCLC* limited stage small-cell lung cancer, *ES-SCLC* extensive stage small-cell lung cancer, *PCI* prophylactic cranial irradiation, *GTV* macroscopic tumor volume, *CTV* clinical target volume, *NYHA* New York Heart Association, *FEV1* forced expiratory pressure in 1 second, *EBUS* endobronchial ultrasound, *eGFR* estimated glomerular filtration rate, *CT* computed tomography, *MRI* magnetic resonance imaging, *PET-CT* positron emission tomography, *Gy* gray

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Appendix

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Declarations

Conflict of interest J. Gnüchtel, D. Vordermark, and D. Medenwald declare that they have no competing interests.

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Treatment patterns in stage III non-small-cell lung cancer patients: a population-based study using German cancer registry data

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Abstract

Purpose Lung cancer remains the leading cause of cancer-related mortality worldwide, mostly due to delayed diagnosis. The objective of this study is to examine the treatment patterns and overall survival (OS) outcomes in a cohort of patients diagnosed with stage III non-small cell lung cancer (NSCLC) over a period of 12 years in Germany.

Methods This retrospective study is based on German cancer registry data and included 14,606 stage III NSCLC patients diagnosed during 2007–2018. Three time-periods were defined according to the availability of advanced diagnostic and treatment strategies (2007–2010 low availability era (LAE), 2011–2014 transition era (TE), 2015–2018 modern era (ME)). Patients were categorized according to the treatment they received during those eras. Kaplan–Meier curves and multivariate Cox proportional hazards models were used to investigate the association between being diagnosed during a certain era and survival. The hazard ratio (HR) estimates were reported along with the 95% confidence interval (CI).

Results The median OS rose from 16 months in the LAE to 22 months in the ME. The HR for patients diagnosed and treated in the ME was estimated to be [0.78; 95% CI (0.74–0.83)] compared to those diagnosed and treated in LAE. The benefit was most evident for patients treated by radiotherapy and chemotherapy [HR 0.73 95% CI (0.66–0.82)].

Conclusion This study highlights the importance of diagnostic and treatment advances in improving outcomes for lung cancer patients. Further studies are needed to assess progress in survival rates with current immunotherapy integration.

Keywords Lung cancer · Treatment patterns · Germany · Cancer registries · Survival analysis

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, particularly due to the late diagnosis of patients at an advanced stage (III/IV) (Watanabe et al. 2017). Non-small cell lung cancer (NSCLC), which accounts for 85% of all lung cancer cases, is divided into four stages

based on the TNM system introduced by the American Joint Committee on Cancer (Amin et al. 2017; Zappa and Mousa 2016). Stage III NSCLC describes a heterogeneous population of patients experiencing a ‘locally advanced’ stage of lung cancer that involves adverse prognostic features associated with the primary tumor and/or the existence of metastases within regional lymph nodes (Evison 2020; Pöttgen et al. 2017). According to the Robert Koch Institute, the 5-years relative survival of stage III NSCLC cases was estimated to be 27% and 20% in women and men respectively, compared to 7% and 4% for stage IV patients (Erdmann et al. 2021).

Optimal treatment for stage III NSCLC patients remains a topic of debate. While the current guidelines recommend concurrent chemoradiotherapy (CRT) as the ‘standard of care’ for the majority of stage III patients, factors such as, tumor sub-stage and resectability, along with the patient profile (lung function, comorbidities, and age), may all affect the treatment strategy and subsequently survival (Ettinger et al. 2022; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft and AWMF) 2022). In order to determine the

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ideal treatment plan for a NSCLC patient, it is therefore imperative for the tumor to be accurately assessed.

The landscape of advanced lung cancer management has undergone significant transformation over the past decade, primarily due to advancements in diagnostic and treatment strategies. Key improvements include the use of F-fluorodeoxyglucose positron emission tomography (F-FDG PET/CT) imaging and intensity-modulated radiation therapy (IMRT), alongside changes in chemotherapy regimens, the introduction of immunotherapy, and the emergence of targeted therapies for specific genetic mutations (Brahmer et al. 2018; Hallqvist et al. 2017; Hu et al. 2016; Mäurer et al. 2022; Mok et al. 2019; Nestle et al. 2020; Planchard et al. 2022; Sura et al. 2008). These advancements have led to measurable improvements in survival outcomes for patients diagnosed with non-small cell lung cancer (NSCLC).

Considering these developments, the aim of this study was to (1) describe the patterns of treatment in a cohort of patients with stage III NSCLC over different time periods and (2) investigate if being diagnosed and treated in recent time periods resulted in an improvement in overall survival.

Materials and methods

Data source and study population

This retrospective study is based on German population-based cancer registry data, collected and sent annually to the German Centre for Cancer Registry Data (Zentrum für Krebsregisterdaten, ZfKD) at the Robert Koch Institute (RKI) (Kraywinkel et al. 2014). Upon receiving the data, the ZfKD then undergoes data quality checks before producing a pooled anonymized dataset available for research purposes. The pooled dataset contains information on gender, month and year of birth, date of diagnosis, tumor topography and morphology, tumor grading and stage, and data on delivered treatments and death events.

This study used pooled nationwide NSCLC data, representing all patients diagnosed in Germany from 2007 to 2018. State cancer registries were included only if the overall proportion of Death Certificate Only (DCO) cases did not exceed 13% in 2007–2018 (EUROCARE-5 study) (Rossi et al. 2015). In addition, cancer registries that did not record treatment data or had a high percentage of its treatment information missing were excluded. Only six federal states (Baden-Württemberg, Saarland, Brandenburg, Mecklenburg–Western Pomerania, Saxony, and Thuringia) met the inclusion/exclusion criteria.

Patients diagnosed with stage III NSCLC (International Classification of Diseases for Oncology-ICD C34) during the period of 2007–2018 were included in our analysis. Stage III was defined using the Union for International

Cancer Control TNM Classification 8th edition and was further categorized into IIIA, IIIB and IIIC (Amin et al. 2017). The different histological subtypes of NSCLC were identified through their respective ICD-0 histology codes (Bray et al. 2021).

Cases were excluded if they were diagnosed by means of an autopsy, DCO, or had missing information on survival status and exact date of death. In addition, patients with a prior history of lung cancer or multifocal lung cancers were also excluded.

In our dataset, information on treatment was available as a binary variable (surgery yes/no, radiotherapy yes/no, chemotherapy yes/no). We categorized treatment into six groups: Surgery only, Surgery + Radiotherapy, Surgery + Chemotherapy, Radiotherapy only, Radiotherapy + Chemotherapy, Chemotherapy only, and Surgery + Radiotherapy + Chemotherapy. Since our study is focused on treatment patterns, untreated cases or cases with missing treatment information were not included in our analysis.

Definition of time-periods

The time-periods in our study are defined based on key developments in NSCLC diagnosis and treatment in Germany. The low availability era (2007–2010) corresponds to the initial implementation of FDG-PET for treatment planning (Bundesausschuss 2007). The ‘transition era’ (2011–2014) represents the period of growing utilization of IMRT. By 2011, IMRT was employed in over 10% of treated lung cancer cases, a substantial increase from less than 5% in 2008, and its usage continued to escalate, exceeding 25% by 2013 (Forschungsdatenzentrum 2016). Finally, the modern era (2015–2018) represents a period when both FDG-PET and IMRT were widely available and utilized, signifying the most advanced diagnostic and treatment methods available during the study period.

Outcome measure

Our primary outcome was overall survival (OS), measured from the date of cancer diagnosis to the date of death from any cause. Patients lost to follow-up before death or still alive at the last vital status assessment were right-censored at the date of the last vital status assessment or at the censor date (31 December 2018).

Statistical analysis

Demographic and clinical characteristics according to the time-period groups were described using common descriptive statistics. Differences between these groups were evaluated using appropriate statistical tests, with the resulting *p* values indicating the level of significance. The median

OS and the observable 3-years overall survival rates were reported to describe the survival of patients diagnosed within a certain time-period and for patients in our predefined treatment groups. Kaplan–Meier curves were used to visualize and estimate the 3-years survival rates. Differences in survival across the time-period groups were assessed using the log-rank test. After stratifying patients according to their respective treatment group, we conducted a multivariate analysis using the Cox proportional hazards model to investigate the association between being diagnosed during a certain era and survival. The Cox model adjusted for sex, age, stage subtype, and histology. We also adjusted for the treatment variable in an additional model to measure the general effect of the time-periods on survival. The hazard ratio (HR) estimates were reported along with their respective 95% confidence interval (CI).

Subgroup and sensitivity analysis

We conducted a subgroup analysis, stratifying our sample according to the sub-stages IIIA, IIIB, and IIIC as defined by TNM 8th edition. This updated classification, introduced in 2016, included the creation of sub-stage IIIC and revisions to the definitions of the existing sub-stages IIIA and IIIB. These changes could potentially lead patients diagnosed in the modern era with these two sub-stages, to appear to have

better survival. To address potential bias, we conducted a sensitivity analysis, reapplying our multivariate analysis using the definitions of sub-stages from the 7th edition (Edge and Compton 2010). Furthermore, to address potential biases associated with the varied process of recording treatment information across the included cancer registries, an additional sensitivity analysis was performed, taking into account the different cancer registries included from both East and West Germany.

All analyses were conducted in R statistical software version 3.2.3 (Team 2013).

Results

Patients characteristics

In total, our analysis included 14,606 NSCLC stage III patients diagnosed between 2007 and 2018 (Table 1). The mean age at diagnosis for the study population was 67.3 ± 9.9 years. The mean age was more or less the same across the three time-periods with the age distribution showing slight differences. While the majority of the patients were men (74%), the later eras showed an increase in the proportion of women patients reaching 28% in 2015–2018. The most common pathologies across the three time-periods

Table 1 Characteristics of NSCLC stage III treated patients 2007–2018

	Total	2007–2010	2011–2014	2015–2018	<i>P</i> value
Number	14,606	3980	5493	5133	
Age mean (SD)	67.3 (9.9)	67.0 (9.9)	67.4 (10.0)	67.4 (9.9)	0.170
< 50	661 (4.5)	224 (5.6)	247 (4.5)	190 (3.7)	<0.001
50–64	5134 (35.1)	1217 (30.6)	1969 (35.8)	1948 (38.0)	
65–79	7456 (51.0)	2235 (56.2)	2726 (49.6)	2495 (48.6)	
> 80	1355 (9.3)	304 (7.6)	551 (10.0)	500 (9.7)	
Gender <i>n</i> (%)					<0.001
Women	3776 (25.9)	896 (22.5)	1432 (26.1)	1448 (28.2)	
Men	10,830 (74.1)	3084 (77.5)	4061 (73.9)	3685 (71.8)	
Clinical stage at diagnosis <i>n</i> (%)					0.365
IIIA	6524 (44.7)	1779 (44.7)	2452 (44.6)	2293 (44.7)	
IIIB	5696 (39.0)	1524 (38.3)	2132 (38.8)	2040 (39.7)	
IIIC	2386 (16.3)	677 (17.0)	909 (16.5)	800 (15.6)	
Histology <i>n</i> (%)					<0.001
Squamous-cell carcinoma	7111 (48.7)	2000 (50.3)	2597 (47.3)	2514 (49.0)	
Adenocarcinoma	5440 (37.2)	1344 (33.8)	2052 (37.4)	2044 (39.8)	
Large cell carcinoma	453 (3.1)	182 (4.6)	167 (3.0)	104 (2.0)	
Other specified	1374 (9.4)	381 (9.6)	559 (10.2)	434 (8.5)	
Other unspecified	228 (1.6)	73 (1.8)	118 (2.1)	37 (0.7)	
Survival					
Median OS, months (95% CI)	18 (17–19)	16 (15–17)	17 (16–18)	22 (21–23)	
3-year survival, % (95% CI)	30.5 (29.7–31.3)	26.2 (24.9–27.6)	29.8 (28.6–31.0)	37.1 (35.4–39.0)	

were squamous cell carcinoma and adenocarcinoma. With regard to sub-stage present at diagnosis, 44.7% of the patients were diagnosed at IIIA, in comparison to 39.0% IIIB and 16.3% IIIC. The distribution of the sub-stages also showed no differences across the time eras.

Treatment patterns

The three most common treatment modalities received by the patients across the three eras were: radiotherapy + chemotherapy, radiotherapy only, and chemotherapy only (Fig. 1). The bimodal treatment of surgery + radiotherapy was the least delivered mode of treatment. The administration of radiotherapy + chemotherapy, the tri-modal treatment of surgery + chemotherapy + radiotherapy, and treatment with “surgery only” and “chemotherapy only” increased over time. Surgery + chemotherapy + radiotherapy increased from 8.9% in 2007–2010 to 10.8% in the modern era, while surgery only increased from 12.3% to 14.4% respectively.

Surgery + radiotherapy and radiotherapy only both decreased over time (Appendix 1).

Survival analysis

Our entire sample showed a median OS of 18 months (95% CI 17.0–19.0). The observed 3-years OS was 30.5% (95% CI 29.7–31.3) (Table 1). The 3-years survival rate increased by more than 10 percentage points from the 2007–2010 time-period 26.2% (95% CI 24.9–27.6) to the modern era 37.1% (95% CI 35.4–39.0). This was also reflected in the median OS, which rose from 16 months (95% CI 15.0–17.0) in the low-availability era to 17 months (95% CI 16.0–18.0) in the transition era, to finally 22 months (95% CI 21.0–23.0) in the most recent era. Stratifying the cases according to treatment received across the time-periods, median OS estimates revealed the same pattern (Appendix 1). Patients diagnosed in the modern era always showed a better OS no matter which treatment they received (Fig. 2, Appendix 1).

Fig. 1 Bar plot showing distribution of treatment strategies of stage III NSCLC across the time periods

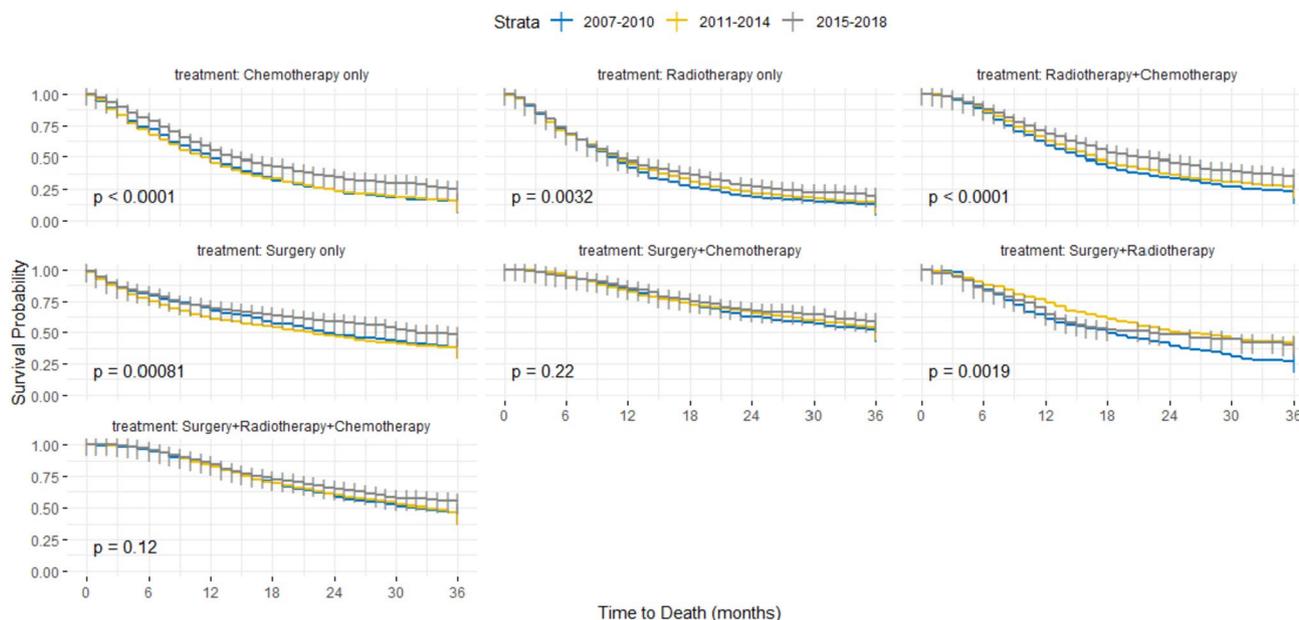
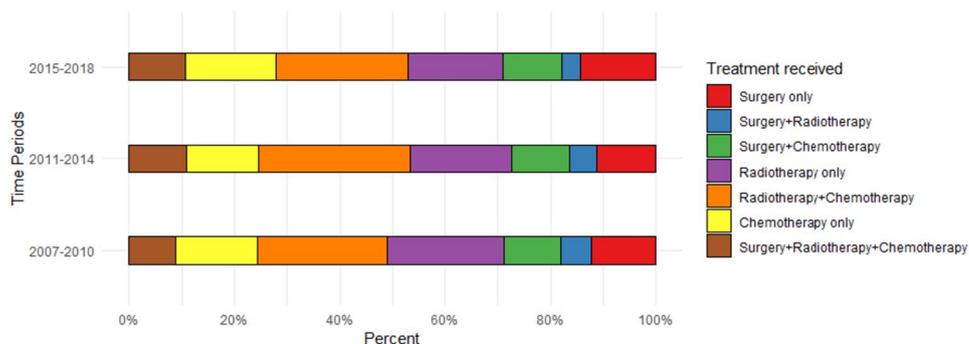


Fig. 2 Survival according to treatment received across the three time-periods

KM estimates demonstrated that patients who received chemotherapy only, radiotherapy + chemotherapy, and surgery + radiotherapy experienced the most significant improvement in survival (Appendix 1). Adjusting for age, sex, histology, and cancer sub-stage in our cox proportional-hazards model, the effect of time was clear (Table 2). All patients diagnosed and treated in the modern era consistently showed a lower hazard of dying when compared to our reference group (2007–2010) [HR 0.78 95% CI (0.74–0.83)]. This effect was strongest for patients treated by radiotherapy + chemotherapy [HR 0.73 95% CI (0.66–0.82)]. Further adjusting for the different cancer registries included did not alter our results (Appendix 2).

Subgroup analysis

To address the different treatment strategies that are based on cancer sub-stage, we further stratified our sample according to the sub-stage present at diagnosis. Surgery only was the most common treatment that patients diagnosed with sub-stage IIIA received. Patients diagnosed at sub-stages IIIB and IIIC were more likely to receive radiotherapy + chemotherapy and chemotherapy only (Fig. 3). Similar to our

unstratified estimates, the median OS and 3-year survival rates were always higher in patients diagnosed in the later eras, regardless of the sub-stage (Fig. 4, Appendix 1). Our cox proportional hazard models further highlighted this improvement in survival. Patients diagnosed in the transition and modern era consistently showed a lower hazard of overall mortality when compared to patients diagnosed in the early era, especially for patients receiving radiotherapy + chemotherapy at sub-stages IIIA [Modern era: IIIA HR 0.60, 95% CI (0.49–0.75)] and IIIC [Modern era: IIIC HR 0.69, 95% CI (0.56–0.85)] (Table 3). Changing how we defined the sub-stages using the 7th edition, did not alter our results (Appendix 2).

Discussion

Our study describes the treatment patterns for stage III NSCLC patients in Germany between 2007 and 2018, while focusing on comparing the treatment modalities and overall survival outcomes of cases diagnosed and treated during different time-periods. Our findings showed an improvement in overall survival for patients diagnosed and treated

Table 2 Hazard ratios comparing patients diagnosed in 2011–2014 and 2015–2018 to reference group (2007–2010) stratified according to treatment received

	Surgery only	Surgery + radiotherapy	Surgery + chemotherapy	Radiotherapy only	Radiotherapy + chemotherapy	Chemotherapy only	Surgery + radiotherapy + chemotherapy	Total ^a
2007–2010								
2011–2014	1.06 (0.91–1.23)	0.66 (0.53–0.82)*	0.96 (0.80–1.15)	0.94 (0.86–1.04)	0.91 (0.83–0.99)*	1.02 (0.91–1.14)	0.97 (0.81–1.16)	0.94 (0.89–0.99)*
2015–2018	0.79 (0.67–0.92)*	0.74 (0.56–0.97)*	0.84 (0.69–1.04)	0.84 (0.76–0.94)*	0.73 (0.66–0.82)*	0.77 (0.68–0.88)*	0.82 (0.66–1.00)	0.78 (0.74–0.83)*

Cox models adjusted for age, sex, histology, and cancer sub-stage

^aAdjusted for treatment in addition to baseline variables

*Indicates statistical significance

Fig. 3 Bar plot showing distribution of treatment strategies of stage III NSCLC according to sub-stage during 2007–2018

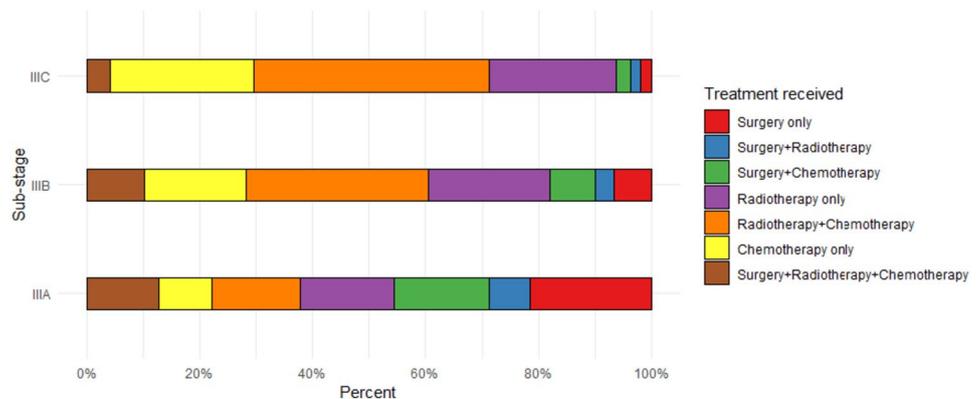


Fig. 4 Survival according to cancer sub-stage across the three time-period

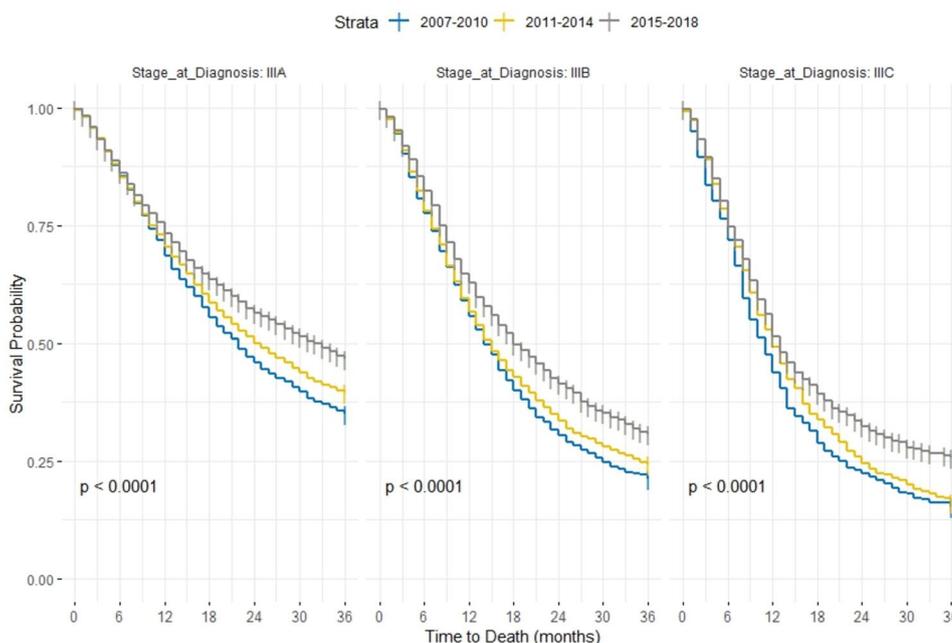


Table 3 Sub-stage stratified hazard ratios comparing patients diagnosed in 2011–2014 and 2015–2018 to reference group (2007–2010) stratified according to treatment received

	Surgery only	Surgery + radiotherapy	Surgery + chemotherapy	Radiotherapy only	Radiotherapy + chemotherapy	Chemotherapy only	Surgery + radiotherapy + chemotherapy	Total ^a
IIIA								
2007–2010								
2011–2014	1.05 (0.85–1.22)	0.65 (0.49–0.85)*	0.97 (0.77–1.22)	0.92 (0.79–1.09)	0.73 (0.61–0.88)*	1.11 (0.88–1.40)	0.96 (0.74–1.23)	0.91 (0.84–0.98)*
2015–2018	0.75 (0.61–0.90)*	0.66 (0.46–0.95)*	0.73 (0.55–0.96)*	0.93 (0.77–1.11)	0.60 (0.49–0.75)*	0.86 (0.67–1.10)	0.84 (0.62–1.12)	0.77 (0.70–0.84)*
IIIB								
2007–2010								
2011–2014	1.27 (0.92–1.73)	0.66 (0.45–0.98)*	0.99 (0.72–1.36)	0.93 (0.80–1.07)	0.98 (0.85–1.12)	1.00 (0.84–1.19)	0.86 (0.65–1.13)	0.96 (0.89–1.04)
2015–2018	0.95 (0.67–1.32)	0.89 (0.54–1.45)	1.10 (0.78–1.54)	0.78 (0.66–0.91)*	0.82 (0.70–0.96)*	0.71 (0.59–0.84)*	0.75 (0.55–1.03)	0.79 (0.73–0.86)*
IIIC								
2007–2010								
2011–2014	0.91 (0.37–2.24)	0.74 (0.39–1.91)	0.74 (0.33–1.67)	0.97 (0.78–1.20)	0.94 (0.79–1.12)	0.94 (0.76–1.17)	2.08 (1.01–4.25)	0.97 (0.87–1.08)
2015–2018	0.88 (0.39–1.98)	0.84 (0.35–1.99)	0.89 (0.35–2.20)	0.84 (0.66–1.07)	0.69 (0.56–0.85)*	0.82 (0.64–1.04)	1.27 (0.54–2.94)	0.79 (0.69–0.89)*

Cox regression models were adjusted for age, sex, and histology

^aAdjusted for treatment in addition to baseline variables

*Indicates statistical significance

in more recent years compared to those diagnosed earlier, with the largest improvement seen in patients treated with surgery + radiotherapy and radiotherapy + chemotherapy.

Considering that our study used time-periods as a proxy for improvements in diagnosis and treatment and our analysis only included treated cases, our results suggest that

advancements in diagnostic tools like FDG-PET and treatment methods such as IMRT could have contributed to the observed improvements in survival. We base this assumption on findings from multiple studies that highlight the potential of these techniques in enhancing oncological outcomes and reducing treatment-related toxicity. For instance, a recent cohort study by the young DEGRO Trial Group assessed the effect of radiotherapy treatment planning on overall survival and found that in stage III NSCLC patients diagnosed during 2010–2013, the use of PET/CT resulted in better oncological outcomes (HR = 0.80, CI 0.56–1.16) (Mäurer et al. 2022). This was also presented in the findings of Nestle et al., where the authors found that F-FDG PET-based reduction of radiotherapy target volume decreased the risk of locoregional progression compared to conventional target (CT)-based planning [HR 0.57, 95% CI 0.30–1.06] (Nestle et al. 2020). Similarly, the growing application of IMRT in concurrent chemoradiotherapy has shown potential in enhancing survival by minimizing the risk of life-threatening toxicity through precise and targeted delivery, as pointed out by Sampath et al. (Sampath 2016).

The randomized phase 3 trial (RTOG 0617) trial has also revealed that standard-dose radiotherapy outperformed high-dose radiotherapy in terms of overall survival, possibly due to fewer treatment-related deaths or severe adverse events (Bradley et al. 2020; Bradley et al. 2015). Furthermore, a secondary analysis associated IMRT with lower rates of severe pneumonitis and cardiac doses, contributing to survival advantages due to reduced toxicity and treatment interruptions (Chun et al. 2017; Koshy et al. 2017). While we suggest that these advancements could explain the improved survival rates in the modern era, especially among the radiotherapy + chemotherapy group, it is also crucial to recognize other possible factors, like developments in chemotherapy regimens or the introduction of immunotherapy. Immunotherapy, recommended for NSCLC treatment in 2018 (Brahmer et al. 2018; Gubens and Davies 2019; Novello et al. 2023) could have contributed significantly to positive outcomes. However, our dataset lacks information on the specific type of chemotherapy administered to the patients and whether they received immunotherapy. This limitation prevents us from conducting a comprehensive investigation into their respective effects on survival rates.

To our knowledge, this is the first study to explore treatment patterns of stage III NSCLC in Germany. As cancer treatments are continuously progressing, the literature and guidelines are evolving, therefore the results from studies across Europe and lung cancer stages are often extrapolated from due to the use of different time-periods in our study. The 2022 update to the German S3 guideline for lung cancer advises that a comprehensive thoracic-oncological tumor board be established to determine the extent of additional diagnostics required, stage the cancer accurately, and make

informed decisions on the best treatment for each individual patient (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft and AWMF) 2022). The guidelines further recommend concurrent chemoradiotherapy (CRT) as the preferred treatment for most patients with stage III NSCLC, including those with inoperable tumors. Additionally, the combination of immunotherapy with CRT is advised for selected patients with a PD-L1 (Programmed cell death receptor ligand 1) expression level of 1% or more. Considering that our study sample was diagnosed over a 12 year time period (2007–2018), the trend towards the bimodal treatment modality of radiotherapy + chemotherapy as the preferred treatment for stage III NSCLC was evident. This group of patients, along with those treated with surgery + radiotherapy demonstrated the largest improvement in survival.

Our study also revealed considerable variation in treatment modalities across the different sub-stages of NSCLC. Most patients diagnosed at stage IIIA were treated with either surgery or a combination of surgery and chemotherapy. In contrast, about 75% of cases at stages IIIB and IIIC were treated with either radiotherapy + chemotherapy or radiotherapy alone. These findings were also in line with guideline-recommended treatment. Importantly, all sub-stages experienced an improvement in overall survival, indicating that advancements in diagnostic and therapeutic strategies are benefiting a wide range of patients. It is also worth noting that the proportions of the diagnosed sub-stages did not change across the eras, with almost half of the cases presenting with stage IIIA during each time-period. This confirms that the improvements in survival seen in our results were not a result of possible stage migration. Our sensitivity analysis also excluded the potential bias arising from the different classifications of the sub-stages during our study period.

The key strength of our study is the broad, representative sample size, spanning six German population-based registries over 12 years, representing a population of around 22.4 million (~27% of the entire German population). This is particularly valuable since clinical trials often focus on younger, healthier patients, potentially introducing selection bias. To address the high proportions of death certificate only (DCO) cases within the state registries, we excluded registries with DCO proportions exceeding the recommended 13% to ensure reliable survival estimates. We also addressed potential bias arising from different registry documentation methods. However, our study faces limitations due to lack of data on tumor operability and patient profile, which are crucial in deciding the treatment approach, including the option of surgery. Consequently, we could not ascertain whether the absence of surgery was due to inoperability or patient's unfitness. Furthermore, our dataset did not include information on radiation dosage, surgical procedure details, chemotherapy type, treatment intent (curative/palliative),

or treatment delivery date. To circumnavigate these limitations, we only included treated cases in our analysis and we grouped the cases diagnosed within a 3-years time period according to the treatment combination received.

Despite these limitations, our study provides valuable insights into the evolution of stage III NSCLC treatment patterns in Germany over a 12-years span. This knowledge is critical as it helps in understanding how changes in treatment modalities, diagnostic tools, and other factors may impact overall survival outcomes. As treatments continue to progress, it will be crucial to conduct further research to fully understand the interplay of these variables and how they can be optimized to improve patient outcomes.

Conclusion

Our results indicate an improvement in survival for stage III NSCLC patients in Germany. This improvement could be partly explained by the more extensive use of FDG-PET in tumor diagnosis, alongside a general improvement in treatment procedures. Considering how immunotherapy is currently incorporated in the treatment plan, further studies with access to extensive treatment information are recommended to measure improvements in survival across time.

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Availability of data and material This study was based on the German national cancer registry data. The authors do not own these data and hence are not permitted to share them in the original form (only in aggregate form, eg, publications). Data were provided by the Robert Koch Institute (RKI).

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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