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Direktor: Prof. Dr. Claus Belka

Stellenwert des Planungszielvolumens in der modernen radiotherapeutischen Behandlung lokal fortgeschrittener, inoperabler Lungenkarzinome

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Inhaltsverzeichnis

Publikationen der kumulativen Dissertation

Erstautorenschaft

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1. Einleitung

1.1 Epidemiologie

Das Lungenkarzinom stellt derzeit die weltweit häufigste Krebstodesursache dar und ist durch zunehmend steigende Inzidenz- und weiterhin hohe Mortalitätsraten gekennzeichnet [1-3]. Laut der “International Agency for Research on Cancer” (IARC) der Weltgesundheitsorganisation (WHO) belief sich die Zahl der Neuerkrankungen im Jahr 2020 weltweit auf rund 2,2 Millionen, 1,8 Millionen Menschen hingegen verstarben an ihrem Lungenkarzinom [3]. Im Gegensatz dazu wurden im Jahr 2012 noch 1,8 Millionen Neuerkrankungen und 1,6 Millionen Todesfälle auf der ganzen Welt verzeichnet [4, 5].

Auch in Deutschland spiegelt sich dieser globale Trend wider: Entsprechend der Berichte des Robert-Koch-Instituts erkrankten im Jahr 2018 etwa 57.000 Menschen an Lungenkrebs und bei 45.000 PatientInnen endete die Erkrankung tödlich [6]. Diese Zahlen zeigten, im Vergleich zu den Vorjahren, eine ansteigende Tendenz [7, 8]. Die Inzidenz- und Mortalitätsraten weisen allerdings sowohl auf internationaler als auch nationaler Ebene deutliche geschlechtsspezifische Unterschiede auf [2, 3, 6, 9, 10]. Seit den späten 1990er Jahren steigen die Zahlen bei den Frauen kontinuierlich an, während sie gleichzeitig bei den Männern rückläufig sind [2, 3, 6, 9, 10]. Diese gegensätzliche Entwicklung lässt sich insbesondere auf den zunehmenden Anteil rauchender Frauen in den letzten Jahrzehnten zurückführen, der sich nun, mit einer gewissen Latenz, in steigenden Krebsfällen niederschlägt [3, 6, 10-12].

Rauchen ist weltweit für 80-85% aller Lungenkrebsfälle verantwortlich und bleibt daher nach wie vor der primäre Risikofaktor für die Entstehung von Lungenkarzinomen [9, 13-16]. Auch Expositionen gegenüber Karzinogenen wie Radon, Asbest oder Arsen sowie Infektionen mit Mycobacterium tuberculosis oder humanen Papillomaviren (HPV) stellen mögliche Ursachen dar, spielen allerdings eine deutlich untergeordnete Rolle [17-21].

Trotz erheblicher Fortschritte in unserem Verständnis von Risikofaktoren, Pathogenese und verbesserten Behandlungsmöglichkeiten des Lungenkarzinoms bleibt diese Erkrankung global gesehen weiterhin die führende Krebstodesursache [1, 3]. In Anbetracht des demografischen Wandels ist weltweit sogar eine deutliche Zunahme der Neuerkrankungen in den kommenden Jahren zu erwarten [22-24]. Diese Tatsache betont die klinische sowie ökonomische Notwendigkeit der weiteren wissenschaftlichen Auseinandersetzung mit dieser besonderen Tumorentität [22, 23].

1.2 Kleinzelliges Lungenkarzinom

85-90% aller Lungenkarzinome entfallen auf das nicht-kleinzellige Lungenkarzinom (NSCLC), in den übrigen Fällen handelt es sich meist um ein kleinzelliges Lungenkarzinom (SCLC) [21, 25, 26]. Im Vergleich zum NSCLC zeichnet sich das SCLC durch eine deutlich schnellere Wachstumsrate sowie einer höheren Tendenz zur frühen Metastasierung aus und geht daher mit einer erheblich schlechteren Prognose einher [25-28].

Aufgrund des aggressiven Tumorwachstums präsentieren sich bei Erstdiagnose eines SCLC bereits mehr als 2/3 aller Patienten mit einem fortgeschrittenen Tumorleiden, das Pleura-/Perikardbefall und/oder Fernmetastasen aufweist („extensive stage“, ES) [28, 29]. Nach Jahrzehnten ohne therapeutischen Fortschritt gelang auf Grundlage der Daten der IMpower133-Studie mit Atezolizumab der Durchbruch in der Immuntherapie des klinisch herausfordernden ES-SCLC [30, 31]. Der Anti-PD-L1-Antikörper hat sich seit seiner Zulassung im Jahr 2019 in Kombination mit Carboplatin und Etoposid als der neue Behandlungsstandard für Patienten mit fortgeschrittenen SCLC etabliert [30, 31]. Basierend auf den Ergebnissen der CASPIAN-Studie erhielt im Folgejahr auch Durvalumab als zweiter Anti-PD-L1-Antiköper die Zulassung in der Erstlinientherapie beim ES-SCLC [32, 33]. Ergänzend sollte in diesem Patientenkollektiv neben einer Chemoimmuntherapie auch eine prophylaktische Ganzhirnbestrahlung oder eine konsolidierende Bestrahlung des Mediastinums in Betracht gezogen werden [34-39].

Ist der Tumor lediglich auf einen Hemithorax beschränkt und kann strahlentherapeutisch vollständig mit ausreichender Dosierung erfasst werden, handelt es sich um ein LS-SCLC („limited stage“, LS) [29, 40]. Bei diesen Patienten bleibt die simultane Radiochemotherapie, bestehend aus einer Kombination aus Cisplatin und Etoposid, mit gegebenenfalls anschließender prophylaktischer Ganzhirnbestrahlung nach wie vor der Goldstandard in der Erstlinienbehandlung [39, 41-43].

1.3 Nicht-kleinzelliges Lungenkarzinom

Das NSCLC stellt mit 85-90% den weitaus größten Anteil aller Lungenkarzinome dar [21, 25, 26]. Im Gegensatz zum SCLC wird beim NSCLC im Rahmen der Therapieplanung zunehmend nach Histologie und Molekularbiologie der Tumorzellen differenziert [44]. Das Adenokarzinom ist mit etwa 40-50% der häufigste histologische Subtyp des NSCLC, gefolgt vom Plattenepithelkarzinom mit 25-30% [21, 44, 45]. Weitere histologische Untergruppen wie das großzellige Karzinom oder das adenosquamöse Karzinom sind weitaus weniger verbreitet [21, 44].

Zahlreiche Treibermutationen wie beispielsweise im KRAS-, EGFR-, ALK-, BRAF-, ROS1- oder HER2-Gen lassen sich überwiegend bei Adenokarzinomen nachweisen [44, 46, 47]. Sie spielen eine wichtige Rolle bei der Tumorentstehung und sind daher von erheblicher therapeutischer Relevanz [48-54]. Im Gegensatz dazu sind Treibermutationen bei Plattenepithelkarzinomen weniger verbreitet, in der Behandlung dieser Karzinome spielen die zielgerichteten Tumortherapien daher derzeit noch eine untergeordnete Rolle [55]. Die Forschung zur Identifizierung weiterer Zielstrukturen in der Hoffnung auf neue Behandlungsmöglichkeiten schreitet allerdings weiter voran [56, 57]. Sowohl bei Plattenepithel- als auch Adenokarzinomen wird eine immunhistochemische Bestimmung der PD-L1-Expression zur Evaluation einer Immuncheckpoint-Inhibition empfohlen [58].

Im Zeitalter der personalisierten Medizin ist aufgrund der erheblichen therapeutischen sowie prognostischen Bedeutung eine weitere Differenzierung in Bezug auf die (Immun)Histologie und die Molekularbiologie der Lungenkarzinome daher unerlässlich [44]. Für die Therapieplanung ist die Ausbreitung des Tumors bei Erstdiagnose ebenfalls essenziell [59]. Im Gegensatz zur weit verbreiteten Klassifikation des SCLC in limited bzw. extensive stage (nach der Veterans Administration Lung Study Group) [28, 29, 40] erfolgt beim NSCLC, wie bei den meisten soliden Tumoren, zunächst eine Einteilung entsprechend der etablierten TNM-Kriterien, aus denen anschließend das Stadium gemäß den Leitlinien der Union Internationale Contre Le Cancer (UICC) 8 abgeleitet wird [59-61]. Die Zusammensetzung der jeweiligen Stadien des NSCLC ist in Abbildung 1 dargestellt.

	M0				M1a	M1b	M1c
	N0	N1	N2	N3		Jedes N	
T1a	IA1	IIB	IIIA	IIIB	IVA	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVA	IVB

Abbildung 1: Stadieneinteilung des NSCLC anhand der TNM-Klassifikation (nach UICC 8) [60, 61]

Prinzipiell erfolgt die Therapie anhand des Tumorstadiums unter Berücksichtigung des Allgemeinzustands und der Komorbiditäten des Patienten sowie (immun)histologischen und molekularbiologischen Eigenschaften des Tumors [62].

Im Stadium I, II und IIIA (T3N1, T4N0, T4N1) ist die bevorzugte Therapie die kurative Tumorresektion [63, 64]. Im Stadium II und IIIA sollte nach R0-Resektion zudem eine

Cisplatin-basierte Chemotherapie ergänzt werden, bei Vorliegen einer EGFR-Mutation (Deletion im Exon 19, Punktmutation L858R im Exon 21) muss ebenfalls eine zielgerichtete Therapie mit Osimertinib in Betracht gezogen werden [63-69]. Bei EGFR- und ALK-Wildtyp, allerdings hoher PD-L1-Expression auf den Tumorzellen (≥ 50%) sollte bei Patienten mit hohem Rezidivrisiko nach vollständiger Resektion und anschließender platinbasierter Chemotherapie auch eine Erhaltungstherapie mit Atezolizumab angeboten werden [70, 71]. Basierend auf aktuellen Erkenntnissen kann im Stadium II und IIIA auch eine neoadjuvante, platinbasierte Chemotherapie zur präoperativen Tumorreduktion in Erwägung gezogen werden, bei Patienten mit einer PD-L1-Expression ≥ 1% sollte diese mit dem Checkpoint-Inhibitor Nivolumab ergänzt werden [72-75]. Gegenstand aktueller Forschung ist der perioperative Einsatz von Durvalumab und Pembrolizumab bei Patienten mit resektablem NSCLC im Stadium II-IIIB [76, 77]. Eine adjuvante Radiatio nach kompletter Tumorresektion wird generell nicht empfohlen, bei Inoperabilität oder Patientenwunsch bietet die stereotaktische Bestrahlung („Stereotactic Ablative Body Radiation Therapy“, SABR/SBRT) in den frühen Stadien allerdings eine alternative Behandlungsmöglichkeit [63, 78, 79].

Das Stadium III stellt aufgrund seiner Heterogenität eine besondere klinische Herausforderung dar und erfordert eine multimodale Behandlung [60, 61]. Es stehen zahlreiche Behandlungsmöglichkeiten zur Verfügung, die im interdisziplinären Tumorboard individuell an den Patienten angepasst werden müssen. Im Stadium IIIA (mit bulky N2-Konstellation), IIIB sowie IIIC gilt eine definitive Radiochemotherapie als der Goldstandard [80-82]. Hierbei sollte eine Cisplatin-basierte Chemotherapie simultan zur Bestrahlung verabreicht werden [83-86]. Sollte der Patient aufgrund seines Allgemeinzustands oder seiner Komorbiditäten einer solchen Therapie nicht zugänglich sein, besteht die Möglichkeit einer sequentiellen Radiochemotherapie, gegebenenfalls mit Änderung der Fraktionierung (hypofraktionierte Bestrahlung) [63, 87-89]. Die wegweisenden Ergebnisse der Phase-III-Studie PACIFIC haben gezeigt, dass der Einsatz des PD-L1-Inhibitors Durvalumab nach einer definitiven, platinbasierten Radiochemotherapie sowohl das mediane progressionsfreie Überleben (16.8 vs. 5.6 Monate) als auch das Gesamtüberleben (Fünf-Jahres-Überlebensrate von 43% vs. 33%) signifikant verlängert [90-92]. Basierend auf diesen herausragenden und klinisch bedeutsamen Daten wurde Durvalumab im September 2018 EU-weit als einjährige Konsolidierungstherapie nach definitiver Radiochemotherapie ohne Progress bei Patienten mit lokal fortgeschrittenem, inoperablen NSCLC zugelassen [90-92]. Voraussetzung für die Anwendung des Immuntherapeutikums ist allerdings eine PD-L1-Expression ≥ 1% auf den Tumorzellen [93]. Seit Juni 2021 besteht für Patienten mit inoperablem, lokal fortgeschrittenem NSCLC (IIIB/C), die

nicht für eine Radiochemotherapie in Frage kommen, die Möglichkeit einer Immunmonotherapie mit dem PD-L1-Inhibitor Cemiplimab [94, 95]. Allerdings nur sofern keine therapierelevanten Treiberaberrationen und eine PD-L1-Expression ≥ 50% auf den Tumorzellen vorliegen [94, 95]. Die Zulassung wurde im März 2023 erweitert, sodass Cemiplimab in dieser Patientenkohorte nun bereits bei einer PD-L1-Expression ≥ 1% in Kombination mit einer platinbasierten Chemotherapie angewandt werden darf [96].

Etwa die Hälfte aller NSCLC-Patienten sind bereits bei Erstdiagnose fernmetastasiert [97]. Abgesehen von wenigen potenziell kurativen Fällen (oligometastasierte Erkrankungen), befindet sich der Großteil der Patienten in einer palliativen Behandlungssituation [98-101]. Im Gegensatz zu der bis vor einigen Jahren noch ausschließlich verfügbaren palliativen Chemotherapie werden die Therapieansätze beim metastasierten NSCLC heutzutage wesentlich durch (immun)histochemische und molekularpathologische Marker mitbestimmt [49-52, 102-122]. Bei Vorliegen therapierelevanter Treibermutationen (wie beispielsweise einer EGFR-, ALK-, BRAF V600-, ROS1-, RET-Alteration) sollte daher primär eine zielgerichtete Tumortherapie eingeleitet werden [49-52, 102-118]. Falls keine behandelbaren Mutationen vorhanden sind, sollte unabhängig vom PD-L1-Status eine platinhaltige Chemoimmuntherapie angeboten werden [123-130]. Eine PD-L1-Expression ≥ 50% der Tumorzellen ermöglicht im Rahmen der Zulassung allerdings eine Monotherapie mit Atezolizumab, Cemiplimab oder Pembrolizumab in der Erstlinienbehandlung [94, 131-134].

2. Erstautorenschaft

Association of planning target volume with patient outcome in inoperable stage III NSCLC treated with chemoradiotherapy: A comprehensive single-center analysis [135].

2.1 Hintergrund der Publikation

Die Strahlentherapie hat neben der Chemotherapie einen sehr hohen Stellenwert in der Behandlung lokal fortgeschrittener, inoperabler nicht-kleinzelliger Lungenkarzinome [81, 84, 136-140]. Bei der Erstellung eines individualisierten Bestrahlungsplans ist die exakte Bestimmung der Zielvolumina von großer Bedeutung [141]. Die ICRU (International Commission on Radiation Units and Measurements) hat erstmalig im Jahr 1993 die Konzepte von GTV (Gross Tumor Volume), CTV (Clinical Target Volume) und PTV (Planning Target Volume) als die drei Hauptvolumina in der Strahlentherapie eingeführt [142]. Bei diesem ICRU-Report 50 handelt es sich um einen international anerkannten Leitfaden, der eine einheitliche und strukturierte Vorgehensweise zur Bestimmung der Zielvolumina empfiehlt [142]. Er wurde im Laufe der letzten Jahrzehnte durch ergänzende Berichte kontinuierlich weiterentwickelt, um den aktuellen Stand der Technik und Forschung widerzuspiegeln [142-144].

Unter dem GTV versteht man die makroskopische Tumorausbreitung, die heutzutage meistens durch bildgebende Verfahren erfasst wird [142, 145]. Wurde der Tumor im Vorfeld der Bestrahlung bereits operativ reseziert, kann definitionsgemäß kein GTV mehr abgegrenzt werden [142, 145]. Das CTV hingegen beinhaltet das GTV (falls keine Resektion stattgefunden hat) und umfasst zusätzlich die mikroskopische Tumorinfiltration [142, 143]. Da diese bildgebend nicht darstellbar ist, beruhen die CTV-Säume in der Regel auf historisch gewonnenen Patientendaten [145]. Eine gewisse Anpassung des CTVs ist durch Kenntnis der Infiltrationswege und -grenzen unter Beachtung individueller Patientenmerkmale dennoch möglich [145]. Das PTV berücksichtigt darüber hinaus Ungenauigkeiten, die bei der Planung und Ausführung der Strahlentherapie auftreten können wie beispielsweise Abweichungen bei der Lagerung des Patienten sowie Bewegungen der Zielvolumina durch Atmung oder Peristaltik [142, 146]. Durch einen zusätzlichen Sicherheitssaum wird eine korrekte Dosisabdeckung des GTVs und CTVs gewährleistet [142, 146]. Es handelt sich daher nicht um ein anatomisches, sondern ein geometrisches Volumenkonzept, dessen Konturen durchaus auch außerhalb des Patienten verlaufen können [142, 143].

Entsprechend den Empfehlungen der ESTRO-ACROP (European Society for Radiotherapy and Oncology - Advisory Committee on Radiation Oncology Practice) sollte die Definition der Zielvolumina bei lokal fortgeschrittenen Lungenkarzinomen anhand einer kontrastmittelverstärkten CT-Bildgebung sowie eines Ganzkörper-FDG-PET-CTs erfolgen [147, 148]. Idealerweise sollte die radiologische Diagnostik bei Therapiebeginn dabei nicht älter als 3 Wochen sein [147]. Das CTV sollte mit einem Abstand von 5-8 mm das GTV umranden, der Sicherheitssaum für das PTV hingegen basiert meist auf hausinternen Klinikstandards und ist abhängig von den jeweils verwendeten Bestrahlungsgeräten [147, 149]. Es ist jedoch zu betonen, dass diese Empfehlungen lediglich Richtlinien darstellen und immer individuell an den einzelnen Patienten angepasst werden sollten [147, 150]. Des Weiteren müssen in der Therapieplanung die Risikoorgane berücksichtigt werden, die bei Lungenkarzinomen in erster Linie das Lungengewebe selbst, aber auch benachbarte Organe wie den Ösophagus, das Herz sowie das Rückenmark umfassen und meist den dosislimitierenden Faktor für die zu verabreichende Strahlentherapie darstellen [147] [151, 152]. Die eindeutige Abgrenzung zwischen Zielvolumina und Risikoorganen führt zu einer höheren Präzision und Sicherheit der Bestrahlung [142]. Die klare und einheitliche Definition der Zielgrößen erleichtert zudem die Vergleichbarkeit sowie die Kommunikation zwischen unterschiedlichen Behandlungszentren, sowohl auf nationaler als auch auf internationaler Ebene, und vereinfacht die Analyse umfangreicher Datensätze, insbesondere in multizentrischen Studien [142, 153].

Die simultane Radiochemotherapie gilt als Goldstandard in der Behandlung lokal fortgeschrittener Lungenkarzinome, geht allerdings auch mit einer Vielzahl an strahlentherapiebedingten Nebenwirkungen einher [152]. In den ersten 6 Monaten nach Bestrahlung treten bei bis zu 20% aller Patienten eine klinisch relevante Strahlenösophagitis oder -pneumonitis auf, deutlich später können sich eine chronische Lungenfibrose oder Kardiotoxizität manifestieren [152]. Die Auftretenswahrscheinlichkeit dieser unerwünschten Begleiterscheinungen korreliert unter anderem mit der Höhe der applizierten Strahlendosis und dem Bestrahlungsvolumen [80, 154-160]. In der individuellen Bestrahlungsplanung besteht die Herausforderung daher vor allem darin zwar eine ausreichende Tumorbestrahlung zu gewährleisten, aber gleichzeitig die strahlentherapieassoziierte Toxizität so gering wie nur möglich zu halten [152, 154]. Dank erheblicher technologischer Fortschritte in der Strahlentherapie ist es heutzutage möglich den Tumor gezielter zu bestrahlen und dabei das umliegende, gesunde Gewebe besser zu schonen [140]. Die technische Weiterentwicklung hat mit der Einführung der IMRT (Intensity-modulated radiotherapy) verglichen mit der 3D-CRT (conformal radiotherapy) sowohl zu einer deutlichen Verbesserung der Überlebensraten als auch zu einer Reduktion der Toxizität beigetragen [161-166].

Die Größe des bestrahlten Volumens geht allerdings nicht nur mit vermehrten strahlentherapiebedingten Nebenwirkungen, sondern auch mit einer erhöhten Mortalität einher [166-171]. Kong et al. zeigten 2016, dass Patienten mit einem lokal fortgeschrittenen NSCLC im Stadium III und einem GTV < 100 cm^3 nicht nur in der univariaten (p=0.040), sondern auch in der multivariaten Analyse (p=0.017) eine signifikant bessere Zwei-Jahres-Gesamtüberlebensrate aufwiesen als Patienten mit einem GTV ≥ 100 cm^3 [166]. Auch die Arbeit von Tucker et al. aus dem Jahr 2016 umfasste eine Kohorte von 468 Patienten mit NSCLC im Stadium IIIA/B, die mit einer simultanen Radiochemotherapie behandelt wurden [171]. Ein GTV ≥ 125 cm^3 korrelierte hierbei ebenfalls sowohl in der univariaten (p<0.0001) als auch der multivariaten Analyse (p<0.001) mit einem deutlich schlechteren Gesamtüberleben [171]. Darüber hinaus konnte in zahlreichen weiteren Studien das GTV als wichtiger prognostischer Marker für das Gesamtüberleben bei Patienten mit NSCLC hervorgehoben werden [166-171]. Zudem scheint es auch in anderen Tumorentitäten wie Mundhöhlen-, Nasopharynx- oder Ösophaguskarzinomen eine durchaus bedeutende prognostische Rolle zu spielen [172-175], die Relevanz von PTV als das eigentlich bestrahlte Zielvolumen hingegen wird nicht beleuchtet [166-175].

Das Planungszielvolumen (PTV) kann stark variieren [149] und der prognostische Wert für NSCLC-Patienten im Stadium III ist weiterhin unklar. In früheren Studien konnte das PTV zwar als ein wichtiger Faktor für die Qualität der Bestrahlung sowie die behandlungsbedingte Toxizität hervorgehoben werden [157], die aktuelle Studienlage zum Einfluss von PTV auf das Patientenüberleben ist allerdings sehr limitiert. Das Ziel dieser wissenschaftlichen Arbeit war es daher an die bereits bestehende Evidenzlage anzuknüpfen und einerseits die Auswirkungen von PTV auf das Patientenüberleben zu analysieren sowie andererseits einen Volumen-Cut-Off zu definieren, der den größten Einfluss auf das Gesamtüberleben hat.

2.2 Deutsche Zusammenfassung

In die Studie wurden 122 Patienten eingeschlossen, die zwischen 2011 und 2018 (vor der Zulassung von Durvalumab) eine definitive Radiochemotherapie (RCT) am Universitätsklinikum der LMU München als Teil eines multimodalen Ansatzes für NSCLC im Stadium IIIA/B erhielten [135]. Die Erhebung der Patientendaten erfolgte sowohl retro- als auch prospektiv und die Zielvolumina wurden anhand eines hausinternen Standards definiert, der in engem Einklang mit den im März 2018 veröffentlichten Leitlinien der ESTRO-ACROP steht [135, 147].

In der univariaten Analyse wurden zunächst mehrere Planungszielvolumina (PTV) mit einem Cut-Off im Bereich von 500 bis 900 cm^3 auf ihren Zusammenhang mit dem Gesamtüberleben analysiert [135]. Hierbei stellten sich sowohl ein PTV ≥ 600 cm^3 als auch ein PTV ≥ 700 cm^3 als signifikante Einflussfaktoren heraus [135]. In den ergänzend durchgeführten multivariaten Analysen, die unter anderem Parameter wie das Alter, das Geschlecht, die Gesamtbestrahlungsdosis und die Histologie beinhalteten, erwies sich lediglich PTV ≥ 700 cm^3 mit einem p-Wert von 0.025 als unabhängiger prognostischer Marker für das Gesamtüberleben [135]. Um die prognostische Rolle von PTV ≥ 700 cm^3 zu bestätigen, erfolgte daraufhin ein Propensity-Score-Matching (PSM) [135].

Zusammenfassend betrachtet, konnte PTV ≥ 700 cm^3 als Volumen-Cut-Off identifiziert werden, der den größten Einfluss auf das Gesamtüberleben hat und mit einer deutlich verminderten Lebenserwartung einhergeht [135]. In Zusammenschau dieser Ergebnisse sollte das PTV daher zukünftig als Stratifizierungsfaktor in multimodalen klinischen Studien für inoperable NSCLC im Stadium III Berücksichtigung finden [135].

2.3 Englische Zusammenfassung – English summary

This study included a total of 122 patients who received definitive chemoradiotherapy (CRT) at the LMU University Hospital in Munich between 2011 and 2018 (prior to Durvalumab approval) as part of a multimodal approach for stage IIIA/B NSCLC [135]. Patient data were assessed in retrospective as well as prospective manners and the target volumes were defined using an in-house standard that closely adheres to the ESTRO-ACROP guidelines published in March 2018 [135, 147].

In the initial univariate analysis, several planning target volumes (PTV) ranging from 500 to 900 cm^3 were analyzed for their association with overall survival [24]. Both PTV ≥ 600 cm^3 and PTV ≥ 700 cm^3 were found to be significant factors [24]. In the following multivariate analyses including parameters such as age, gender, total dose of radiotherapy and histology, only PTV ≥ 700 cm^3 emerged as an independent prognostic marker for

overall survival with a p-value of 0.025 [135]. Propensity-Score-Matching (PSM) analysis further verified the beneficial effect of ≥ 700 cm^3 on overall survival [135].

In conclusion, PTV ≥ 700 cm^3 was identified as a volume-cut-off that has the greatest impact on overall survival and is associated with detrimental outcomes [135]. PTV should therefore be considered as a stratification factor in future clinical trials focusing on inoperable stage III NSCLC [135].

3. Ko-Autorenschaft

Planning target volume as a predictor of disease progression in inoperable stage III non-small cell lung cancer patients treated with chemoradiotherapy and concurrent and/or sequential immune checkpoint inhibition [176].

3.1 Hintergrund der Publikation

Die Einführung der Immuncheckpoint-Inhibitoren hat neue, vielsprechende Therapieoptionen geschaffen und damit die Behandlung nicht-kleinzelliger Lungenkarzinome innerhalb weniger Jahre grundlegend verändert [177]. Immuncheckpoints dienen als natürliche negative Rückkopplungsmechanismen, um eine überschießende Immunreaktion zu verhindern [178-181]. Diese Signalwege machen sich Tumorzellen allerdings zu Nutze, um eine Immunantwort gegen sich selbst zu blockieren und dadurch die Progression des Tumors zu begünstigen [178-180]. Zu den bisher am besten beschriebenen und untersuchten Checkpoints gehören CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) sowie PD-1 (programmed cell death protein 1) und dessen Ligand PD-L1 [178, 181].

Als Oberflächenrezeptor wird CTLA-4 sowohl von T-Helfer- (CD4+) als auch zytotoxischen T-Zellen (CD8+) exprimiert und führt durch die Bindung an CD86 der antigenpräsentierenden, insbesondere der dendritischen Zellen, zu einer Hemmung der T-Zellaktivierung und -proliferation [181-184]. Hodi et al. zeigten in einer Phase III-Studie, dass die Gabe eines Anti-CTLA-4-Antikörpers wie Ipilimumab bei Patienten mit einem inoperablen und bereits vorbehandelten metastasierten Melanom mit einer signifikanten Verlängerung des Gesamtüberlebens im Vergleich zur Kontrollgruppe, die ausschließlich mit einem Vakzin (gp100) therapiert wurde, einhergeht [185]. Diese Ergebnisse führten daher im Jahr 2012 in Europa erstmalig zur Zulassung eines Antikörpers als mögliche Behandlungsoption in der Therapie eines fortgeschrittenen malignen Melanoms [186].

Im Hinblick auf das NSCLC spielt vor allem die Interaktion zwischen PD-1 und PD-L1 eine entscheidende Rolle. Beim PD-L1 handelt es sich um ein membranständiges Protein, das von zahlreichen Tumorzellen exprimiert wird und mit dem PD-1-Rezeptor, der sich unter anderem an der Oberfläche von T-Lymphozyten befindet, interagiert [180, 181, 183, 187]. Diese Wechselwirkung hemmt die Aktivierung sowie die Proliferation der zytotoxischen T-Zellen und resultiert in einer erheblich abgeschwächten Immunreaktion des Körpers [181, 183, 187]. Im letzten Jahrzehnt sind PD-1 und PD-L1 daher als mögliche Angriffspunkte von Immuncheckpoint-Inhibitoren wichtiger Bestandteil immunonkologischer Forschung geworden. Die Hoffnung besteht darin, dass durch den gezielten Einsatz von Antikörpern die durch PD-1/PD-L1 vermittelte Signalkaskade unterbrochen und dadurch die Antitumor-Immunität der T-Zellen wiederhergestellt wird [181]. Der

Wirkmechanismus von Anti-PD-1- und Anti-PD-L1-Antikörpern wird in Abbildung 3 veranschaulicht.

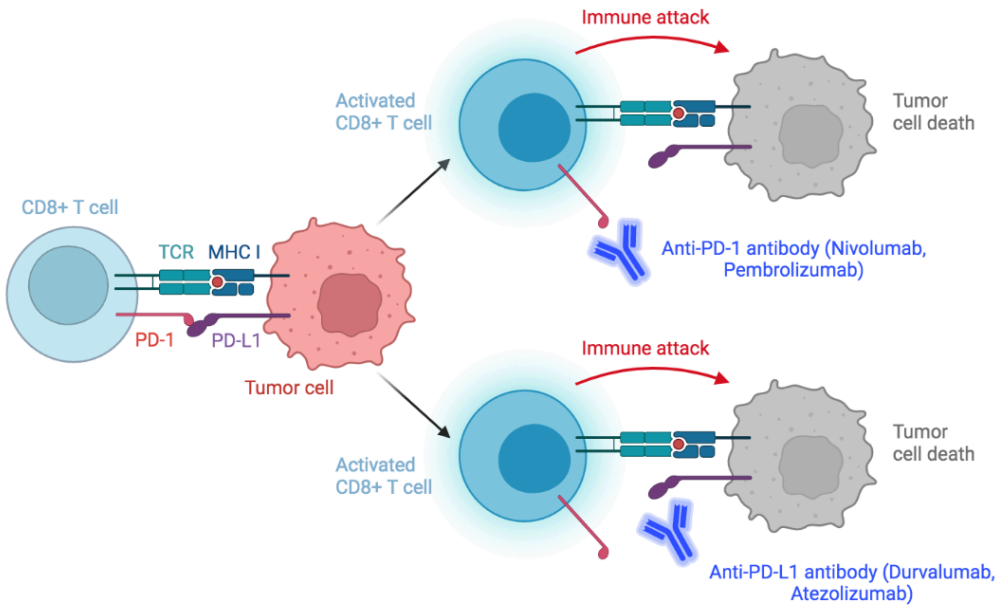

Abbildung 3: Übersicht über den Wirkmechanismus von Anti-PD-1- und Anti-PD-L1-Antikörpern [188] (Die Grafik wurde anhand einer Vorlage von BioRender.com erstellt und modifiziert) [189]

Aufgrund zahlreicher Veröffentlichungen mit vielversprechenden klinischen Ergebnissen [190-193] wurden Nivolumab sowie Pembrolizumab als humane monoklonale Anti-PD-1-Antikörper im Jahr 2015 zunächst als neue Behandlungsmöglichkeit in der Therapie des fortgeschrittenen malignen Melanoms in Europa zugelassen [186].

Der bahnbrechende Durchbruch in der Therapie lokal fortgeschrittener nicht-kleinzelliger Lungenkarzinome gelang unter anderem durch die Phase III-Studie CheckMate-017 [194]. In dieser Veröffentlichung wurden 272 NSCLC-Patienten im Stadium IIIB/IV mit plattenepithelialer Histologie und Krankheitsprogress während oder nach einer platinbasierten Erstlinien-Chemotherapie auf eine Behandlung mit Nivolumab oder Docetaxel randomisiert [194]. Dabei ergab sich sowohl ein signifikant längeres progressionsfreies Überleben (3.5 vs. 2.8 Monate) als auch Gesamtüberleben (Ein-Jahres-Überlebensrate von 42% vs. 24%) bei den mit Nivolumab therapierten Patienten [194]. Hervorzuheben ist insbesondere, dass diese Ergebnisse unabhängig von der PD-L1-Expression erzielt wurden, die weder prognostische noch prädiktive Aussagekraft hatte [194]. Eine ergänzend durchgeführte klinische Studie der Phase III (CheckMate-057) verdeutliche den Nutzen von Nivolumab auch bei Patienten mit einem Nicht-Plattenepithelkarzinom der Lunge [195]. In den nachfolgenden Jahren bewährte sich der Überlebensvorteil von Ni-

volumab gegenüber der bisherigen Standard-Chemotherapie mit Docetaxel (Zwei-Jahres-Überlebensrate von 23% vs. 8% bei Plattenepithelkarzinomen bzw. 29% vs. 16% bei Nicht-Plattenepithelkarzinomen der Lunge) [196, 197]. Die bemerkenswerten Ergebnisse dieser Studien führten im August 2016 zur Zulassung von Nivolumab als mögliche Therapieoption in der Behandlung lokal fortgeschrittener oder metastasierter nicht-kleinzelliger Lungenkarzinome nach Versagen einer vorherigen Chemotherapie, und zwar unabhängig von der dem Tumor zugrundeliegenden Histologie und der PD-L1-Expression [194-197].

Auf Grundlage dieser positiven Entwicklungen konnte in weiteren Studien ebenfalls ein erheblicher Durchbruch in der Immuntherapie beim fortgeschrittenen NSCLC erzielt werden. So basierten beispielsweise die wegweisenden Ergebnisse der Phase-III-Studie PACIFIC auf der Erprobung von Durvalumab, welches im September 2018 EU-weit als einjährige Konsolidierungstherapie nach definitiver platinbasierter Radiochemotherapie ohne Progress bei Patienten mit lokal fortgeschrittenem, inoperablen NSCLC zugelassen wurde [90-92]. Die initial geplante Phase II-Studie NICOLAS zur Untersuchung von Nivolumab als Konsolidierungstherapie nach definitiver Radiochemotherapie bei NSCLC Patienten im Stadium III wurde nach den Ergebnissen der PACIFIC-Studie erweitert [198, 199]. Im Rahmen der Studie sollte nun die simultane Gabe von Nivolumab zur platinbasierten Radiochemotherapie mit anschließender Konsolidierung bei lokal fortgeschrittenen NSCLC im Stadium III näher beleuchtet werden [198, 199]. Die Kombinationstherapie ging zwar nicht mit unerwarteten Nebenwirkungen oder einem erhöhten Risiko für eine schwere Pneumonitis (≥ Grad 3 nach CTCAE, Common Terminology Criteria for Adverse Events) einher, allerdings konnte der primäre Endpunkt (Ein-Jahres-PFS ≥ 60%) nicht erreicht werden (Ein-Jahres-PFS von 53.7%, zum Vergleich: 55.9% im Durvalumab-Arm der PACIFIC-Studie bei deutlich größeren Patientenkollektiv, aber auch kleinerem Anteil an Patienten im Stadium IIIB von 45% vs. 63% in der NICOLAS-Studie) [90-92, 198, 199]. Im Laufe der Jahre folgten zahlreiche weitere Studien im Bereich der Immuntherapie, die die Behandlung des NSCLC, insbesondere im fortgeschrittenen Stadium, revolutionierten und auch heutzutage noch Gegenstand aktueller Forschung sind [70, 71, 75-77, 94-96, 123-134].

Doch auch der Einsatz von Immuntherapeutika wie Checkpoint-Inhibitoren geht mit gewissen Limitationen einher. Nicht alle Patienten profitieren gleichermaßen von einer Immuntherapie, einige entwickeln, aus bisher noch unklaren Ursachen, teilweise sogar Resistenzen im Verlauf der Behandlung [179, 187, 200-203]. Letztendlich wird die breite Anwendung von Immuncheckpoint-Inhibitoren nicht nur durch variierende Ansprechraten der Patienten, sondern auch durch das Auftreten unerwünschter Nebenwirkungen begrenzt [204-207]. Immunvermittelte Nebenwirkungen können sich prinzipiell an jedem

Organsystem manifestieren, besonders häufig sind allerdings kutane, gastrointestinale, endokrine oder pulmonale Auswirkungen zu beobachten [204-207]. Unerwünschte, immunassoziierte Ereignisse sind in der Regel von geringer Intensität, gut behandelbar und reversibel, können allerdings bei gewissen Patienten auch lebensbedrohlich verlaufen [204-207]. Daher ist eine sorgfältige Patientenselektion unerlässlich, um zwischen Respondern und Non-Respondern einer Immuntherapie unterscheiden zu können und dadurch Patienten, die mit einer hohen Wahrscheinlichkeit nicht von einer solchen Behandlung profitieren nicht grundlos potenziellen Nebenwirkungen auszusetzen [179, 205, 208-216].

Die Immuntherapie hat die Behandlung des NSCLC grundlegend verändert. In den letzten Jahren wurde sie, bei fehlenden therapierbaren Treibermutationen, umfassend in die Erstlinienbehandlung integriert – entweder in Kombination mit einer Chemotherapie oder, bei ausgewählten Patienten mit einer hohen PD-L1-Expression, als Monotherapie. In Hinblick auf diese Entwicklungen und die damit einhergehenden neuen Therapiestandards sollte nun ergänzend zur Erstautorenschaft die Bedeutung von PTV in der Behandlung lokal fortgeschrittener, inoperabler NSCLC im Stadium III mit einer Chemoradiotherapie in Kombination mit Durvalumab bzw. Nivolumab evaluiert werden.

3.2 Deutsche Zusammenfassung

Diese prospektive Studie umfasste eine Kohorte von 33 Patienten mit einem inoperablen NSCLC im Stadium III, die zwischen 2017 und 2020 am Universitätsklinikum der LMU München einer Kombination aus Radiochemo- und Immuntherapie unterzogen wurde [176]. Die Immuntherapie bestand entweder aus der Verabreichung des PD-1-Inhibitors Nivolumab (11 Patienten) im Rahmen der Phase II-Studie NICOLAS (ETOP 6-11) oder des PD-L1-Inhibitors Durvalumab (22 Patienten) entsprechend der PACIFIC-Studie [90, 176, 198, 199]. Die Daten all dieser Patienten wurden prospektiv erhoben und die Zielvolumina wurden anhand eines hausinternen Standards definiert, der in engem Einklang mit den im März 2018 veröffentlichten Leitlinien der ESTRO-ACROP steht [147, 176].

In den univariaten Analysen wurden zunächst mehrere Planungszielvolumina (PTV) auf ihren Zusammenhang mit dem progressionsfreien Überleben (PFS) analysiert, hierbei zeigte sich vor allem bei Patienten mit einem PTV ≥ 900 cm^3 ein signifikant kürzeres PFS von 6.9 vs. 22.8 Monaten (p=0.020) - die Signifikanz konnte in den ergänzend erfolgten multivariaten Analysen bestätigt werden [176]. Dieser Zusammenhang spiegelte sich insbesondere bei Patienten im Stadium IIIC und einem PTV ≥ 900 cm^3 wider: in dieser Patientengruppe betrug das PFS lediglich 3.6 im Vergleich zu 22.8 Monaten im übrigen behandelten Kollektiv [176].

Schlussfolgernd konnte PTV ≥ 900 cm^3 als prognostischer Faktor für den Krankheitsprogress herausgearbeitet werden und sollte daher unter Berücksichtigung dieser Ergebnisse zukünftig als Stratifizierungsfaktor in multimodalen klinischen Studien für inoperable NSCLC im Stadium III in Erwägung gezogen werden [176].

3.3 Englische Zusammenfassung – English summary

This prospective study involved 33 patients with unresectable stage III NSCLC who underwent chemoradiotherapy and immune checkpoint inhibition at the LMU University Hospital in Munich between 2017 and 2020 [176]. The immunotherapy consisted of either administration of the PD-1 inhibitor Nivolumab (11 patients) within the phase II NICOLAS trial (ETOP 6-11) or the PD-L1 inhibitor Durvalumab (22 patients) according to the PACIFIC study [90, 176, 198, 199]. Patient data were assessed in prospective manners and target volumes were defined using an in-house standard closely aligned with ESTRO-ACROP guidelines published in March 2018 [147, 176].

In the initial univariate analysis, several planning target volumes were first analyzed for their association with progression-free survival (PFS) showing a significantly shorter PFS of 6.9 compared to 22.8 months (p=0.020), especially among patients with a PTV ≥ 900

cm^3 [176]. The significance was further confirmed in the supplementary performed multivariate analyses [176]. This correlation was particularly evident in patients with stage IIIC and a PTV ≥ 900 cm^3: in this subgroup the PFS was only 3.6 in comparison to 22.8 months in the rest of the treated population [176].

In summary, PTV ≥ 900 cm^3 was found to be a predictor of disease progression and should hence be considered as a stratification factor in future multimodal clinical trials for inoperable stage III NSCLC [176].

4. Eigenanteil an den Publikationen

4.1 Erstautorenschaft

Association of planning target volume with patient outcome in inoperable stage III NSCLC treated with chemoradiotherapy: A comprehensive single-center analysis [135].

Diese wissenschaftliche Arbeit wurde fast vollständig von mir selbst verfasst. Ich war maßgeblich an der Konzeption und Planung der Studie beteiligt, in Zusammenarbeit mit Herrn PD Dr. Manapov habe ich die grundlegende Forschungsidee entwickelt und ausgearbeitet. Nach eigenständiger intensiver Recherche über bereits vorhandene Literatur erfolgten die selbstständige Erhebung und anschließende Auswertung der klinischen Patientendaten. Darüber hinaus habe ich selbstständig eine umfassende statistische Analyse durchgeführt sowie die Daten im wissenschaftlichen Gesamtkontext interpretiert. Hierbei standen mir vor allem Dr. Taugner und Dr. Käsmann beratend und unterstützend zur Seite. Abschließend habe ich eigenständig das Manuskript verfasst und in Absprache mit den Koautoren einzelne Überarbeitungen und Revisionen vorgenommen.

4.2 Ko-Autorenschaft

Planning target volume as a predictor of disease progression in inoperable stage III non-small cell lung cancer patients treated with chemoradiotherapy and concurrent and/or sequential immune checkpoint inhibition [176].

Als Koautorin dieser wissenschaftlichen Veröffentlichung habe ich den Erstautor Dr. Taugner sowohl bei der Erhebung als auch der Auswertung und Interpretation der Patientendaten unterstützt. Des Weiteren habe ich aktiv an der Ausarbeitung und Korrektur des Manuskripts mitgewirkt. Insgesamt habe ich durch meinen Arbeitsanteil einen maßgeblichen Beitrag zum Erfolg dieses Papers geleistet.

5. Veröffentlichung I

cancers

MDPI

Article

Association of Planning Target Volume with Patient Outcome in Inoperable Stage III NSCLC Treated with Chemoradiotherapy: A Comprehensive Single-Center Analysis

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Simple Summary: Non-small cell lung cancer (NSCLC) in stage III is often inoperable and highly heterogeneous. The primary gross tumor volume is prognostically relevant in several types of cancer, including oral carcinoma, B-cell lymphoma, and sarcoma. The planning target volume (PTV), including the primary tumor and involved lymph node stations, can vary widely, and its prognostic value for stage III is unclear. We aimed to evaluate the impact of the PTV for overall survival (OS), progression-free survival, and loco-regional control in 122 consecutive patients treated with definitive chemoradiotherapy (CRT). Median follow-up for the entire cohort was 41.2 (range: 4–108) months; median overall survival (OS) reached 20.9 (95% CI: 14.5–27.3) months. In a multivariate analysis including age, gender, total radiation dose, and histology, PTV ≥ 700 ccm was found to be an independent prognostic factor for OS (hazard ratio (HR): 1.705, 95% confidence interval (CI): 1.071–2.714, $p = 0.025$). In conclusion, non-operable stage III NSCLC patients with PTV ≥ 700 ccm showed significantly detrimental outcomes after conventionally fractionated CRT. PTV should be considered as a stratification factor in multimodal clinical trials for inoperable stage III NSCLC.

Abstract: Inoperable stage III non-small cell lung cancer (NSCLC) represents a highly heterogeneous patient cohort. Multimodal treatment approaches including radiotherapy have been the new standard of care, with promising outcomes. The planning target volume (PTV), including the primary tumor, involved lymph node stations and safety margins, can vary widely. In order to evaluate the impact of the PTV for overall survival (OS), progression-free survival (PFS) and loco-regional control, we analyzed retrospective and prospective data of 122 consecutive patients with inoperable stage III NSCLC treated with CRT. The majority of patients (93%) received a total dose ≥ 60 Gy and 92% of all patients were treated with concurrent or sequential chemotherapy. Median follow-up for the entire cohort was 41.2 (range: 3.7–108.4) months; median overall survival (OS) reached 20.9 (95% CI: 14.5–27.3) months. PTVs from 500 to 800 ccm were evaluated for their association with survival in a univariate analysis. In a multivariate analysis including age, gender, total radiation dose and histology, PTV ≥ 700 ccm remained a significant prognosticator of OS (HR: 1.705, 95% CI: 1.071–2.714, $p = 0.025$). After propensity score matching (PSM) analysis with exact matching for Union

internationale contre le cancer (UICC) TNM Classification (7th ed.)T- and N-stage, patients with PTV < 700 ccm reached a median PFS and OS of 11.6 (95% CI: 7.3–15.9) and 34.5 (95% CI: 25.6–43.4) months vs. 6.2 (95% CI: 3.1–9.3) ($p = 0.057$) and 12.7 (95% CI: 8.5–16.9) ($p < 0.001$) months in patients with PTV ≥ 700 ccm, respectively. Inoperable stage III NSCLC patients with PTV ≥ 700 ccm had significantly detrimental outcomes after conventionally fractionated CRT. PTV should be considered as a stratification factor in multimodal clinical trials for inoperable stage III NSCLC.

Keywords: NSCLC; multimodal treatment; stage III; survival; prognostic factor

1. Introduction

Lung cancer is the leading cause of cancer deaths worldwide, with an estimated 1.8 million deaths in 2018 [1,2]. Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases and is typically diagnosed at an advanced stage [3,4]. Inoperable stage III NSCLC represents a special entity due to the significant heterogeneity of the tumor and patient characteristics, as well as the multimodal approach required to treat it [5]. For these patients, concurrent chemoradiotherapy (CRT) remains the cornerstone of multimodal treatment [6–11]. According to pivotal trials concerning the intensification of the multimodal approach in inoperable stage III NSCLC, the planning target volume (PTV) was defined as an important factor for the quality of radiation delivery, treatment-related toxicity and patient outcome. In 2011, Salama et al. conducted a secondary analysis of the Cancer and Leukemia Group B (CALBG) 30,105 trial and found that a larger PTV and smaller total lung volume/PTV ratio were associated with increasing pulmonary toxicity in a univariate analysis [12]. Initial and long-term results of the Radiation Therapy Oncology Grou (RTOG) 0617 trial confirmed PTV as a prognosticator in inoperable stage III NSCLC treated with concurrent CRT in univariate and multivariate analyses [13,14]. Moreover, radiation therapy quality assurance within the PROCLAIM trial (Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous Non-Small-Cell Lung Cancer) revealed that stage IIIB and PTV were associated with major violations in the delivered treatment plans [15].

Therefore, the purpose of the present study was to analyze the effects of PTV on patient outcome in inoperable stage III NSCLC treated with CRT and to define a volume cut-off that had the most impact on overall survival.

2. Patients and Methods

2.1. Patient Characterstics

This study included 122 consecutive patients who received concurrent or sequential conventionally fractionated CRT as part of a multimodal approach for stage IIIA/B (UICC 7th edition) NSCLC between 2011 and 2018 (prior to Durvalumab approval). An institutional review board (IRB), including the local ethics committee, approved this analysis (approval number: 17-230). Patients treated between January 2011 and December 2015 were included retrospectively and informed consent specifically for the retrospective part was not required by the IRB. Starting from January 2016, all patients were included prospectively and gave their informed consent.

Prior to the actual treatment, patient characteristics including tobacco consumption, performance status according to Eastern Cooperative Oncology Group (ECOG) and patients' comorbidities were assessed. The majority of patients (96.7%) received a positron emission tomography (PET) computed tomography (CT) scan for treatment-planning. Screening for brain metastases was performed prior to treatment in all patients with cranial contrast-enhanced magnetic resonance imaging (MRI) in 54 (44.3%) patients and cranial contrast-enhanced CT in 64 (55.7%) patients. All patients underwent

pulmonary function testing and routine blood testing in order to evaluate liver and kidney function as well as complete blood cell count. Treatment was discussed at multidisciplinary tumor boards with experienced thoracic surgeons classifying the tumors as unresectable. All patients with an ECOG performance status ≥ 2, poor lung function (diffusing capacity of the lung for carbon monoxide (DLCO) < 40%, forced expiratory volume in 1 second (FEV1) < 1 L or on long-term oxygen supply), total radiation therapy (RT) dose ≤ 54 Gy and TNM-stage other than stage III, were excluded.

2.2. Chemoradiotherapy

All patients were planned and treated between 2011 and 2018 at one tertiary cancer center. Based on conventional planning-CT as well as PET-CT scans in the treatment position, thoracic radiation therapy (TRT) was planned and carried out in the supine position and arms overhead using WingSTEP^{TM} (Innovative Technologie Völp, Innsbruck, Austria). In all cases, the target volumes were defined according to an in-house standard which is in close accordance to the later published European Society for Therapeutic Radiology and Oncology Advisory Committee in Radiation Oncology Practice (ESTRO-ACROP) guidelines [16]. If patients received induction chemotherapy, the residual primary tumor volume was delineated and cranio-caudal dimensions of clinical target volume (CTV) included initially involved lymph-node stations. Tumor motion management protocol was not routinely performed. PTV margins were 6 mm axial and 9 mm cranio-caudal beyond the CTV. Conventionally fractionated TRT was administered to the primary tumor and the involved lymph nodes with a median cumulative radiation dose of 66 Gy. Radiation delivery was performed using a linear accelerator (LINAC) with megavoltage capability of 6–15 MV with either 3D-CRT in 49 (40%) patients, intensity-modulated radiotherapy (IMRT, step and shoot, 38 patients) or volumetric modulated arc therapy (VMAT, 35 patients) in 73 (60%) patients. Image-guidance was performed with a cone-beam CT twice a week.

2.3. Patient Follow-Up

CT or PET-CT scans, routine complete blood work, lung function testing and clinical examinations were performed every 3 months in the first two years after therapy and twice yearly thereafter. Based on radiographic findings including CT, PET-CT or MRI, local and loco-regional progression (LP) along with distant metastases (DM) were calculated. Cytological or histological specimens to confirm disease progression were not obligatory. Median follow-up was calculated as the median time to loss or end of follow-up after the last day of radiotherapy in patients who were not documented as deceased. Progression-free survival (PFS) was defined as the time from the end of radiotherapy until disease progression or death. Overall survival (OS) was calculated from the end of radiotherapy until death. Regional recurrence was defined as progression/relapse in the ipsilateral lung or mediastinal/hilar lymph nodes.

2.4. Statistical Analysis

All statistics were performed using SPSS version 25 (IBM, Armonk, NY, USA). Univariate analysis was performed based on a comprehensive review of literature for PFS and OS with following parameters: age, gender, T- and N-stage, histology, RT dose and different PTV sizes between 500 ccm and 900 ccm. Multivariate analysis using Cox regression was carried out with PTV ≥ 600 ccm and ≥700 ccm as the two significant PTV values and other parameters showing a trend in the univariate analysis. Thereafter, we applied propensity score matching (PSM) using the R plug-in for IBM SPSS 25 [17–24] and performed an additional sensitivity analysis with exact matching of T- and N-stage.

3. Results

3.1. Patient and Tumor Characteristics

A summary of patient and tumor characteristics of the entire cohort, as well as the retrospectively- and prospectively-assessed subgroups, is shown in Table 1. The entire cohort consisted of 122 consecutive NSCLC patients with inoperable stage IIIA/B disease (UICC 7th edition stage) treated before Durvalumab approval. All patients received conventionally fractionated TRT. Median age was 68.5 with 81 (66.4%) patients older than 65 years. Forty-one (33.6%) were female and 81 (66.4%) male. On pre-treatment staging, 13 (10.7%), 20 (16.4%), 33 (27.0%) and 56 (45.9%) had T1, T2, T3 and T4 disease, and 15 (12.3%) N0, 9 (7.4%) N1, 44 (36.1%) N2 and 54 (44.3%) N3 disease, respectively. In the histological evaluation, 59 (48.4%) patients had squamous cell carcinomas (SCC), 52 (42.6%) had adenocarcinomas (AC) and in 11 (9.0%) patients, the tumor was classified as not otherwise specified (NOS). One hundred and thirteen (93%) patients received radiotherapy to a total dose ≥ 60 Gy (median total dose: 66 Gy; range 60–70 Gy). Concurrent CRT was delivered in 97 (79.5%) patients and 15 (12.3%) patients received sequential CRT. Ten (8.2%) patients were treated with TRT alone. Seventy-one patients (58.2%) received intravenous cisplatin at a dose of 20 mg/m^2 on days 1–4 and oral vinorelbine (Navelbine) 50 mg/m^2 on days 1, 8, and 15, every four weeks for two courses according to the German Intergroup Lung Trial (GILT) study [25]. The median follow-up for the entire cohort was 41.2 months (range: 3.7–108.4); median PFS and OS were 7.1 (95% CI: 5.9–8.4) and 20.9 (95% CI: 14.5–27.3), respectively.

Table 1. Patient and tumor characteristics of the entire cohort and both subgroups.

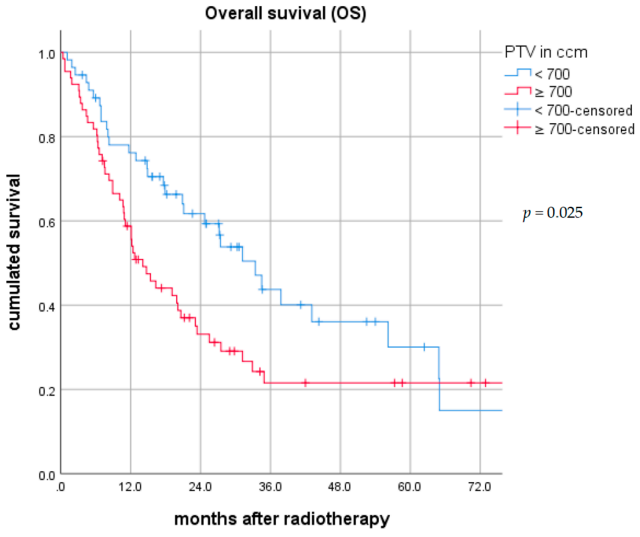
Parameter	Entire Cohort *N* (%)	Retrospective Subgroup *N* (%)	Prospective Subgroup *N* (%)
Total	122	86	36
Age, Years			
≥65	81 (66.4)	58 (67.4)	23 (63.9)
<65	41 (33.6)	28 (32.6)	13 (36.1)
Gender			
Male	81 (66.4)	54 (62.8)	27 (75.0)
Female	41 (33.6)	32 (37.2)	9 (25.0)
T-stage			
1	13 (10.7)	7 (8.1)	6 (16.7)
2	20 (16.4)	16 (18.6)	4 (11.1)
3	33 (27.0)	27 (31.4)	6 (16.7)
4	56 (45.9)	36 (41.9)	20 (55.6)
N-stage			
0	15 (12.3)	9 (10.5)	6 (16.7)
1	9 (7.4)	7 (8.1)	2 (5.6)
2	44 (36.1)	29 (33.7)	15 (41.7)
3	54 (44.3)	41 (47.7)	13 (36.1)
Histology			
Squamous cell carcinoma (SCC)	59 (48.4)	38 (44.2)	21 (58.3)
Adenocarcinoma (AC)	52 (42.6)	41 (47.7)	11 (30.6)
Not otherwise specified (NOS)	11 (9.0)	7 (8.1)	4 (11.1)
Radiographic imaging			
Positron emission tomography (PET)-CT	118 (96.7)	82 (95.3)	36 (100.0)
CT	4 (3.3)	4 (4.7)	0 (0.0)
Treatment			
Concurrent chemoradiation (CRT)	55 (45.1)	32 (37.2)	23 (63.9)
Induction chemotherapy + CRT	42 (34.4)	36 (41.9)	6 (16.7)
Sequential chemo and radiotherapy	15 (12.3)	11 (12.8)	4 (11.1)
Radiotherapy only	10 (8.2)	7 (8.1)	3 (8.3)
Total RT dose ≥ 60 Gy	113 (92.6)	77 (89.5)	36 (100.0)
Total RT dose > 54 Gy and <60 Gy	9 (7.4)	9 (10.5)	0 (0.0)

3.2. Univariate and Multivariate Analysis

Patients older than 65 years had a median OS of 20.1 (95% CI: 14.0–26.2) vs. 25.5 (95% CI: 6.7–44.3) months (p = 0.066). Female patients had a median OS of 31.2 (95% CI: 24.1–38.3) vs. 16.3 (95% CI: 9.6–23.0) months for men (p = 0.022). Median OS/PFS was 20.6/17.6, 15.4/7.1, 12.9/6.4 and 25.5/6.6 months for patients with T1, T2, T3 and T4 disease, respectively (p = 0.753/0.330). For patients with N0, N1, N2 and N3 disease, median OS/PFS was 32.9/9.3, 23.4/7.2, 20.6/6.9 and 17.6/6.9 (p = 0.582/0.591), respectively. Patients with AC, SCC and NOS had a median OS/PFS of 27.2/7.4, 19.9/7.1, 12.7/5.6 months (p = 0.091/0.636), respectively. Patients irradiated to a total dose of at least 60 Gy had a longer overall survival of 23.1 (95% CI: 16.3–29.9) vs. 6.6 (95% CI: 5.7–7.5) months than others (p = 0.079). However, a total dose of ≥60 Gy was not a prognosticator of improved PFS (p = 0.352). PTV as a continuous variable showed a strong association with OS (p < 0.001). A significant correlation between PTV and patient outcome in the univariate analysis was demonstrated for PTV < 600 ccm and PTV < 700 ccm, whereas PTV 500 ccm, 800 ccm and 900 ccm showed no significant association with outcome.

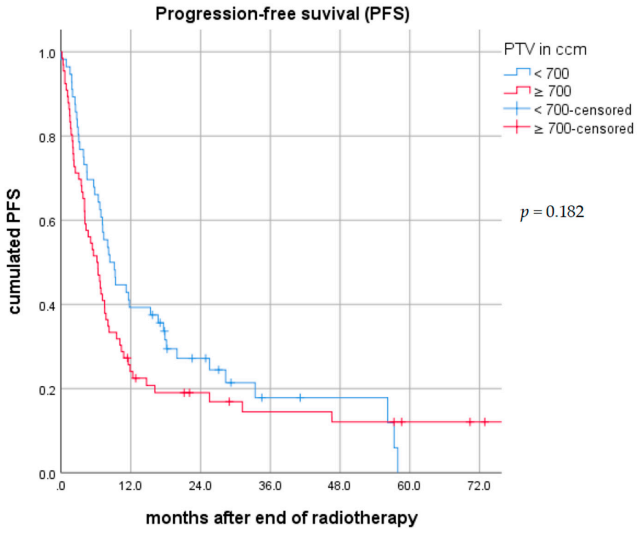
For PTV < 600 ccm (n = 36, 29.5%), median OS was 34.5 (95% CI: 18.5–50.5) vs. 14.8 (95% CI: 8.0–21.6) months (p = 0.022) and median PFS was 8.2 (95% CI: 2.5–13.8) vs. 6.4 (95% CI: 4.5–8.2) months (p = 0.220).

For PTV < 700 ccm (n = 56, 45.9%), median OS was 33.4 (95% CI: 24.8–42.0) vs. 14.1 (95% CI: 9.7–18.5) months (p = 0.025) (Figure 1A) and median PFS was 8.4 (95% CI: 5.9–10.8) vs. 6.2 (95% CI: 4.1–8.2) months (p = 0.182) (Figure 1B). The median regional recurrence-free survival (RRFS) was 17.9 (95% CI: 0.0–43.2) vs. 10.0 (95% CI: 7.2–12.7) months (p = 0.163) in patients with PTV < 700 ccm vs. PTV ≥ 700 ccm, respectively (Figure 1C).

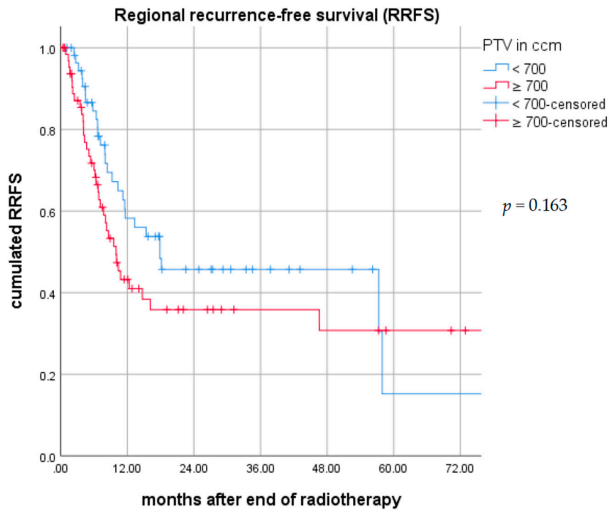


(**A**)

Figure 1. *Cont.*



(**B**)



(**C**)

Figure 1. (**A**). Overall survival (OS) in the entire cohort by planning target volume (PTV) < 700 ccm vs. ≥700 ccm. (**B**) Progression-free survival (PFS) in the entire cohort by PTV < 700 ccm vs. ≥700 ccm. (**C**) Regional recurrence-free survival (RRFS) in the entire cohort by PTV < 700 ccm vs. ≥700 ccm.

Multivariate analysis was performed separately for PTV ≥ 600 ccm and ≥700 ccm, as well as parameters showing a trend in the univariate analysis ($p < 0.1$) including age (≥65 years), gender, total dose of radiotherapy < 60 Gy and histology using Cox regression. For PTV ≥ 600 ccm, the hazard ratio (HR) was 1.715 (95% CI: 1.017–2.890, $p = 0.043$) and for ≥700 ccm, a HR of 1.705 (95% CI: 1.071–2.714, $p = 0.025$) was reached. It was shown that PTV ≥ 700 ccm was significant in the multivariate analysis.

Based on this result, all further calculations were carried out with PTV ≥ 700 ccm as a cut-off. Other parameters in the multivariate analysis with PTV ≥ 700 ccm showed the following results: for patients ≥ 65 years, the HR for death was 1.570 (95% CI: 0.945–2.609, $p = 0.082$); for male patients, the HR was 1.462 (95% CI: 0.896–2.387, $p = 0.129$); for total dose of radiotherapy < 60 Gy, the HR was 1.914 (95% CI: 0.863–4.246; $p = 0.110$); and for histology of SCC or NOS, the HR was 1.411 (95% CI: 0.983–2.026, $p = 0.062$). PTV ≥ 700 ccm was only a significant prognosticator for patients with SCC; median OS was 18.0 (95% CI: 11.8–24.2) vs. 35.4 (95% CI: 25.4–45.4) months ($p = 0.010$). For patients with AC, median OS was 43.5 (95% CI: 27.0–59.9) vs. 48.1 (95% CI: 30.7–65.5) months ($p = 0.244$).

3.3. PSM Analysis with Parameters Showing a Trend in Univariate Analysis

Patients with PTV < 700 ccm were matched at a 1:1 ratio to patients with ≥700 ccm. Propensity score (PS) matching was carried out with the parameters showing a trend in the univariate analysis (age, gender, RT total dose ≥60 Gy and histology) by nearest neighbor matching. The matched cohort consisted of 86 patients. In the subgroup with PTV < 700 ccm, there were 5 (11.6%), 8 (18.6%), 9 (20.6%) and 21 (48.8%) patients with T1, T2, T3 and T4 disease and 7 (16.3%), 4 (9.3%), 22 (51.2%) and 10 (23.3%) patients with N0, N1, N2 and N3 disease, respectively. In the subgroup with PTV ≥ 700 ccm, there were 1 (2.3%), 8 (18.6%), 13 (30.2%) and 21 (48.8%) patients with T1, T2, T3 and T4 disease and 4 (9.3%), 3 (7.0%), 8 (18.6%) and 28 (65.1%) patients with N0, N1, N2 and N3 disease, respectively. The median follow-up of the PSM cohort reached 44.3 months (range: 3.7–108.4); median OS of all matched patients was 19.9 (95% CI: 12.0–27.8) and median PFS was 7.1 (95% CI: 6.2–8.1) months. Patients with PTV < 700 ccm vs. ≥700 ccm had a median OS of 27.4 (95% CI: 15.2–39.6) vs. 12.4 (95% CI: 8.7–16.1) months ($p = 0.009$) (Figure S1A). Six, 12 and 24-month OS rates were 90.2% vs. 81.4%, 73.2% vs. 57.1% and 52.9% vs. 23.1% for PTV < 700 ccm vs. ≥ 700 ccm, respectively.

In the PTV < 700 ccm subgroup, the median PFS was 7.4 (95% CI: 4.4–10.3) months vs. 6.9 (95% CI: 5.2–8.6) months ($p = 0.320$) in patients with PTV ≥ 700 ccm (Figure S1B). Six, 12 and 24-month PFS-rates were 62.8% vs. 58.1%, 37.2% vs. 21.4% and 15.8% vs. 12.5% for PTV < 700 ccm vs. ≥700 ccm, respectively.

The median loco-regional recurrence-free survival (RRFS) was 17.9 (95% CI: 13.8–21.9) vs. 10.0 (95% CI: 7.6–12.4) months ($p = 0.255$) in patients with PTV < 700 ccm vs. ≥ 700 ccm (Figure S1C). We could not observe a difference in out-of-field recurrence ($p = 0.768$), whereas a trend in in-field-recurrence with better outcome for PTV < 700 ccm was revealed ($p = 0.051$).

It was confirmed that PTV 700 ccm is a significant prognostic factor for patients with SCC only. Patients with PTV < 700 ccm vs. PTV ≥ 700 ccm had an OS of 35.2 (95% CI: 23.8–46.4) vs. 16.8 (95% CI: 10.7–22.8) months ($p = 0.014$).

3.4. Additional PSM Analysis with Exact T- and N-Stage Matching

Patients with PTV < 700 ccm were matched at a 1:1 ratio to patients with PTV ≥ 700 ccm. To each patient with PTV < 700 ccm, one corresponding patient with exactly the same T- and N-stage was matched. The T/N-matched cohort consisted of 58 patients. A summary of patient and tumor characteristics is shown in Table 2. Both subgroups consisted of five (17.2%), six (20.7%), nine (31.0%) and nine (31.0%) patients with T1, T2, T3 and T4 disease and 5 (17.2%), 3 (10.3%), 11 (37.9%) and 10 (34.5%) patients with N0, N1, N2 and N3 disease, respectively. In the subgroup with PTV < 700 ccm, there were 21 (72.4%) patients with age ≥65, 16 (55.2%) males, 16 (55.2%) with SCC or NOS and 28 (96.6%) patients with total dose of ≥60 Gy. In the subgroup with PTV ≥ 700 ccm, there were 24 (82.8%) patients with age ≥65, 23 (79.3%) males, 16 (55.2%) with SCC or NOS and 28 (96.6%) patients with total radiotherapy dose of ≥60 Gy. The median follow-up of the T/N-matched cohort reached

44.3 months (range: 3.7–96.0); median OS was 24.7 (95% CI: 15.2–34.2) and median PFS was 8.2 (95% CI: 6.0–10.5) months.

Table 2. PTV < 700 ccm vs. PTV ≥ 700 ccm patients in the T/N-exact matched cohort.

Parameter	PTV < 700 ccm N (%)	PTV ≥ 700 ccm N (%)
Total	29	29
Age, Years		
≥65	21 (72.4)	24 (82.8)
<65	8 (27.6)	5 (17.2)
Gender		
Male	16 (55.2)	23 (79.3)
Female	13 (44.8)	6 (20.7)
T-stage		
1	5 (17.2)	5 (17.2)
2	6 (20.7)	6 (20.7)
3	9 (31.0)	9 (31.0)
4	9 (31.0)	9 (31.0)
N-stage		
0	5 (17.2)	5 (17.2)
1	3 (10.3)	3 (10.3)
2	11 (37.3)	11 (37.3)
3	10 (34.5)	10 (34.5)
Histology		
Squamous cell carcinoma (SCC)	14 (48.3)	12 (41.4)
Adenocarcinoma (AC)	13 (44.8)	13 (44.8)
Not otherwise specified (NOS)	2 (6.9)	4 (13.8)
Treatment		
Concurrent chemoradiation (CRT)	13 (44.8)	13 (44.8)
Induction chemotherapy + CRT	10 (34.5)	9 (31.0)
Sequential chemo and radiotherapy	3 (10.3)	4 (13.8)
Radiotherapy only	3 (10.3)	3 (10.3)
Total RT dose ≥ 60 Gy	28 (96.6)	28 (96.6)
Total RT dose > 54 Gy and <60 Gy	1 (3.4)	1 (3.4)
Patient Cohort		
Retrospective evaluation	21 (72.4)	21 (72.4)
Prospective evaluation	8 (27.6)	8 (27.6)

In the T/N-matched patients with PTV < 700 ccm vs. ≥700 ccm, a median OS of 34.5 (95% CI: 25.6–43.4) vs. 12.7 (95% CI: 8.5–16.9) months ($p < 0.001$) was reached (Figure 2A). The 6, 12 and 24-month OS rates were 96.4% vs. 72.4%, 85.7% vs. 51.8% and 75.0% vs. 16.0%, respectively. In the PTV < 700 ccm subgroup, the median PFS was 11.6 (95% CI: 7.3–15.9) months vs. 6.2 (95% CI: 3.1–9.3) months ($p = 0.057$) in patients with PTV ≥ 700 ccm (Figure 2B). The 6, 12 and 24-month PFS rates were 82.8% vs. 51.7%, 44.8% vs. 14.3% and 24.0% vs. 7.7%, respectively. The median regional recurrence-free survival (RRFS) was 57.9 (95% CI: 9.1–106.7) vs. 2.0 (95% CI: 4.6–12.6) months ($p = 0.036$) in patients with PTV < 700 ccm vs. PTV ≥ 700 ccm, respectively (Figure 2C).

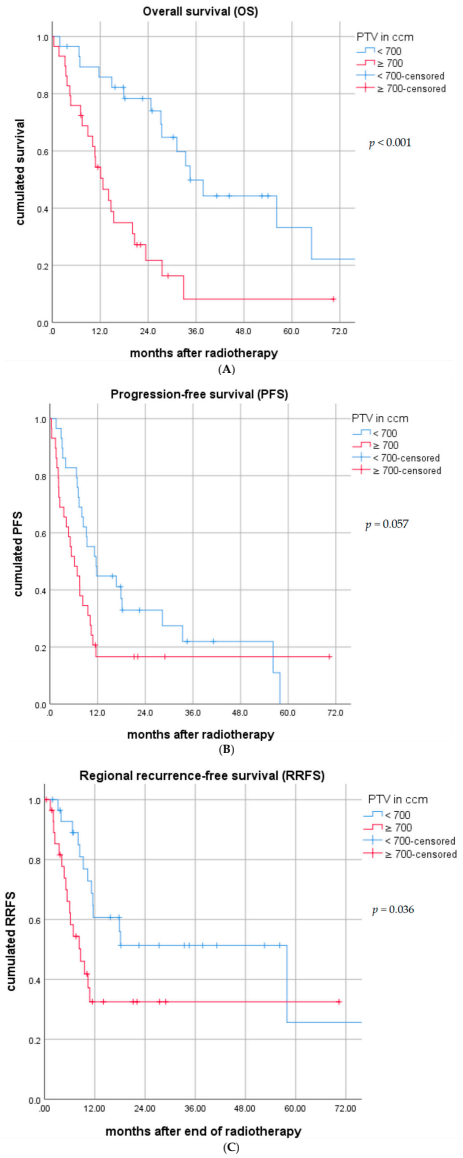


Figure 2. (**A**) Overall survival (OS) in the T/N-exact matched cohort by PTV < 700 ccm vs. ≥700 ccm. (**B**) Progression-free survival (PFS) in the T/N-exact matched cohort by PTV < 700 ccm vs. ≥700 ccm. (**C**) Regional recurrence-free survival (PFS) in the T/N-exact matched cohort by PTV < 700 ccm vs. ≥700 ccm.

Compared to the entire cohort, PTV ≥ 700 ccm was revealed to be a significant prognostic factor independent of tumor histology in the T- and N-matched cohort. Patients with SCC and PTV < 700 ccm vs. ≥ 700 ccm had an OS of 24.7 (95% CI: 1.7–47.8) vs. 14.7 (95% CI: 6.8–22.6) months ($p = 0.049$) whereas patients with AC and PTV < 700 ccm vs. PTV ≥ 700 ccm had an OS of 37.8 (95% CI: 27.2–52.5) vs. 12.1 (95% CI: 6.9–17.3) months ($p = 0.001$).

4. Discussion

The aim of the present study was to provide a comprehensive analysis of the role of PTV (including the primary tumor and involved lymph node stations) in inoperable stage III NSCLC treated with CRT. Analyzed data were retrospectively and prospectively collected at a single tertiary cancer center. One hundred twenty-two consecutive cases with a total radiation dose to the primary tumor of at least 54 Gy were evaluated.

The main conclusion of the analysis is that PTV is continuously associated with patient outcome after the completion of CRT. Furthermore, the univariate, multivariate and PSM analyses performed demonstrated that PTV ≥ 700 ccm had the greatest impact on patient survival (PFS, OS) and may be considered as a stratification factor in clinical trials for inoperable stage III NSCLC. According to the PSM analysis with exact T- and N-stage matching, a significant difference in OS and a clear trend for PFS was elucidated. Patients with PTV < 700 ccm had a 12-month PFS rate of 45% vs. only 14% in patients with PTV ≥ 700 ccm. More frequent in-field recurrences in patients with PTV ≥ 700 ccm were also documented ($p = 0.051$). Furthermore, patients with PTV < 700 ccm reached a median OS of 34.5 vs. only 12.7 (95% CI: 8.7–16.1) months in patients with PTV ≥ 700 ccm ($p < 0.001$).

In lung cancer, an increasing tumor volume is associated with a significant decline in patient outcome. More than a decade ago, Werner-Wasik et al. performed a secondary analysis of the Radiation Therapy Oncology Group 93–11 Phase I–II dose escalation study in inoperable NSCLC and revealed that patients with smaller (gross tumor volume (GTV) ≤ 45 cm^3) tumors had a longer OS and PFS than patients with larger (GTV > 45 cm^3) tumors. GTV was defined as a sum of the volumes of the primary tumor and involved lymph nodes; the analysis also found that dose escalation had no effect on patient outcome in the treated cohort [26].

Basaki et al. evaluated 71 patients with stage III NSCLC treated with definitive (chemo)radiation and reported that total tumor volume and primary tumor volume, but not nodal volume, significantly influenced OS [27]. In contrast, both nodal and primary tumor volumes were associated with OS and local control in patients with stage III NSCLC after CRT in a retrospective review from the Dana–Farber Cancer Institute [28]. A multicenter prospective observational study (Trans-Tasman Radiation Oncology Group (TROG) 99.05) on 509 eligible stage I–II NSCLC patients treated with definitive TRT demonstrated the complex relationship between tumor volume and survival. At first, a larger primary tumor volume was associated with shorter survival (HR = 1.060, 95% CI: 1.01–1.12, $p = 0.029$). However, once the effects of T- and N-stage were corrected for, the association waned (HR = 1.029, 95% CI: 0.96–1.10, $p = 0.39$). There was still evidence that a larger primary tumor volume, regardless of T- and N-stage, was associated with an increased risk of death in the first 18 months [29].

A retrospective analysis from Dehing-Oberije et al. on 270 consecutive patients with stage I–III NSCLC radically treated with (chemo) radiation also reported a prognostic role for both, i.e., volume of the primary tumor and involved nodes as well as number of positive lymph nodes stations [30]. According to the ESTRO-ACROP guidelines for locally advanced NSCLC, published in 2018, positive (involved) lymph node stations will be included in the CTV and thus also in the PTV [16]. To avoid methodical discrepancies, we analyzed the PTV which considered the total tumor volume itself, the clinical target volume with positive lymph node stations, as well as safety margins for potential patient positioning and setup errors.

Importantly, the results of our analysis are in close accordance with previously published data from Wiersma et al. Both are studies from high volume cancer centers that included inoperable stage III NSCLC patients treated with CRT. Furthermore, both analyses evaluated the role of PTV and

found that 700 ccm as a cut off is important for patient outcome [31]. In contrast to Wiersma et al. however, we also evaluated PTV as a continuous variable. In addition, we tested different PTVs from 500 to 800 ccm and performed a PSM analysis with exact T- and N-stage matching to confirm its prognostic role. A short overview of studies confirming a prognostic role of PTV in NSCLC patients treated with conventionally fractionated CRT is provided in Table 3.

Table 3. Short review of literature.

Authors	Paper Name	Year	Results
Wiersma, T.G., et al.	Concurrent chemoradiotherapy for large-volume locally advanced non-small cell lung cancer	2013	The single-center, retrospective study included 121 NSCLC stage III patients treated with CRT between 2004 and 2011. Median follow-up for all patients was 37.6 months. Median OS and PFS were 15.7 and 11.6 months, respectively, OS for patients with PTV > 700 ccm was 14.5 vs. 26.5 months for PTV ≤ 700 ccm ($p = 0.009$).
Bradley, J.D., et al.	Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617)	2015	The open-label randomized, two-by-two factorial phase 3 study included 166 patients with unresectable NSCLC stage III treated with CRT between 2007 and 2011. On univariate analysis, increasing values of GTV and PTV were associated with an increased risk of death. On multivariate analysis, PTV was among the factors predicting OS.
Bradley, J.D., et al.	Long-term results of RTOG 0617 trial: standard- versus high-dose chemoradiotherapy with or without Cetuximab for unresectable stage III non-small-cell lung cancer	2020	Long-term results of the RTOG 0617 trial have confirmed a small PTV as a prognostic factor for better OS in inoperable stage III NSCLC treated with concurrent CRT.
Present study	Association between planning target volume and patient outcome in inoperable stage III NSCLC treated with chemoradiotherapy	2020	The single-center, retrospective and prospective study included 122 NSCLC stage III patients treated with CRT between 2011 and 2018. Median follow-up for all patients was 41.2 months. Median OS and PFS were 20.9 and 7.1 months, respectively, median OS for patients with PTV > 700 ccm was 14.1 vs. 33.4 months for PTV ≤ 700 ccm ($p = 0.025$).

NSABP: National Surgical Adjuvant Breast and Bowel Projec, RTOG: the Radiation Therapy Oncology Group, GOG: the Gynecologic Oncology Group.

The results of our analysis suggest that for inoperable stage III NSCLC patients with PTV ≥ 700 ccm, the multimodal approach definitely needs to be further refined. The incorporation of immune checkpoint inhibition (CPI) into the treatment paradigm may play a special role in this group of patients. A secondary analysis of trials establishing CPI as a consolidation treatment after CRT in patients with PTV ≥ 700 ccm will be of particular importance. Also, a proof of novel neoadjuvant concepts including chemoimmunotherapy may be promising in this subgroup. Another important point will be the optimization of tumor motion control during CRT. The use of abdominal compression and deep inspiration breath hold, as well as the establishment of four-dimensional cone-beam CT technology for daily image guidance, will help to reduce positioning and setup errors.

Important limitations of the present analysis are its single-center design and lack of comprehensive toxicity data. Nevertheless, the analyzed cohort consists exclusively of patients with inoperable stage III NSCLC and the definition of PTV was based on the Fluorodeoxyglucose (FDG)-PET/CT in treatment position. In the absolute majority of patients, target volumes were defined according to the international guidelines (ESTRO-ACROP). Finally, a comprehensive statistical evaluation including PSM analysis with exact T- and N-stage matching was done to confirm the prognostic role of PTV.

5. Conclusions

The present study revealed that PTV (including the primary tumor and involved lymph node stations) is an important prognosticator in patients with inoperable stage III NSCLC treated with conventionally fractionated CRT. Patients with PTV ≥ 700 ccm represent a special subgroup with significantly lower loco-regional control, worse PFS and worse OS. We recommend evaluating PTV as an additional stratification factor in clinical trials of multimodal therapy in inoperable stage III NSCLC.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6694/12/10/3035/s1, Figure S1: (A). Overall survival (OS) in the PSM cohort by PTV < 700 ccm vs. ≥700 ccm. (B). Progression-free survival (PFS) in the PSM cohort by PTV < 700 ccm vs. ≥700 ccm. (C). Regional recurrence-free survival (RRFS) in the PSM cohort by PTV < 700 ccm vs. ≥700 ccm.

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SHORT REPORT

Planning target volume as a predictor of disease progression in inoperable stage III non-small cell lung cancer patients treated with chemoradiotherapy and concurrent and/or sequential immune checkpoint inhibition

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Summary
Background. The present study evaluates outcome after chemoradiotherapy (CRT) with concurrent and/or sequential Programmed Cell Death 1 (PD-1) or Ligand 1 (PD-L1) immune checkpoint inhibition (CPI) for inoperable stage III NSCLC patients depending on planning target volume (PTV). *Method and patients.* Prospective data of thirty-three consecutive patients with inoperable stage III NSCLC treated with CRT and sequential durvalumab (67%, 22 patients) or concurrent and sequential nivolumab (33%, 11 patients) were analyzed. Different PTV cut offs and PTV as a continuous variable were evaluated for their association with progression-free (PFS), local–regional progression-free (LRPFS), extracranial distant metastasis-free (eMFS) and brain-metastasis free-survival (BMFS). *Results.* All patients were treated with conventionally fractionated thoracic radiotherapy (TRT); 93% to a total dose of at least 60 Gy, 97% of patients received two cycles of concurrent platinum-based chemotherapy. Median follow-up for the entire cohort was 19.9 (range: 6.0–42.4) months; median overall survival (OS), LRFS, BMFS and eMFS were not reached. Median PFS was 22.8 (95% CI: 10.7–34.8) months. Patients with PTV ≥ 900ccm had a significantly shorter PFS (6.9 vs 22.8 months, p = 0.020) and eMFS (8.1 months vs. not reached, p = 0.003). Furthermore, patients with PTV ≥ 900ccm and stage IIIC disease (UICC-TNM Classification 8th Edition) achieved a very poor outcome with a median PFS and eMFS of 3.6 vs 22.8 months (p < 0.001) and 3.6 months vs. not reached (p = 0.001), respectively. PTV as a continuous variable also had a significant impact on eMFS (p = 0.048). However, no significant association of different PTV cut-offs or PTV as a continuous variable with LRPFS and BMFS could be shown. The multivariate analysis that was performed for PTV ≥ 900ccm and age (≥ 65 years), gender (male), histology (non-ACC) as well as T- and N-stage (T4, N3) as covariates also revealed PTV ≥ 900ccm as the only factor that had a significant correlation with PFS (HR: 5.383 (95% CI:1.263–22.942, p = 0.023)). *Conclusion.* In this prospective analysis of inoperable stage III NSCLC patients treated with definitive CRT combined with concurrent and/or sequential CPI, significantly shorter PFS and eMFS were observed in patients with initial PTV ≥ 900ccm.

Keywords Chemoradiotherapy · Checkpoint inhibition · Non-small cell lung cancer · Tumor volume · Prediction

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Introduction

Lung cancer is the most frequent cause of cancer-related mortality worldwide [1]. Inoperable, locally advanced lung cancer is a very heterogeneous disease in terms of macroscopic tumor extent and patient prognosis. Historically only ten to thirty percent of these patients survive five years after multimodal treatment [2–4].

Regarding inoperable stage III NSCLC, the implementation of CPI as one of the key components of a multimodal approach has already led to an unprecedented improvement in progression-free survival (PFS) and OS [5–8]. In particular, the ground-breaking PACIFIC phase III trial demonstrated a three-year survival rate of 57% and a median PFS of 16.8 months [9, 10]. In addition, the first clinical reports on chemoradioimmunotherapy have confirmed the PACIFIC findings concerning patient outcome [7, 11–13].

Prior to the actual use of durvalumab maintenance therapy after chemoradiotherapy (CRT), planning target volume (PTV) has been considered an important prognosticator for patient outcome and treatment-related toxicity in inoperable stage III NSCLC [14–16]. Two retrospective mono-institutional analyses, in particular, reported that a PTV cut-off of 700ccm had a significant negative impact on patient outcome after conventional CRT [17, 18].

In the present prospective study, we evaluated the impact of PTV on PFS, local–regional progression-free (LRPFS), extracranial distant metastasis-free (eMFS) as well as brain-metastasis free-survival (BMFS) after CRT with concurrent and/or sequential Programmed Cell Death 1 (PD-1) or Ligand 1 (PD-L1) immune checkpoint inhibition (CPI).

Methods

This study included data of 33 prospectively enrolled patients who received concurrent and/or sequential conventionally fractionated CRT and CPI treatment as part of a multimodal approach for inoperable UICC 8th edition stage IIIA-C NSCLC between 2017 and 2020. More precisely, CPI consisted of either sequential administration of durvalumab or conventional and sequential administration of nivolumab. All patients gave informed consent to the treatment and the prospective collection of their data for research purposes. The local ethics committee agreed to the analysis and publication of the patients' data (17–230). All patients enrolled, were treated at a single tertiary cancer center, with either the PD-1 inhibitor nivolumab in the ETOP 6–14 NICOLAS phase II study (33%, 11 patients) or the PD-L1 inhibitor durvalumab according to the PACIFIC trial (67%, 22 patients) as part of a maintenance therapy and are henceforth referred to as the NICOLAS and PACIFIC subgroup.

Prior to treatment, radiographic imaging was performed using positron emission tomography (PET)-CT in 32 (97%) patients and CT in 1 (3%) patient. Cranial contrast-enhanced MRI was performed in 31 (94%) patients before starting treatment, two patients (6%) received contrast-enhanced cranial CT. All patients underwent pulmonary function testing and received routine blood work in order to assess kidney and liver function as well as a complete blood count. In all cases, multimodal treatment was reviewed in the multidisciplinary tumor boards. The therapeutic approach was discussed with each individual patient. Patients with an initial performance status ECOG ≥ 2 or poor lung function (DLCO $< 40\%$, FEV1 < 1 L or on long-term oxygen supply) were excluded.

Based on conventional planning-CT as well as PET-CT scans in the treatment position, conventionally fractionated thoracic radiotherapy (TRT) was planned and delivered while patients were supine with their arms positioned overhead in a dedicated positioning and immobilization device - WingSTEP™ (Innovative Technologie Völp, Innsbruck, Austria). The target volumes were defined according to the European Society for Therapeutic Radiology and Oncology-Advisory Committee on Radiation Oncology Practice (ESTRO-ACROP) guidelines published in 2018 [19]. If patients were pre-treated with induction chemotherapy, only the residual primary tumor volume was contoured as gross tumor volume (GTV) and lymph node stations involved before chemotherapy were included in the clinical target volume (CTV). PTVs were generated by adding axial/cranio-caudal margins of 6/9 mm to the CTVs.

TRT was administered to the primary tumor and involved lymph nodes up to a median total dose of 63.6 Gy in 2.12 Gy single dose fractions. Radiation was delivered on a Linear accelerator (LINAC) with megavoltage capability using Volumetric Modulated Arc Therapy (VMAT) in all patients. Image-guidance was performed with a cone-beam CT at least twice a week.

All patients received a platinum-based doublet; 32 patients (97%) were treated concurrently with TRT and one patient (3%) was treated sequentially. Seventeen patients (51.5%) received at least one cycle of induction chemotherapy prior to TRT.

Durvalumab maintenance treatment at a dose of 10 mg/kg every two weeks for up to 12 months, until disease progression or the evidence of unacceptable toxicity was administered in 22 (67%) patients according to the PACIFIC trial [5, 9].

Eleven (33%) patients were enrolled in the phase II NICOLAS-trial (ETOP 6–14) and treated with concurrent nivolumab, chemotherapy and TRT, followed by nivolumab maintenance treatment every four weeks up to one year, until disease progression or the onset of unacceptable toxicity [6].

In the first two years after therapy, routine blood work, lung function testing, clinical examinations and CT or PET-CT

scans were arranged every 3 months, thereafter twice a year. If clinically indicated, cranial contrast-enhanced MRI and bone-scintigraphy were additionally performed. Response was assessed according to RECIST 1.1. Local and local–regional progression (LP) along with new extracranial distant metastases (eDM) and brain metastases (BM) were documented with CT, PET-CT or MRI scans. Cytological or histological confirmation of progressive disease was not obligatory. All volumetric parameters were extracted from the radiation treatment plans. Median follow-up was calculated as the median time to loss or end of follow-up after the last day of radiotherapy in patients who were not documented as deceased. Progression-free survival (PFS) was defined as the time from the end of TRT until the occurrence of either disease progression or death. Overall survival (OS) was also calculated from the end of TRT. Time to death or metastasis (TTDM) included extracranial distant metastases (eDM) and brain metastases (BM) from the end of TRT. Univariate analysis of OS, PFS, LRPFS, eMFS and BMFS was carried out with following parameters: age, gender, T- and N-stage, histology, PD-L1 status and different PTVs. All statistics were performed using IBM SPSS version 25 (IBM, Armonk, New York, USA).

Results

The entire cohort consisted of 33 consecutive patients with inoperable UICC 8th edition stage IIIA-C NSCLC. A summary of patients' characteristics is shown in Table 1.

The median age was 62.0 (range 43.8–76.9) years with 15 patients (45.5%) older than 65 years. Nine patients (27%) were female and 24 (73%) were male. In the histological evaluation, 13 (39%) patients had squamous-cell-carcinoma (SCC), 18 (55%) had adenocarcinoma (AC) and in 2 (6%) patients the tumor was classified as not otherwise specified (NOS). PD-L1 status was assessed in 28 (85%) patients prior to multimodal treatment. 26 (93% of patients tested) were listed as PD-L1 > 1% (median 60%). All 33 patients completed conventional fractionated radiotherapy to a total dose ≥ 60.0 Gy (median total dose: 63.6 Gy). Median PTV was 675.6 (range: 204.5–1234.5) ccm. Concurrent CRT was performed in 32 (97%) patients and one (3%) patient received sequential chemotherapy and TRT. The predominant concurrent chemotherapy regimen administered in 27 (82%) patients consisted of cisplatin and vinorelbine. Eleven (33%) patients were treated within the NICOLAS trial and received concomitant nivolumab (4 × 360 mg Q3W) during CRT and thereafter (480 mg Q4W) for up to one year (median cycles: 9, range: 3–14). The other 22 (67%) patients received durvalumab maintenance therapy for up to 24 cycles after the end of CRT based on the PACIFIC trial (10 mg/m^2 Q2W; median cycles: 14, range: 2–24).

Table 1 Patient and treatment characteristics

	N (%)
Total	33 (100)
Age	62.0
median years	15 (45.5)
> 65 years	
Gender	24 (72.6)
Male	9 (27.4)
Female	
T-stage	3 (9.1)
1	7 (21.2)
2	8 (24.2)
3	15 (45.5)
4	
N-stage	6 (18.2)
0	1 (3.0)
1	12 (36.4)
2	14 (42.4)
3	
UICC 8th edition	9 (27.3)
IIIA	16 (48.5)
IIIB	8 (24.2)
IIIC	
PTV size	675.6
Median ccm	6 (18.2)
≥ 900ccm	
Histology	13 (39.4)
-Squamous cell carcinoma (SCC)	18 (54.5)
-Adenocarcinoma (AC)	2 (6.1)
-Not otherwise specified (NOS)	
PD-L1-status	28 (84.8)
tested in	26 (78.8)
≥ 1%	13 (39.4)
≥ 50%	
Radiographic imaging	32 (97.0)
PET-CT	31 (93.9)
cMRI	
Treatment	32 (97.0)
Concurrent chemoradiation (CRT)	17 (51.5)
Induction chemotherapy	11 (33.3)
NICOLAS	22 (66.7)
PACIFIC	
Median Follow-up	19.9
Months after CRT	
OS	100%
6-month	93.3%
12-month	87.0%
18-month	
PFS	87.5%
6-month	67.7%
12-month	40.0%
18-month	
eMFS	87.5%
6-month	74.2%
12-month	56%
18-month	

The median follow-up for the entire cohort was 19.9 (range: 6.0–42.4) months, median PFS was 22.8 (95% CI: 10.7–34.8) and median TTDM was 26.3 (95% CI: 3.6–49.0) months whereas median OS, median BMFS as well as eMFS were not reached.

For PFS, no significant difference could be revealed between the NICOLAS and the PACIFIC subgroup, with a median PFS of 22.7 (95%CI:9.1–36.4) months vs not reached (p = 0.831). The same was true for patients treated with or without induction chemotherapy, with a median PFS of 21.9 months vs not reached (p = 0.853).

Furthermore, disease stage (UICC 8th edition) had no significant impact on PFS (IIIA: median not reached, IIIB: median 22.8 months, IIIC: median 11.8 months, p = 0.810). Patients with stage IIIC disease had only a numerical inferior PFS (11.8 vs 22.8 months, p = 0.545) compared to the rest of the cohort.

No influence of PD-L1 status on PFS could be shown, neither for 0% vs. ≥ 1%

(p = 0.764, 26.3 vs 14.0 months median) nor for < 50 vs ≥ 50% (p = 0.459, 11.0 vs 14.6 months median). No significant impact of patient- (age and gender) and tumor-related (histology, T- and N-stage) characteristics on PFS was documented. For detailed results see Table 2.

However, a significant correlation between PTV and PFS was demonstrated for PTV ≥ 900ccm with a median PFS of 6.9 (95%CI: 0.3–13.6) vs 22.8 (95%CI:10.0–35.5) months (p = 0.020) Fig. 1. The corresponding 6-, 12- and 18-months PFS-rates were 60%, 20% and 0% compared to 93%, 77% and 48%, respectively Fig. 2. To further clarify the influence of PTV ≥ 900ccm as a prognostic cut-off, we also tested it for LRPFS and TTDM: A trend was observed for TTDM with a median TTDM of 8.0 vs 26.3 months (p = 0.089), but there was no significant impact on LRPFS (13.2 vs. 24.8 months, p = 0.064). We found no influence of PTV ≥ 900ccm on BMFS (15.8 vs. 32.5 months, p = 0.296). However, median eMFS was 8.1 (95%CI: 0.0–17.1) months in patients with PTV ≥ 900ccm vs not reached with PTV < 900ccm (p = 0.003) Fig. 3. The corresponding 6-, 12- and 18-months eMFS-rates were 60%, 20% and 0% compared to 93%, 85% and 66%, respectively.

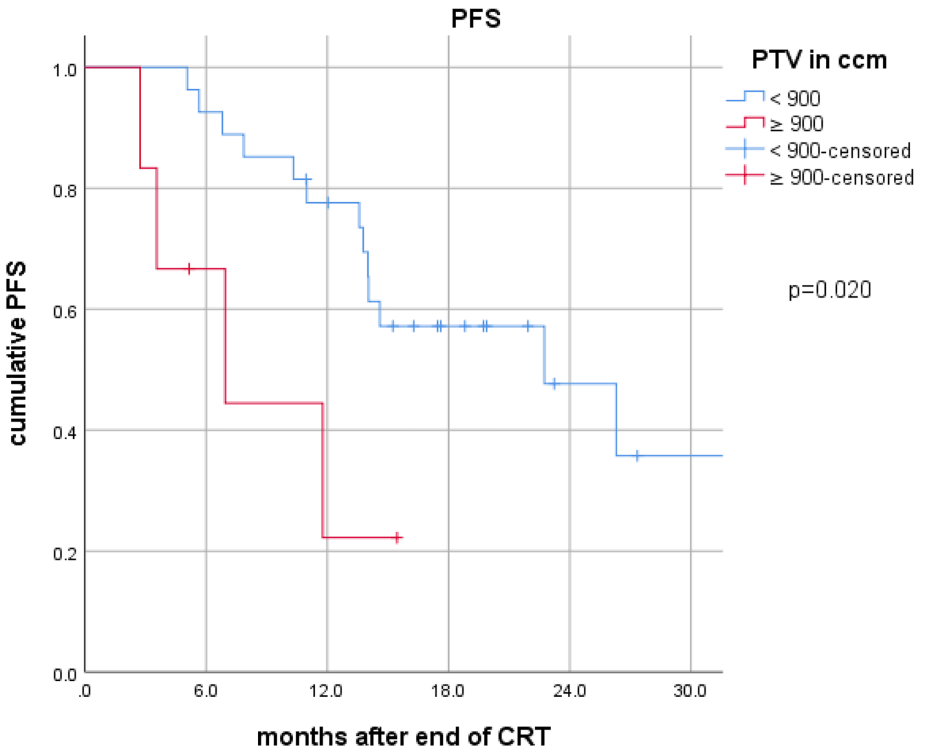
Three patients (9%) with PTV ≥ 900ccm also presented with UICC stage IIIC disease; their median PFS was 3.6 (range 2.7–11.8) months after TRT in contrast to a median PFS of 22.8 (95%CI: 10.3–32.2) months in other patients (p < 0.001). Their median eMFS was 3.6 months vs not reached (p = 0.001).

In the multivariate analysis performed for PTV ≥ 900ccm as well as age (≥ 65 years), gender (male), histology (non-ACC) and T- and N-stage (T4, N3) as covariates, PTV ≥ 900ccm was the only factor that significantly correlated with PFS (HR: 5.383 (95% CI:1.263–22.942, p = 0.023)).

Moreover, we evaluated PTV as a continuous variable and discovered a significant impact on eMFS (p = 0.048; see Table 3).

Table 2 Results of the univariate analysis (Log-Rank test)

	Entire cohort N (%)	PFS (*p*)	LRPFS (*p*)	eMFS (*p*)
Total	33 (100)			
Age > 65 years	15 (45.5)	0.126	0.423	0.869
Gender -Male	24 (72.6)	0.484	0.746	0.901
T-stage 4	15 (45.5)	0.702	0.885	0.858
N-stage 3	14 (42.4)	0.965	0.858	0.194
UICC-stage IIIC	8 (24.2)	0.150	0.343	0.065
PTV-size ≥ 900ccm	6 (18.2)	0.020	0.064	0.003
Histology -SCC + NOS	15 (45.5)	0.708	0.413	0.842
PD-L1-status ≥ 1% ≥ 50%	26 (78.8) 13 (39.4)	0.764 0.459	0.759 0.850	0.880 0.666
Treatment Induction chemotherapy NICOLAS vs. PACIFIC	31 (93.9) 11 (33.3) vs. 22 (66.7)	0.853 0.831	0.530 0.872	0.504 0.732
Subgroup with UICC stage IIIc and a PTV ≥ 900ccm	3 (9.1%)	p < 0.001	0.123	0.001



Patient PFS stratified according to PTV (remaining number of patients / number of death or progress)

moths	0	6	12	18
< 900 ccm	27 / 0	25 / 2	20 / 6	10 / 11
≥ 900 ccm	6 / 0	3 / 2	1 / 4	0 / 4

Fig. 1 F Kaplan–Meier curves of progression-free survival (PFS) for all patients stratified according to the planning target volume (PTV)

Discussion

The aim of the present study was to evaluate the role of PTV (including the primary tumor and involved lymph node stations) on disease progression in patents with inoperable stage III NSCLC treated with CRT combined with concurrent and/or sequential CPI. Prospectively collected data of thirty-three patients were analyzed.

In accordance with the current ESTRO-ACROP guidelines for inoperable stage III NSCLC, involved lymph node stations were included in the clinical target volume (CTV). In addition, corresponding safety margins for potential patient positioning and setup errors were added in order to generate a PTV [19]. For the majority of patients, a recent PET-CT was available to delineate the target volume and if induction chemotherapy was administered in advance,

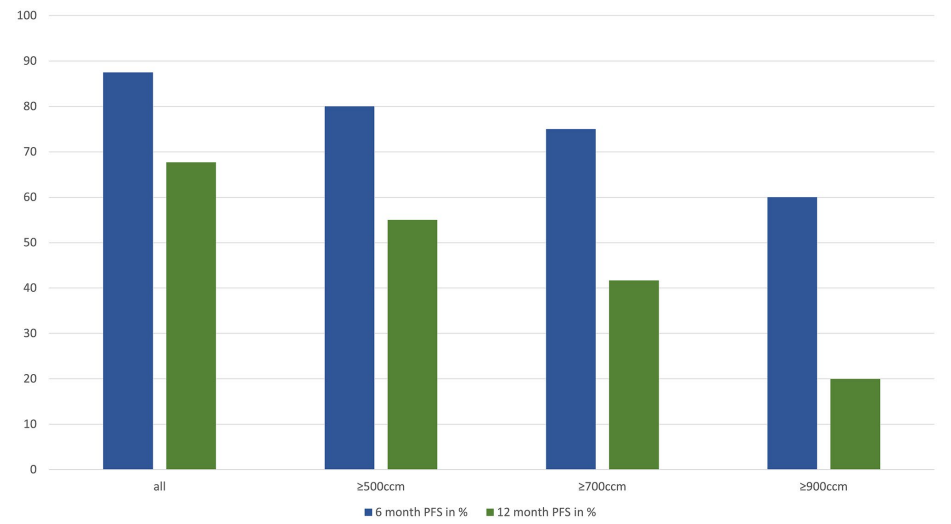


Fig. 2 Progression-free survival (PFS) rate at 6 and 12 months regarding planning target volume (PTV)

imaging before and after induction was carefully considered [20].

Although these results are preliminary due to the limited number of patients and the short follow-up (median 19.9 months), we found a significantly shorter PFS and eMFS in patients with very large PTV ≥ 900ccm. For eMFS, a predictive role of PTV as a continuous variable was also revealed. Moreover, the deterioration of PFS and eMFS was more pronounced when PTV ≥ 900ccm was combined with stage IIIC disease (UICC 8th edition): In this subgroup PFS was only 3.6 (range: 2.7–11.8) months vs 22.8 (95%CI: 10.3–32.2) months in the rest of the treated cohort and eMFS was 3.6 months vs not reached ($p = 0.001$). Interestingly, a larger PTV was not associated with a significant increase in locoregional recurrences as well as intracranial relapse.

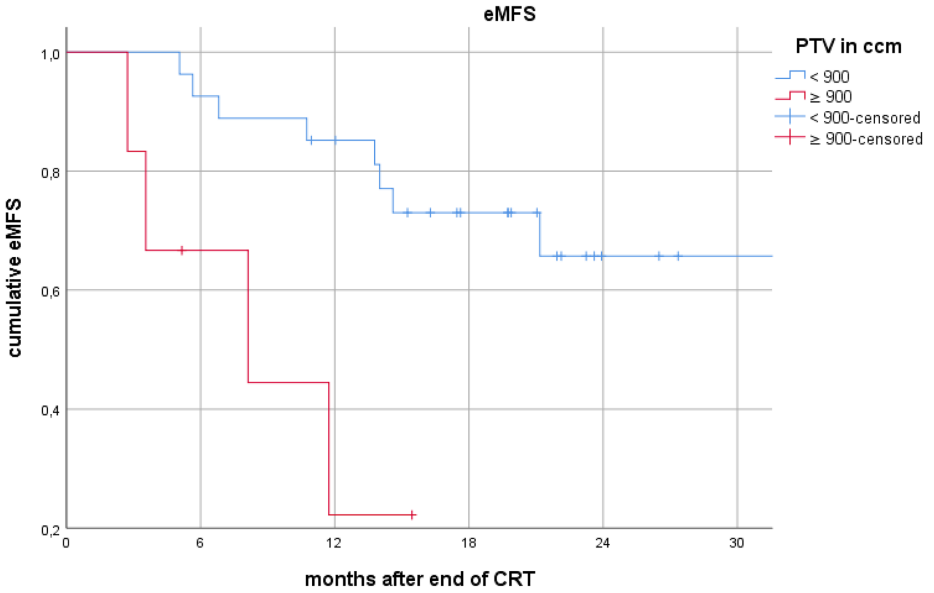
Historically, PTV has been a strong prognosticator regarding patient outcome in inoperable lung cancer. The Radiation Therapy Oncology Group 93–11 Phase I-II dose-escalation study confirmed an inferior PFS and OS for patients with larger tumors. In fact, patients with smaller (≤ 45cm3) tumors had a longer median survival time (MST) and a better PFS than patients with larger (> 45cm3) tumors (29.7 vs 13.3 months, $p < 0.0001$ and 15.8 vs 8.3 months, $p < 0.0001$) [21].

PTV was also validated as an important prognostic factor in the dose-escalation phase III RTOG 0617 study for inoperable stage III NSCLC [15, 16]. The open-label randomized, two-by-two factorial phase III study included 166 patients with unresectable NSCLC stage III treated with CRT between 2007 and 2011. On univariate analysis Bradley et al. indicated that increasing values of GTV and PTV are associated with increased risk of death. On multivariate analysis, PTV was among the factors predicting OS [15]. Long-term results of the RTOG 0617 trial have confirmed smaller PTV as a prognostic factor for better OS in inoperable stage III NSCLC treated with concurrent CRT [16].

Retrospective mono-institutional analyses of conventional CRT in inoperable stage III NSCLC revealed a PTV cut-off of 700ccm to have a significant impact on patient survival [17, 18].

In the PACIFIC trial, patients with inoperable stage IIIB disease (UICC 7th edition) were equally distributed between the durvalumab (44.5%) and placebo (45.1%) arm, however this trial did not provide any information about the impact of PTV on patient outcome [5, 9, 10, 22]. Shaverdian et al. [23, 24] reported no impact of PTV on patient eligibility for durvalumab maintenance therapy after CRT and no effect of PTV on the onset of pneumonitis during a durvalumab maintenance therapy.

Two studies on CRT combined with concurrent and/or sequential anti-PD-1 inhibitors (LUN 14–179 and NICOLAS) reported a significantly lower PFS and OS in patients with UICC 7th edition stage IIIB disease [6, 7, 25, 26]. In our study, the subgroup of patients with both PTV ≥ 900ccm



Patient eDMFS stratified according to PTV (remaining number of patients / number of death or eM)

moths	0	6	12	18
< 900 ccm	27 / 0	25 / 2	22 / 4	14 / 7
≥ 900 ccm	6 / 0	3 / 2	1 / 4	0 / 4

Fig. 3 Kaplan–Meier curves of extracranial distant metastasis-free (eMFS) for all patients stratified according to the planning target volume (PTV)

and stage IIIC disease (UICC 8th edition) had a very short PFS and eMFS despite successfully completed trimodal therapy.

Considering the apparent limitations of our analysis, namely its single-center design, limited patient number and a median follow-up of 19.9 months, it is of potential interest

Table 3 Outcome for PTV < 900ccm vs PTV ≥ 900ccm and results of the univariate analysis

Months after CRT	OS in % <//≥900ccm	PFS in % <//≥900ccm	LRPFS in % <//≥900ccm	eMFS in % <//≥900ccm	BMFS in % <//≥900ccm
3	100//100	100//83	100//100	100//83	100//100
6	100//100	93//60	100//100	93// 60	100//100
9	100//100	85//40	96//80	89//40	96//80
12	96//80	77//20	88//60	85//20	88//60
15	92//80	56//20	75//50	72//20	79//60
	OS	PFS	LPFS	eMFS	BMFS
p-values for PTV <//≥900ccm (log-rank)	0.415	0.020	0.064	0.003	0.296
p-values for PTV as a continuous variable (cox regression)	0.245	0.129	0.108	0.048	0.653

to re-evaluate these findings in a larger patient collective to confirm an impact of PTV on the course of disease and long-term patient outcome.

In summary, the present results show a significant deterioration of PFS and eMFS in inoperable stage III NSCLC patients with very large PTV (≥ 900ccm). This negative effect was more pronounced in patients with stage IIIC disease (UICC 8th edition). Our findings suggest a potential role for induction treatment in this subgroup of patients. Several studies investigating induction therapy for definitive CRT combined with concurrent and/or sequential CPI are ongoing or planned [27–31].

Conclusion

The present study revealed that PTV ≥ 900 cc has a significant impact on PFS and eDMFS in inoperable stage III NSCLC patients treated with definitive CRT combined with concurrent and/or sequential CPI.

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Data availability The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate All patients provided signed informed consent. The study was approved by the Institutional Review Board of the University hospital of the Ludwig-Maximilians-University (approval number: 17–230) and was conducted according to local and federal regulations and the Declaration of Helsinki.

Informed consent All study participants provided written informed consent. Informed consent was obtained from all individual participants included in the study.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its subsequent amendments or comparable ethical standards. This research did not involve any animal research.

Conflict of interests The authors declare no conflict of interest. Farkhad Manapov receives an Institutional research grant for participating or running clinical studies from Astrazeneca (outside of the study mentioned in the manuscript).

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9. Lebenslauf

Aus datenschutzrechtlichen Gründen sind keine persönlichen Informationen hinterlegt

10. Publikationsliste

1. **Karin M**, Taugner J, Käsmann L, Eze C, Roengvoraphoj O, Tufman A, Belka C, Manapov F.
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