Aus der Klinik und Poliklinik für Strahlentherapie und Radioonkologie der
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Retrospektive Analyse von Patienten mit einem lokal-fortgeschrittenem nicht-kleinzelligen Lungenkarzinom die von 2006 bis 2016 mit einer primären Radiochemotherapie in der Klinik und Poliklinik für Strahlentherapie und Radioonkologie LMU behandelt wurden

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Zusammenfassung:

Das Lungenkarzinom ist verantwortlich für die meisten Krebstoten in Deutschland und weltweit. Der Behandlungsstandart von Patientinnen und Patienten mit inoperablen lokal fortgeschrittenen nicht-kleinzelligen Lungenkarzinome ist die definitive Radiochemotherapie, gefolgt von einer Durvalumab-Erhaltungstherapie abhängig vom PD-L1 Status.
Das Gesamtüberleben und progressionsfreie Überleben der so behandelten Patienten variiert jedoch immens. Zur Individualisierung der Therapieplanung ist es darum wichtig die Möglichkeiten der Prognosestellung zu verbessern.
In der Arbeit „Survival score to characterize prognosis in inoperable stage III NSCLC after chemoradiotherapy" wurde ein einfach anwendbarer Prognosescore basierend auf den grundlegenden Patientendaten zu Alter, Geschlecht, Tabakkonsum, Histologie und Atelektase, jeweils bei Diagnosestellung in einer retrospektiven Kohorte mit 99 Patienten entwickelt und in einer prospektiven Patientenkohorte validiert.
Die Bedeutung der bildgebenden Nachsorge nach einer definitiven Radiochemotherapie ist für Patienten mit lokal fortgeschrittenem, inoperablem Lungenkarzinom unangefochten. In „How much primary tumor metabolic volume reduction is required to improve outcome in stage III NSCLC after chemoradiotherapy? A single-centre experience" wurde in einer Kohorte mit 60 Patienten der Rückgang des metabolischen Primärtumorvolumens in einem post-therapeutischen PET/CT im Vergleich zu jenem vor einer Radiochemotherapie erfasst. Eine Reduktion von mindestens 80% zeigte hierbei einen signifikanten positiven Einfluss auf das Gesamtüberleben.
Somit wurden zwei Verfahren zur genaueren Prognosestellung von NSCLC Patienten im inoperablem UICC-Stadium III entwickelt.

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1. Einleitung

1.1 Epidemiologie

Das Lungenkarzinom führt zu 19,4% aller Krebstode weltweit und ist somit verantwortlich für die meisten Krebstoten. Es starben 2012 weltweit 1,6 Millionen Menschen und 1,8 Millionen Menschen erkrankten neu an Lungenkrebs [1, 2]. Das Lungenkarzinom ist laut World Cancer Report der WHO 2014 das häufigste Malignom bei Männern und das dritthäufigste bei Frauen [3]. Die hohe Todesrate kann zudem mit der hohen Aggressivität des Lungenkarzinoms begründet werden: Das 5-Jahres-Überleben liegt weltweit bei gerade einmal 10 - 15% [3]. In Deutschland erkrankten 2013 etwa 53.500 Menschen an Lungenkrebs, rund 34.690 Männer (65%) und 18.810 Frauen (35%). Es starben 2013 hierzulande 29.708 Männer (66%) und 15.140 Frauen (34%) an Lungenkrebs. Das 5-Jahres-Überleben lag 2013 in Deutschland bei 16% für Männer und bei 21% für Frauen [4, 5]. Bei Männern ist ein Rückgang der Inzidenzrate und bei Frauen ein Anstieg ebenjener zu beobachten. Insgesamt wird, auch aufgrund der demografischen Entwicklung, jedoch eine weitere Zunahme der Erkrankungs- und Todesfälle erwartet [5].

1.2 Grundlagen

Das Lungenkarzinom wird in das kleinzellige (SCLC) und das nicht-kleinzellige Karzinom (NSCLC) unterteilt. Das nicht-kleinzellige Karzinom wird weiter in das Plattenepithelkarzinom, das Adenokarzinom und das großzellige Karzinom unterteilt. Heutzutage erfolgt insbesondere beim Adenokarzinom eine immer präzisere Klassifizierung biologischer / molekularbiologischer Entitäten [6].
Der Hauptrisikofaktor für die Entwicklung eines Lungenkarzinoms ist das Rauchen [7]. Dabei ist auch die Intensität des Tabakkonsums entscheidend und erhöht insbesondere das Risiko für die Entwicklung eines SCLC und eines Plattenepithelkarzinoms [8, 9]. Auch andere Noxen wie Radon [10], Asbest [11], Luftverschmutzung [12–14], Chemikalien und Stäube [15, 16] erhöhen das Lungenkrebsrisiko. Häufige Initialsymptome des Lungenkarzinoms sind Husten (8-75%), Luftnot (3-60%), Gewichtsverlust (0-86%), Brustschmerzen (20-49%), Hämoptysen (6-35%), Knochenschmerzen (6-25%), Veränderungen der Endphalangen (0-20%), Schwächegefühl (0-10%) und Fieber (0-20%) [17].

1.3 Kleinzelliges Lungenkarzinom (SCLC)

Das SCLC macht ungefähr 12-15% der Lungenkarzinome aus und ist durch eine aggressive Tumorbiologie mit früher lymphogener und hämatogener Metastasierung sowie hoher Proliferationsrate gekennzeichnet [18]. SCLCs stammen aus den neuroendokrinen APUD-Zellen des Bronchus; deshalb exprimieren sie neuroendokrine Marker und führen häufig zu paraneoplastischen Syndromen [19]. Bereits bei Erstdiagnose präsentieren sich rund 70% der Patienten mit einem ausgedehnten Tumorleiden mit Pleura- oder Perikardbefall und/oder Fernmetastasen

(extensive stage, ES). Lediglich 30% der Patienten haben bei Erstdiagnose einen einseitigen Lungenbefall, mit einem Tumor, der sicher innerhalb eines Bestrahlungsfeldes erfasst werden kann (limited stage, LS) [20–22]. Die relative 5-Jahres-Überlebensrate für das LS-SCLC ist 21,3%, jedoch nur 2,8% für ES-SCLC [23]. Für das LS-SCLC ist der Behandlungsstandart eine kombinierte Radiochemotherapie gefolgt von einer prophylaktischen Ganzhirnbestrahlung [24–31].
Der neue Goldstandard in der Behandlung von ES-SCLC ist eine kombinierte Chemo-Immun-Therapie mit Atezolizumab, Carboplatin und Etoposid [32]. Bei gutem Ansprechen kann auch hier prophylaktisch eine Ganzhirnbestrahlung angeboten werden [33, 34] sowie eine konsolidierende Radiatio des Mediastinums [35–38]

1.4 Nicht-Kleinzelliges Lungenkarzinom (NSCLC)

Das häufigste Lungenkarzinom ist mit 85% das NSCLC [18]. Im Allgemeinen handelt es sich, verglichen mit dem SCLC, um langsamer proliferierende, somit weniger chemotherapiesensible und langsamer metastasierende Tumore. Deshalb sind lokale Therapieverfahren wie Operation oder ablative Bestrahlung, vor allem in Frühstadien der Erkrankung, entscheidend. Die Behandlung des NSCLC ist zunehmend differenziert in Bezug auf das jeweilige Tumorstadium sowie auf die genaue Histologie und Molekularbiologie der Tumorzellen. In der letzten Dekade wurden vor allem Unterschiede der Tumorgenetik und des Ansprechens auf zielgerichtete Therapien zwischen Adeno- und Plattenepithelkarzinomen immer deutlicher [39].
Etwa 30-35% aller Lungenkarzinome sind eher zentral in der Lunge gelegene Plattenepithelkarzinome (squamous cell lung cancer, SCC) [18]. Das SCC zeigt üblicherweise sowohl endobronchiales als auch invasives Wachstum in das peribronchiale Weichgewebe und Lungenparenchym und in die benachbarten Lymphknoten. Daraus können Kompressionen der Pulmonalgefäße resultieren sowie ausgedehnte Atelektasen durch Verlegung von Hauptbronchien [40]. Typischerweise zeigen sich histomorphologisch Verhornungszeichen und Interzellularbrücken sowie Zellen mit polygonaler Form, die in faserigem keratinreichem Stroma eingebettet sind [40–42]. Es wird zwischen pillärem, klarzelligem, kleinzelligem und basaloidem Wachstumsmuster unterschieden sowie zwischen unterschiedlichen Differenzierungsgraden [42]. Molekularbiologisch findet sich am häufigsten eine Mutation von TP53 sowie CDKN2A (P16), PIK3CA, PTEN, MLL2 und KEAP1 [43, 44]. Zwar spielt die molekulare zielgerichtete Therapie beim SCC noch keine große Rolle, jedoch ergibt sich hieraus Hoffnung auf die Entwicklung neuer Therapiemöglichkeiten [45–47]. Entscheidend für die Therapie fortgeschrittener Stadien ist zunehmend die immunhistochemische Bestimmung der PD-L1-Expression in Bezug auf die Erfolgsaussicht einer möglichen Immun-Checkpoint-Inhibition [48].
Das Adenokarzinom der Lunge macht etwa 40-50% aller Lungenkarzinome aus und ist der häufigste Lungenkrebs bei Nicht-Rauchern [18]. Typischerweise liegt es eher in der Peripherie der Lunge, ist häufig schleimbildend und wird histomorphologisch in lepidische, azinäre, papilläre, mikropapilläre und solide Tumore unterteilt [6, 42, 49]. Von zunehmender therapeutischer Be-

deutung ist beim Adenokarzinom der Lunge jedoch die Molekularpathologie. So zeigt sich beispielsweise bei Nicht-Rauchern mehrheitlich eine Treibermutation im HER2- oder EGFR-Gen und/oder ein ALK- oder ROS1-Fusionsprotein, für die molekulare, zielgerichtete Therapien zur Verfügung stehen [50, 51]. Aber auch bei Rauchern mit Adenokarzinom treten Treibermutationen im ALK-, BRAF-, EGFR-, HER2-, KRAS-, PIK3CA- und ROS1-Gen auf, wobei insbesondere zielgerichtete Therapien bei EGFR- und ALK-, ROS1-Mutationen ein integraler Bestandteil der Behandlung fortgeschrittener Tumorstadien sind [50, 52, 53]. Beim Adenokarzinom ist ebenso eine immunhistochemische Bestimmung der PD-L1-Expression zur Evaluation einer Immun-Checkpoint-Inhibition in der aktuellen AWMF S3-Leitlinie empfohlen [48].
Den kleinsten Anteil der Lungenkarzinome machen großzellige Karzinome mit ungefähr 3-9% aus[18]. Diese sind eher in der Peripherie der Lunge gelegen und können in die Thoraxwand einwachsen. Namensgebend sind die histomorphologisch großen Zellen mit großen Zellkernen [40].
Neben der Histologie und Molekularbiologie ist zur Therapieplanung des NSCLC eine genaue Erfassung der initialen Ausbreitung der Erkrankung unerlässlich. Diese wird nach UICC Version 8 TNM klassifiziert und in Stadium IA-IVB eingeteilt (Union International Contre Le Cancer) [54]. Laut aktueller AWMF S3-Leitlinie „Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms“ sollte bei NSCLC nach Durchführung der Basisdiagnostik (Anamnese, klinische Untersuchung, Röntgen Thorax, Laboruntersuchungen, Sonografie oder CT- Abdomen und CT-Thorax sowie Bronchoskopie), bei kurativer Behandlungsintention im klinischen UICC Stadium IB–IIIB und im metastasierten Stadium IVA mit M1B eine erweiterte Diagnostik in Hinblick auf Metastasen extrathorakaler Lokalisation mittels MRT Schädel und Ganzkörper-18F-fluoro-deoxyglucose-Positron-Emissions-Tomographie mit simultaner Computer-Tomographie-Bildgebung (FDG-PET/CT) erfolgen [48, 55, 56]. Alternativ kann eine Knochenszintigrafie und ein CT Abdomen bzw. Sonografie Abdomen oder eine MRT des ganzen Körpers angefertigt werden [48]. Die kombinierte FDG-PET/CT-Bildgebung ist jedoch zu bevorzugen, da sie, aufgrund der besseren räumlichen Zuordnung, eine präzisere Beurteilung von etwaigen Metastasen, des mediastinalen Lymphkonten- und des Tumorstadiums erlaubt [57–60]. Werden hierbei mediastinale Lymphknotenveränderungen festgestellt, sollte eine definitive pathologische Evaluation mittels bronchioskopischer - oder ösophagoskopischer - ultraschallgesteuerter Biopsie erfolgen und, falls dies nicht möglich ist, eine chirurgische Sicherung, z. B. mittels Mediastinoskopie [48]. Zur Therapieplanung ist zudem eine genaue Funktionsdiagnostik der Lunge und eine internistische Abklärung zur Evaluation einer klinischen und funktionellen Operations- bzw. (Radio-) Chemotherapiefähigkeit unerlässlich [61–67]. Zudem sollten Komorbiditäten wie COPD, Herzerkrankungen, die Raucheranamnese sowie der Allgemeinzustand und das Alter des Patienten in die Therapieplanung miteinfließen [68–73].

1.5 Behandlung des NSCLC nach Tumorstadium

Bei NSCLC des UICC Stadium I und II sowie IIIA mit T3N1-Konstellation ist die primäre Therapie der Wahl die chirurgische Resektion in kurativer Intention [48, 74]. Das Standardverfahren

ist eine Lobektomie mit systematischer Dissektion der ipsilateralen Lymphknoten. Bei ausgedehntem Befall ist eine Bilobektomie oder eine Pneumonektomie notwendig; auch eine Manschettenresektion ist möglich, sofern damit ein ausreichender Sicherheitsabstand bei der Resektion eingehalten werden kann. Fünf-Jahres-Überlebensrate nach Resektion eine NSCLC im Frühstadium unterscheiden sich stark und reichen von 69-89% für das Stadium IA bis 24-44% für das Stadium IIIA mit T3N1 [75, 76]. Die perioperative Letalität ist durchschnittlich 3,5% [77], steigt jedoch mit zunehmendem Alter [78]. Die durchschnittliche Morbidität bei offenen Operationen des Lungenkarzinoms ist rund 30% [77]; die höchste Morbidität verursachen ausgedehnte Operationen wie beispielsweise Pneumektomien [79]. Im Stadium II und IIIA sollte nach R0-Resektion eine adjuvante, Cisplatin-basierte Chemotherapie erfolgen [48, 80–82]. Ist funktionell oder klinisch eine Operation nicht möglich, sollte eine primäre definitive Bestrahlung durchgeführt werden [83]. Falls möglich, sollte diese, in den frühen Stadien UICC I-IIA ohne Lymphknotenbefall, als stereotaktische ablative Bestrahlung (Stereotactic ablative radiotherapy; SABR) erfolgen, da somit Resultate ähnlich einer Lobektomie erzielt werden können [84–86]. Ist dies nicht möglich, kann eine moderat hypofraktionierte [87, 88] oder normofraktionierte Radiotherapie angeboten werden [83].

Einen Sonderfall bilden die sogenannten Pancoast-Tumore. Dies sind Tumore im Lungenapex, die rasch die obere Thoraxwand mit Wirbelkörpern, Rippen sowie die subklavikulären Gefäße, den Plexus brachialis und das Ganglion stellatum infiltrieren [89]. Aufgrund der häufig bereits bei Diagnosestellung nicht mehr gegebenen Operabilität, vor allem im Hinblick auf die Möglichkeit einer R0-Resektion, wird eine neoadjuvante Radiochemotherapie empfohlen [90–92]. Ist eine Operation funktionell nicht möglich oder auch nach neoadjuvanter Radiochemotherapie nicht möglich, sollte eine definitive Radiochemotherapie durchgeführt werden [93, 94]. Im Anschluss kann, unter Berücksichtigung des PD-L1-Status, eine Konsolidierung mit dem Immun-Checkpoint-Inhibitor Durvalumab erfolgen [95].

Bei NSCLC des Stadium III handelt es sich um eine sehr heterogene Erkrankung in Bezug auf die Tumorlokalisation und -ausdehnung (T1-4) sowie den Lymphknotenbefall (N0-3). Eine multimodale Behandlung in erfahrenen Zentren, abgestimmt in interdisziplinären Tumorboards, ist deshalb unabdingbar. Es stehen dabei heutzutage eine Vielzahl an Behandlungsoptionen wie Chemotherapie, Strahlentherapie, Operation, Immun-Checkpoint-Inhibition und deren Kombinationen zur Verfügung [96–104]. Eine intensive multimodale Therapie kann jedoch sehr belastend und toxisch für die Patienten sein und ist spätestens seit der Implementierung der konsolidierenden Immun-Checkpoint-Inhibition mit einer langen Therapiedauer und hohen Therapiekosten verbunden [95, 105–109]. Umso wichtiger ist deshalb die genaue prätherapeutische Diagnostik der Patienten: Zum einen, wie oben bereits beschrieben, in Bezug auf das genaue Ausmaß des Tumorbefalls; so können Patienten mit nur einem befallenen Lymphknotenlevel mediastinal primär operiert werden [110, 111], Patienten mit mehreren befallenen Stationen sollten jedoch einer neoadjuvanten [112] oder definitiven Radiochemotherapie [113, 114] oder neoadjuvanten Chemotherapie [115–117] zugeführt werden. Zum anderen ist eine präzise prätherapeutische Diagnostik von hoher Relevanz aufgrund der meist vorliegenden Vielzahl an Komorbiditäten, die eine Operation oder intensive Chemotherapie häufig unmöglich machen

[118]. Im UICC Stadium IIIA mit (T1/2) N2-Konstellation, IIIB und IIIC ist, falls der Allgemeinzustand des Patienten es erlaubt, eine definitive simultane, Cisplatin-basierte Radiochemotherapie bis zu einer normofraktionierten Gesamtdosis von 60 bis 66Gy die Standardbehandlung [119–124]. Falls aufgrund von Komorbiditäten oder eines reduzierten Allgemeinzustandes dies nicht möglich ist, kann auch eine sequentielle Chemo- und Strahlentherapie, ggf. mit moderat hypofraktionierter Bestrahlung und das Ausweichen auf weniger toxische Chemotherapieprotokolle, wie z. B. einer Carboplatin-basierte Doublette, angeboten werden [96, 99, 122, 125–130]. Insbesondere die Bestrahlungstechnik wird weiterhin kontinuierlich verbessert und sollte heutzutage bildgesteuert in hochkonformaler intensitätsmodulierter Strahlentherapie (Intensity Modulated Radiation Therapy, IMRT) bzw. volumenmodulierter Strahlentherapie (Volumetric Arc Therapy, VMAT) erfolgen. Im Zuge dessen konnten das Gesamtüberleben und das progressionsfreie Überleben verlängert sowie auch eine Reduktion der Nebenwirkungen herbeigeführt werden [131–135]. Eine Eskalation der applizierten Bestrahlungsdosis scheint hingegen keinen Benefit bei erhöhter Toxizität zu verursachen [136]. Eine bahnbrechende Neuentwicklung des letzten Jahrzehnts, mit nahezu einer Verdreifachung des medianen PFS auf 16,8 Monate und einer Drei-Jahres-Überlebensrate von 57%, stellt die Zulassung einer einjährigen Konsolidierungsbehandlung mit dem Immun-Checkpoint-Inhibitor Durvalumab, nach definitiver platinbasierter Radiochemotherapie für PD-L1-positive NSCLC Patienten, dar [95, 137, 138].
Etwa 35-40% der Patienten mit NSCLC haben bereits bei Erstdiagnose Metastasen und werden deshalb dem UICC-Stadium IV zugeordnet [18]. Insbesondere Patienten im Stadium IV a mit bis zu vier Fernmetastasen [48, 139, 140] in einem extrathorakalen Organ (M1b) oder einem separaten Tumorknoten in einem kontralateralen Lungenlappen (M1a ohne malignen Pleura- oder Perikarderguss) kann jedoch eine aggressive multimodale Behandlung analog zur Therapie des Stadiums III angeboten werden, falls die singuläre Metastase einem lokal ablativen Verfahren wie SABR oder Operation zugänglich ist [48, 141–145]. Bei Patienten mit disseminierter Metastasierung oder großflächigem knotigem Pleurabefall ist jedoch primär eine Systemtherapie in palliativer Intention indiziert [48]. Die Behandlung erfolgt nach zunehmend komplexen Algorithmen. Liegen adressierbare Treibermutationen vor - wie insbesondere beim Adenokarzinom eine Mutation von EGFR, EML4-ALK oder ROS1 - so sollte primär eine molekulare zielgerichtete Therapie eingeleitet werden, da sie neben einer guten Wirksamkeit mit wenig Toxizität einhergeht und meist ambulant in Tablettenform durchgeführt werden kann [146–154]. Liegen keine therapierbaren Treibermutationen vor, ist die PD-L1-Expression entscheidend: Bei einer PD-L1 Expression von mehr als 50% kann eine Monotherapie mit Pembrolizumab erfolgreich in der Erstlinienbehandlung angewendet werden [155]. Bei einer PD-L1- Expression der Tumorzellen von < 50% erfolgt, abhängig vom Allgemeinzustand und etwaigen Komorbiditäten, eine Doubletten-Chemotherapie, wenn möglich mit Cisplatin in Kombination mit Pembrolizumab [156–161].

2. Hintergrund der eigenen Publikationen

2.1 Erstautorenschaft: Einfach anwendbarer prognostischer Score

Das Überleben von Patienten mit NSCLC im inoperablem Stadium III zeigt große Unterschiede [162, 163]. Dies liegt vor allem an der großen Heterogenität des Patientenkollektivs in Bezug auf die Tumorausdehnung, aber auch an Faktoren wie Alter [164–166], Geschlecht [167], Komorbiditäten [168–170], zeitliche Länge und Intensität des Tabakkonsums [7, 8, 171–174]. Um die therapeutische Entscheidungsfindung zu vereinfachen, gibt es bereits eine Vielzahl an Scores, welche auf Laborparametern des Blutes, klinischen Biomarkern, dem UICC-Stadium, auf der Erfassung von Komorbiditäten und auf der Einschätzung von allgemeinen Performance-Scores wie dem ECOG-PS (Eastern Cooperative Oncology Group performance score) oder dem Karnofsky-Index basieren [175–178]. Jedoch ist die Erhebung dieser Scores teilweise äußerst kompliziert und benötigt zum Teil spezifische, nicht routinemäßig durchgeführte Untersuchungen, wie spezielle Laboranalysen des Blutes. Ziel der Studie „Survival score to characterize prognosis in inoperable stage III NSCLC after chemoradiotherapy“ [179] war es deshalb, einen vor Therapieeinleitung einfach zu erfassenden und leicht anwendbaren Score zur Vorhersage des Gesamtüberlebens - für Patienten mit NSCLC im inoperablen Stadium III - zu entwickeln, für dessen Kalkulation keine Zusatzuntersuchungen nötig sind.

2.2 Co-Autorenschaft: PT-MV-Reduktion

Trotz stetiger Verbesserungen der multimodalen Therapie von Patienten mit inoperablem NSCLC im UICC-Stadium III kommt es bei der Mehrheit der Patienten innerhalb der ersten zwei Jahre nach Primärtherapie zu einem lokalen Rezidiv oder neuen Fernmetastasen [95, 123, 180, 181]. Deshalb ist eine engmaschige klinische und bildgebende Nachsorge unerlässlich, damit Rezidive oder Metastasen frühzeitig, und somit besser therapierbar, entdeckt werden können [182–187].

Eine zunehmende Bedeutung wird in der Nachsorge inoperabler NSCLC-Patienten im UICC Stadium III, nach Abschluss einer multimodalen Behandlung, dem FDG-PET/CT beigemessen, da es, vor allem im Vergleich zur prätherapeutischen FDG-PET/CT-Bildgebung, eine sehr sensitive Detektion möglicher Lokalrezidive und Fernmetastasen erlaubt [57, 58]. Dabei ist ein relativ neuer Ansatz die Bestimmung des sogenannten metabolischen Tumorvolumens (PT-MV) und dessen posttherapeutische Auswertung [188–190]. In der Arbeit “How much primary tumor metabolic volume reduction is required to improve outcome in stage III NSCLC after chemoradiotherapy? A single-centre experience.“ [191] haben wir deshalb den Einfluss der Reduktion des PT-MV zwischen einem prä- und post-therapeutisch angefertigten PET/CT auf das mediane Gesamtüberleben der Patienten analysiert. Die Datenakquirierung und -auswertung wurden dabei teilweise von mir durchgeführt, sowie Teile der Manuskripterstellung und -bearbeitung.

3. Zusammenfassung der Publikationen

3.1 Deutsche Zusammenfassung

Die Publikationen basieren auf der retrospektiven Analyse von Patienten mit inoperablem NSCLC im UICC-Stadium III, die an unserem Zentrum mit einer definitiven Radiochemotherapie bis Ende 2016 behandelt wurden.

In der Arbeit „Survival score to characterize prognosis in inoperable stage III NSCLC after chemoradiotherapy" haben wir zunächst eine univariante und multivariante Analyse des Einflusses grundlegender prätherapeutischer Patienten- und Erkrankungsdaten in Hinblick auf das Gesamtüberleben der 99 multimodal behandelten Patienten, mit gutem ECOG PS, durchgeführt. Dabei stellten sich Alter (p=0,020), Geschlecht (p=0,007), Dauer des Tabakkonsums in Packungsjahren (p=0,015), tumorassoziierte Atelektase (p=0,004) und Tumorhistologie (p=0,004) als signifikante Parameter heraus. Um einen einfachen Score zu erstellen, wurden diese fünf Faktoren mit jeweils einem Punkt gewichtet, addiert und anschließend in Gruppen mit niedrigem (0-1 Punkte), mittlerem (2-3 Punkte) und hohem (4-5 Punkte) Risiko unterteilt. Es zeigte sich ein signifikant unterschiedliches Überleben zwischen den Untergruppen (p<0.001) mit 1-, 2- und 3-Jahres-Überlebensraten von 100%, 83% und 67% in der niedrigen, 80%, 47% und 24% in der mittleren und 57%, 25% und 18% in der Hochrisikogruppe. Dieses Ergebnis haben wir anschließend in einer prospektiven Patientenkohorte, behandelt zwischen Anfang 2017 und Ende 2018, validiert. Somit wurde ein einfach anwendbarer Prognosescore für Patienten mit NSCLC im UICC-Stadium III vor definitiver Radiochemotherapie erstellt.

In der Arbeit „How much primary tumor metabolic volume reduction is required to improve outcome in stage III NSCLC after chemoradiotherapy? A single-centre experience" haben wir in derselben Kohorte alle 60 Patienten analysiert, die ein PET/CT vor Behandlungsbeginn und sechs Wochen nach Ende der Radiochemotherapie erhalten haben. Es wurden das PT-MV vor und nach der Behandlung verglichen und fünf Untergruppen gebildet: Komplettes Ansprechen (100% PT-MV Reduktion); überwiegendes Ansprechen (80–99% PT-MV Reduktion); moderates Ansprechen (50–79% PT-MV Reduktion); geringes Ansprechen (1–49% PT-MV Reduktion) und Nicht-Ansprechen (keine Veränderung oder Ansteigen des Uptakes). 52 Patienten konnten in die Auswertung eingeschlossen werden (87%). 17 % zeigten ein komplettes, 27% ein überwiegendes, 25% ein moderates, 7% ein geringes Ansprechen und 12% ein Nicht-Ansprechen. Das mediane Gesamtüberleben war 34, 22, 12, 11 und 17 Monate bei Patienten mit komplettem, überwiegendem, moderatem, geringem und Nicht-Ansprechen (p=0,008). In der multivariaten Analyse zeigte sich eine PT-MV Reduktion von mindestens 80% (überwiegendes und komplettes Ansprechen) als ein signifikanter Prädiktor des Gesamtüberlebens (p=0,021; HR 0,36; 95% CI: 0,15 – 0,86).

Insgesamt haben wir somit zwei Verfahren zur genaueren Prognosestellung von NSCLC Patienten im inoperablem UICC-Stadium III entwickelt: Zum einen den Vergleich von PT-MV vor und nach Radiochemotherapie, zur Abschätzung des posttherapeutischen Überlebens. Zum anderen einen einfach vor Therapiebeginn erfassbaren und einfach anwendbaren Score. Diese

Verfahren können in Zukunft Ärzten bei der klinischen Entscheidungsfindung und Therapieplanung bzw. Nachsorgeplanung und posttherapeutischer Überwachung der Patienten helfen.

3.2 Englische Zusammenfassung / summary

The studies are based on retrospective analysis of patients' data treated with definitive chemoradiation at our tertiary cancer centre until the end of 2016 for inoperable UICC stage III NSCLC.

In "Survival score to characterize prognosis in inoperable stage III NSCLC after chemoradiotherapy" we at first performed univariate and multivariate analysis on the influence of basic patient- and tumor-related factors for their impact on overall survival. The data of 99 consecutive patients with performance status ECOG 0–1 was evaluated. Age (P=0.020), gender (P=0.007), pack years (P=0.015), tumor-associated atelectasis (P=0.004) and histology (P=0.004) had a significant impact on overall survival. To create an easy calculatable score, these five factors were scored with one point each, added and then divided into a low (0–1 points), intermediate (2–3 points) and high-risk (4–5 points) subgroup. There was a significant difference in each subgroups survival with1-, 2- and 3-year survival rates were 100%, 83% and 67% in the low, 80%, 47% and 24% intermediate and 57%, 25% and 18% high-risk patients, respectively (P<0.001). The results were then validated in the prospective cohort with 45 patients, treated between 2017 and 2018. An easy-to-use score for inoperable UICC stage III NSCLC patients, prior to receiving multimodal therapy, was created.

In the study "How much primary tumor metabolic volume reduction is required to improve outcome in stage III NSCLC after chemoradiotherapy? A single-centre experience", we analysed data of 60 Patients which had PET/CT scan prior to the start of and 6 weeks after the final day of chemoradiotherapy. PT-MV before and after therapy were compared and divided into five subgroups: complete response (100% PT-MV reduction); major response (80–99% PT-MV reduction); moderate response (50–79% PT-MV reduction); minor response (1–49% PT-MV reduction) and non-response (no change or increase in uptake). Fifty-two patients were included in the analysis (87%). Complete metabolic response was reached in 17%, major response in 27%, moderate responses 25% and minor response in 7%, whereas non-response was documented in 12%. The median overall survival was 34, 22, 12, 11 and 17 months in patients with complete, major, moderate, minor and non-response, respectively (p = 0.008). On multivariate analysis a PT-MV reduction of at least 80% (complete and major metabolic response) was a significant predictor of overall survival (p=0.021, HR 0.36, 95% CI: 0.15–0.86).

Altogether we have created two methods for better prognostication of patients with irresectable NSCLC of UICC stage III: On one hand the comparison of PT-MV before and after chemoradiation to predict post-therapeutic survival. And on the other hand, an easy to adopt pre-therapeutic survival score. Those methods may aid physicians to infer patient clinical outcomes and optimize everyday decision-making for treatment planning, as well as for planning of aftercare and follow-up examinations.

4. Veröffentlichung I

Original Article

Survival score to characterize prognosis in inoperable stage III NSCLC after chemoradiotherapy

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Background: Stage III non-small cell lung cancer (NSCLC) represents a heterogeneous disease regarding principal patient- and tumor characteristics. A simple score may aid in personalizing multimodal therapy.

Methods: The data of 99 consecutive patients with performance status ECOG 0–1 treated until the end of 2016 with multimodal approach for inoperable NSCLC (UICC 7th edition stage IIIA/B) were evaluated. Patient- and tumor-related factors were examined for their impact on overall survival. Factors showing a negative association with prognosis were then included in the score. Three subgroups with low, intermediate and high-risk score were defined. The results were then validated in the prospective cohort, which includes 45 patients.

Results: Most Patients were treated with concurrent (78%) or sequential (11%) chemoradiotherapy. 53% received induction chemotherapy. Median survival for the entire cohort was 20.8 (range: 15.3–26.3) months. Age (P=0.020), gender (P=0.007), pack years (P=0.015), tumor-associated atelectasis (P=0.004) and histology (P=0.004) had a significant impact on overall survival and were scored with one point each. Twelve, 59 and 28 patients were defined to have a low (0–1 points), intermediate (2–3 points) and high-risk (4–5 points) score. Median survival, 1-, 2- and 3-year survival rates were not reached, 100%, 83% and 67% in the low, 22.9 months, 80%, 47% and 24% intermediate and 13.7 months, 57%, 25% and 18% high-risk patients, respectively (P<0.001). Median survival was not reached in prospective cohort; analysis has revealed a trend for the 1-year survival rates with 100% for the low, 93% intermediate and 69% high-risk patients (P=0.100).

Conclusions: The score demonstrated remarkable survival differences in inoperable stage III NSCLC patients with good performance status receiving multimodal therapy.

Keywords: Non-small cell lung cancer (NSCLC); survival-score; prognostic factors; multimodal therapy

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, accounting for 19.4% of all cancer-related deaths (1,2). In 2012, lung cancer resulted in 1.6 million deaths worldwide (3), making it the leading cause of cancer-related death for men and second leading for women worldwide and in Germany with a rising tendency (4).

Up to date, treatment algorithm for patients with non-small cell lung cancer (NSCLC) depend on patients' general condition and tumor stage. Patients with locally-advanced

NSCLC are treated with cost-intensive multimodal therapy consisting of chemotherapy, thoracic irradiation, surgery and checkpoint inhibition (5-12). Stage III NSCLC is a very heterogeneous disease regarding principal patient characteristics such as age, gender, comorbidities and tumor features like histology, localization, tumor dimensions and specificity of lymph node involvement. Furthermore, a multimodal approach can be burdensome and may lead to deterioration of patients' general condition, because of potential hematological and non-hematological toxicity (13,14). Historically, survival of inoperable stage III NSCLC after multimodal approach shows a significant variety (15,16). All of these factors considered, tailored multimodal therapy should be considered the next step for locally-advanced NSCLC.

Physician decision-making may be facilitated by using different prognostic scores (17). Alexander *et al.* recently proposed the "Lung Cancer Prognostic Index" (LCPI), considering different tumor stages and including established and novel factors for the prediction of survival after NSCLC diagnosis (18). The LCPI was defined by 9 variables with different point allocations resulting in a total of 28 points that ultimately classifies the patients into four risk groups. For incurable patients, a more simplistic approach is defined by the Montreal prognostic score depending on clinical biomarkers (19) or the score proposed by Rades *et al.* for patients receiving palliative irradiation (20).

Our study, however, was dedicated to scale heterogeneity in inoperable stage III NSCLC patients with good PS ECOG 0–1 treated with chemoradiotherapy in curative intent and develop a simple heterogeneity score which can be easily adopted in clinical routine.

Methods

Patients

Data were collected on a total of 99 consecutive patients treated with curative-intent multimodal treatment for UICC 7th edition stage IIIA/B NSCLC. All patients gave their informed consent to treatment and the use of acquired data for research purposes. There was ethical committee approval to analyze and publish the patients' data.

All patients were treated at a single tertiary cancer center. Pre-treatment evaluation included: patients' history i.e. tobacco consumption, ECOG PS and comorbidities, pulmonary function testing, radiographic imaging including computed tomography (CT) for all patients and positron emission tomography (PET)-CT in 94% of patients, routine blood work to assess kidney, liver function and blood cell count. Cranial contrast-enhanced MRI was performed in 28 patients before the start of multimodal treatment, all other patients received contrast-enhanced head CT.

Tumor histology was obtained via transbronchial biopsy in 80 patients, via CT-guided-biopsy in 9 patients and with mediastinoscopy in 10 patients. Histological or cytological confirmation of nodal involvement was performed in 67 patients.

Treatment was then discussed and planned in multidisciplinary tumor boards, where all patients tumors were initially classified as inoperable by experienced thoracic surgeons. Therapeutic approach was than discussed with each individual patient.

Patients with initial performance status ECOG >1, recurrent disease or with another neoplasia at initial diagnosis were excluded. Also, we excluded patients who underwent surgery before irradiation as well as those who received SABR or hypofractionated radiotherapy and those treated with primary palliative intent. All patients had follow-up data available until July 2018.

Validation of the score was performed in our own prospective patient cohort with same characteristics as above-mentioned retrospective cohort. To be comparable, the cohort consists of 45 consecutive Patients treated from 01.01.2017 until the implementation of adjuvant durvalumab therapy in our institution.

Multimodal approach

Treatment was planned and delivered at a single tertiary cancer center. Radiation planning and delivery were done while patients were supine, with their arms positioned overhead in WingSTEP™ (Innovative Technologie Völp, Innsbruck, Austria), based on PET-CT in treatment position and conventional Planning-CT-scans. The gross tumor volume (GTV) was defined as the primary tumor and any regionally involved nodes either positive on pre-treatment PET-CT or >1 cm short axis on conventional CT. In patients receiving induction chemotherapy, only residual tumor volume was contoured. A margin of 5–6 mm in all dimensions was added to the GTV to generate the clinical target volume (CTV) taking into consideration anatomical borders and organs at risk. The planning target volume (PTV) margin was 6–8 mm

beyond the CTV. Three-dimensional (3D) conformal radiotherapy was delivered to the primary tumor and involved lymph nodes to a median total dose of 66 Gy. Elective nodal irradiation (ENI) included directly adjacent nodal stations and was delivered to a total dose of 45–54 Gy in 85% of patients. Radiotherapy was delivered on a Linear accelerator (LINAC) with megavoltage capability (6–15 MV) using 3D-CRT in 60% of patients and Intensity-modulated radiotherapy (IMRT) in 40% of patients. Image-guidance was performed with cone-beam CT two or three times a week. All plans were reviewed by several radiation oncologists for quality assurance and appropriateness of treatment.

Patient follow-up

Median follow up for the entire cohort achieved 17.2 months (range, 2.2–92.1 months). For the first 2 years after therapy, all patients underwent CT or PET-CT scans, routine blood works, lung function testing and clinical examination every 3 months and afterwards twice a year. Cranial contrast-enhanced MRI and bone-scintigraphy were performed if clinically indicated. Treatment-related toxicity was graded retrospectively, according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.

Local and loco-regional progression (LP) and new distant metastases (DM) were documented with CT, PET-CT and MRI scans. Histological or cytological verification of progressive disease was not obligatory. Event free survival was calculated as the time until LP, DM or death from the first day of radiation therapy. Overall survival (OS) was calculated from the date of initial diagnosis.

Treatments of recurrent and/or progressive disease were tracked in the database.

Statistical analysis

All statistics were performed with IBM SPSS version 25. Survival curves were estimated with the Kaplan-Meier method. A variety of potential patient- and tumor-associated prognostic factors were analyzed. Cut-offs for non-binary factors were defined by trial and error only using round numbers. Impact on OS was calculated by univariate analysis using Log-rank test. Factors showing a significant negative association with patient prognosis ($P<0.05$) were included in the score and all scored with one point each, to keep the score simple. Furthermore, multivariate analysis using Cox-regression was performed with the predictors significant on univariate analysis. Three prognostic subgroups with low (0–1 points), intermediate (2–3 points) and high (4–5 points) risk score were defined and compared using the Kaplan-Meier method for survival analysis and Kruskal-Wallis-Test for patient-, tumor- and treatment characteristics.

Results

Patient- and tumor characteristics

A summary of patient and tumor characteristics is shown in *Table 1*.

The majority (63%) were males, median age at diagnosis was 67.4 years (range: 43–88 years). ECOG-PS before treatment was 0 in 48 patients and 1 in 51 patients. More patients had stage IIIB (UICC 7th edition) disease (56%), an absolute majority had T-stage 3 (30%) or 4 (40%) and N-stage 2 (36%) or 3 (44%). Median tobacco consumption was 40 PY, 39% suffered from COPD and 9% of patients were never smokers.

Squamous cell carcinoma (SCC) was diagnosed in 42% of patients, adenocarcinoma in 50% and not otherwise specified (NOS) in 8% at initial diagnosis.

Multimodal treatment characteristics

A summary of the multimodal approach characteristics is listed in *Table 2*.

The absolute majority of patients were treated with conventional concurrent chemoradiotherapy (CRT) to a total dose ≥60 Gy (68%). Ten percent of patients were treated with radiotherapy alone, because of poor kidney function or rejection of chemotherapy. Eleven percent were treated in the sequential mode, because they were not feasible for concurrent after induction chemotherapy. Fifty-two percent completed at least one cycle of induction chemotherapy before CRT (standard intentional strategy until mid-2013). The predominant concurrent chemotherapy regimen consisted of cisplatin given intravenously 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 4 weeks for two courses (46% of patients). Median time to CRT start was 2.5 months (range, 0.07–12.22 months). CRT was completed as planned by 95% of the patients with a median total dose of 66 Gy (range, 45–70 Gy). Five patients (5%) could not complete

Table 1 Patient and tumor characteristics

Patient characteristics	All patients	Low risk	Inter-mediate risk	High risk	P value for OS impairment (Log-Rank; Mantel-Cox)
Points in risk score	n=99	n=12	n=59	n=28	<0.001
Mean	2.8	0.75	2.58	4.11	
Range	0–5	0–1	2–3	4–5	
Age, years					
Median	67.4	53.15	66.9	70.6	
Range	43–88	43–78	43–88	61–84	
>60 years	73 (74%)	3 (25%)	42 (71%)	28 (100%)	0.02
Gender					0.007
Male	62 (63%)	3 (25%)	31 (53%)	28 (100%)	
Female	37 (37%)	9 (75%)	28 (47%)	0	
Tobacco consumption					
Median PY	40	15	40	50	
Range	0–150	0–40	0–150	20–90	
≥20 PY	81 (82%)	3 (25%)	50 (85%)	28 (100%)	0.015
Atelectasis before RT	10 (10%)	0 (0%)	7 (12%)	3 (11%)	0.004
Tumor histology					
Non-adenocarcinoma	50 (51%)	0 (0%)	22 (37%)	28 (100%)	0.011
Adenocarcinoma	49 (49%)	12 (100%)	37 (63%)	0 (0%)	
Squamous cell carcinoma (SCC)	42 (42%)	0 (0%)	18 (31%)	24 (86%)	
Not otherwise specified (NOS)	8 (8%)	0 (0%)	4 (7%)	4 (14%)	
ECOG performance status					
0	48 (48%)	9 (75%)	34 (58%)	5 (18%)	0.134
1	51 (52%)	3 (25%)	25 (42%)	23 (82%)	
UICC stage IIIB	55 (56%)	6 (50%)	33 (56%)	16 (57%)	0.23
T-stage					0.737 (T1–3 *vs.* T4)
Unknown	2 (2%)	1 (8%)	1 (2%)	0 (0%)	
1	10 (10%)	1 (8%)	6 (10%)	3 (11%)	
2	17 (17%)	2 (17%)	10 (17%)	5 (18%)	
3	30 (30%)	3 (25%)	20 (34%)	7 (25%)	
4	40 (40%)	5 (42%)	22 (37%)	13 (46%)	
N-stage					0.35 (N0–2 *vs.* N3)
0	10 (10%)	2 (17%)	5 (8%)	3 (11%)	
1	9 (9%)	1 (8%)	6 (10%)	2 (7%)	
2	36 (36%)	4 (33%)	21 (36%)	11 (39%)	
3	44 (44%)	5 (42%)	27 (46%)	12 (43%)	
Tumor localisation					0.611
Central	40 (40%)	6 (50%)	19 (32%)	15 (54%)	
Pancoast	7 (7%)	0 (0%)	7 (12%)	0 (0%)	
Lobular	52 (53%)	6 (50%)	33 (56%)	13 (46%)	

Table 2 Treatment characteristics

Treatment characteristics	All patients	Low risk	Inter-mediate risk	High risk	Kruskal-Wallis-test
N	99	12	59	28	
PET-CT					
Before CRT	93 (94%)	12 (100%)	58 (98%)	23 (82%)	0.013
After CRT	35 (35%)	5 (42%)	23 (39%)	7 (25%)	0.422
Gross tumor volume (cm^3)					
Mean	109.9	80.2	108.5	125.2	
Median	85.3	47	86.8	98	0.215
Range	3–434	7–356	3–385	3–434	
Induction chemotherapy	52 (53%)	8 (67%)	31 (53%)	13 (46%)	0.54
Concomitant chemotherapy	77 (78%)	11 (92%)	48 (81%)	18 (64%)	0.097
Platinum-based	67 (68%)	9 (75%)	43 (73%)	15 (53%)	0.281
Radiation technique: IMRT	40 (40%)	3 (25%)	26 (44%)	11 (39%)	0.508
Total dose (Gy)					
Mean	62.4	62.3	62.3	62.4	0.696
Median	66	66	66	62.5	
<54	13 (13%)	2 (17%)	9 (15%)	2 (7%)	
54.01–60	19 (19%)	2 (17%)	7 (12%)	10 (36%)	
60.01–66	58 (59%)	7 (58%)	37 (63%)	14 (50%)	
>66.01	9 (9%)	1 (8%)	6 (10%)	2 (7%)	
RT completed as planned	94 (95%)	12 (100%)	57 (97%)	25 (89%)	0.312

the whole course of radiotherapy. The therapy was stopped at a median of 58 Gy (range, 49–62 Gy) because of severe pneumonia (3 patients), myocardial infarction (1 patient) and Pulmonary embolism (1 patient).

In the first year after CRT, 29 patients (29%) showed complete remission and 47 patients (47%) partial remission in PET-CT or CT scans. During the observed period, 40% of patients received at least one course of salvage chemotherapy, immunotherapy or combined chemo-immunotherapy because of progressive disease. Seven percent of patients underwent planned surgery and 4% salvage surgery after completion of radiotherapy, 31% received salvage radiotherapy because of metastasis or progression.

Toxicity, overall and event free survival

Rates of radiation pneumonitis and esophagitis did not differ significantly in the risk subgroups. During treatment, 50 patients developed acute esophagitis; grade 3 disease was noted only in 4 patients (4%). Radiation pneumonitis occurred in 25 patients after treatment; 4 patients (4%) presented with grade 3 pneumonitis. No grade 4 and 5 non-hematological toxicity occurred (*Table 3*).

Median event-free survival (EFS) (time to local progression, distant metastasis or death) after CRT start was 8.7 months for all patients. Patients' age, gender and tobacco consumption had no impact on EFS with P values of 0.727, 0.195 and 0.150, respectively. Patients with atelectasis had a median EFS of 4.3 months compared to 9.4 months for those without (P=0.028). An inferior median EFS was also observed for SCC and NOS versus patients with adenocarcinoma with 7.8 and 10.8 months, respectively (P=0.018) (panels A to E in *Figure 1*).

Median OS for all patients was 20.8 months [95% confidence interval (CI): 15.3–26.3]. Patients aged 60 years or younger at initial diagnosis (26%) showed a significantly improved OS with median OS of 26.4 *vs.* 19.3 months in the patients aged >60 years, respectively (P=0.020). Female

Table 3 Outcome, adverse events and survival

Outcome	All patients	Low risk	Intermediate risk	High risk
N	99	12	59	28
Overall survival				
Still alive until Jul 01, 2018	20 (20%)	8 (67%)	11 (19%)	1 (4%)
Median OS (months)	20.8	–	22.9	13.7
1-year	75 (75%)	12 (100%)	47 (80%)	16 (57%)
2-year [N=censored]	42 (42%) [1]	10 (83%)	28 (47%) [1]	7 (25%)
3-year [N=censored]	27 (27%) [5]	8 (67%) [2]	14 (24%) [3]	5 (18%)
Response in CT/PET-CT				
Complete remission	29 (29%)	5 (42%)	18 (31%)	6 (24%)
Partial remission	47 (47%)	6 (50%)	28 (48%)	13 (52%)
Progress observed	69 (70%)	9 (75%)	45 (76%)	15 (56%)
Median event-free survival after CRT start (months)	10.3	29.8	9.8	7.9
Radiation pneumonitis	25 (25%)	2 (17%)	18 (31%)	5 (18%)
2	19 (19%)	2 (17%)	13 (22%)	4 (14%)
3	4 (4%)	0 (0%)	3 (5%)	1 (4%)
Radiation esophagitis	50 (51%)	8 (72%)	33 (56%)	9 (32%)
2	31 (31%)	5 (42%)	21 (36%)	5 (18%)
3	6 (6%)	1 (8%)	4 (7%)	1 (4%)

gender (37%) also appeared to be a significant protective prognostic factor with a median OS of 31.4 months *vs.* 16.9 months for men (P=0.007). Patients who had smoked 20 pack years (PY) or more (82%) displayed a significantly worse median OS of 19.1 *vs.* 40.3 months for those with less than 20 PY (P=0.015). Tumor related lung atelectasis before irradiation (10%) was a significant negative predictor for median OS, with 8.8 *vs.* 22.0 months (P=0.004). Significant negative impact on median OS was also detected for SCC and NOS (50%) *vs.* adenocarcinoma (50%) with a median OS of 18.2 *vs.* 27.9 months respectively (P=0.011) (*Figure 2A,B,C,D,E*).

Five factors significant for OS were included in a multivariate analysis: for patients older than 60 years the hazard ratio (HR) was 1.531 (95% CI: 0.862–2.720; P=0.146), for male patients the HR was 1.745 (95% CI: 1.057–2.881; p=0.030), for patients with 20 or more PY of tobacco consumption the HR was 1.841 (95% CI: 0.931–3.640; P=0.079), for atelectasis before CRT HR was 2.359 (95% CI: 1.180–4.717; P=0.015) and for patients with SCC and NOS the HR was 1.326 (95% CI: 0.826–2.128; P=0.243).

Single-center score

All factors showing a significant negative impact on survival on univariate analysis were included in our heterogeneity score and weighted with one point each. Three subgroups were then defined: low risk (0–1 points) with 12 patients, intermediate risk (2–3 points) consisting of 59 patients and 28 patients with high risk (4–5 points).

The principal patient and tumor characteristics such as ECOG-PS, tumor stage and completeness of multimodal therapy did not differ significantly between risk subgroups, according to Kruskal-Wallis-testing (*Table 2*). We only found significantly more PET-CT based CRT-planning in our low and intermediate risk subgroup. Also, there was no difference in the rates of radiation pneumonitis and esophagitis between the subgroups.

EFS after the first day of CRT (including DM, LP or death) was 29.8 months (95% CI: 23.8–62.3), 9.8 months (95% CI: 11.1–20.1) and 7.9 months (95% CI: 9.2–23.3) for the low, intermediate and high-risk subgroup respectively (P=0.036) (*Figure 1F*).

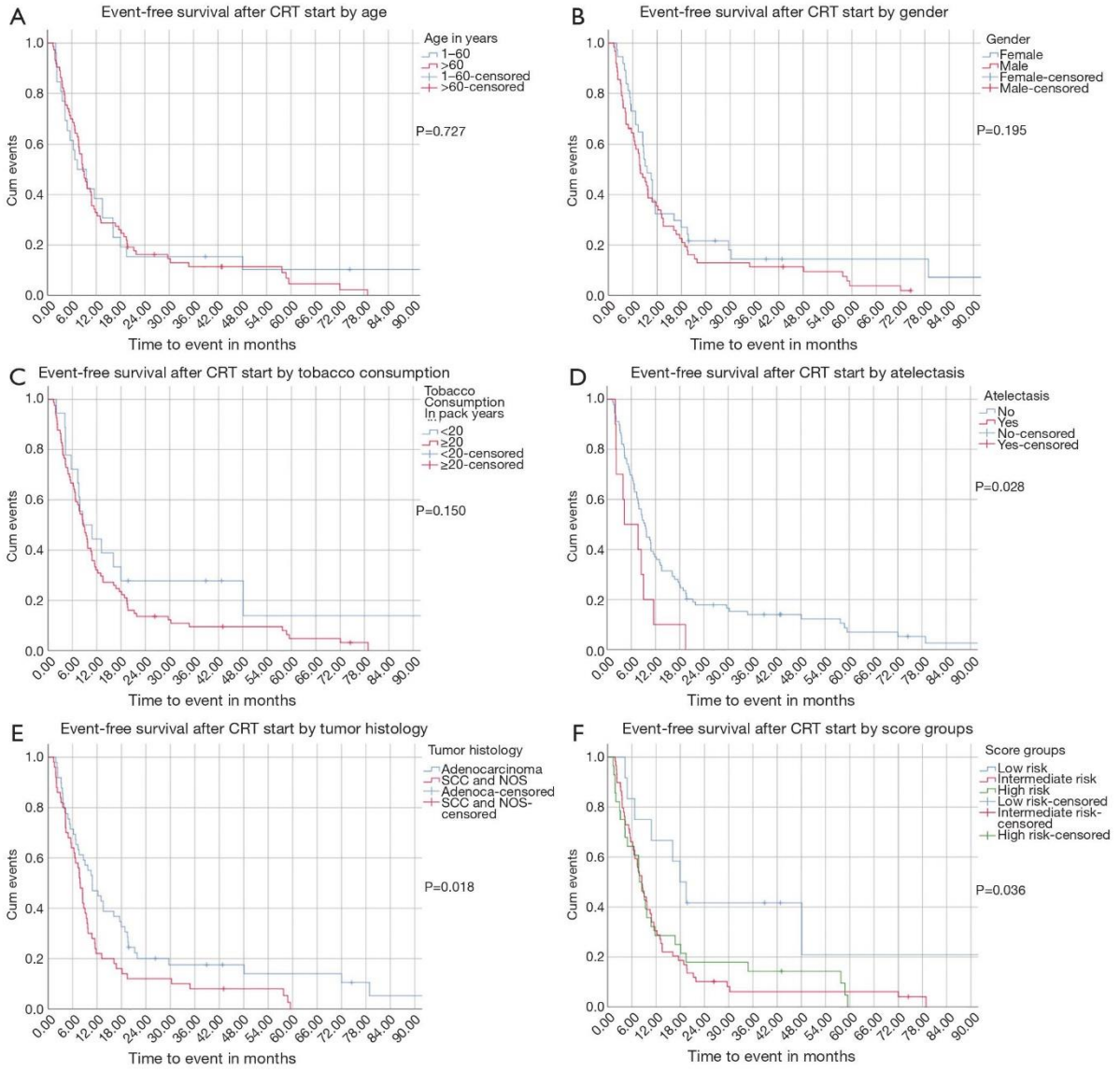

Figure 1 Event-free survival (EFS) by (A) age, (B) gender, (C) tobacco consumption, (D) atelectasis, (E) tumor histology, (F) score groups.

Median OS was not yet reached at the end of surveillance in our low risk subgroup, 1-year survival was 100%, 2-year survival was 83% and 3-year survival was 67%. For the intermediate risk subgroup, median OS was 22.9 months (95% CI: 16.3–29.5), 1-year survival was 95%, 2-year survival was 80% and 3-year survival was 24%.

In the high-risk subgroup, median OS was 13.7 months, 1-year survival was 57%, 2-year survival was 25% and 3-year survival was 18% (Log rank: P<0.001) (*Table 3*; *Figure 2F*).

Calculated with Cox regression the HR compared to all patients for the intermediate risk group was near the baseline (1.079). The HR for the low risk subgroup was 2.129 (95% CI: 1.331–3.405; P=0.002). In the low risk subgroup, the HR was 0.184 (95% CI: 0.067–0.511; P=0.001).

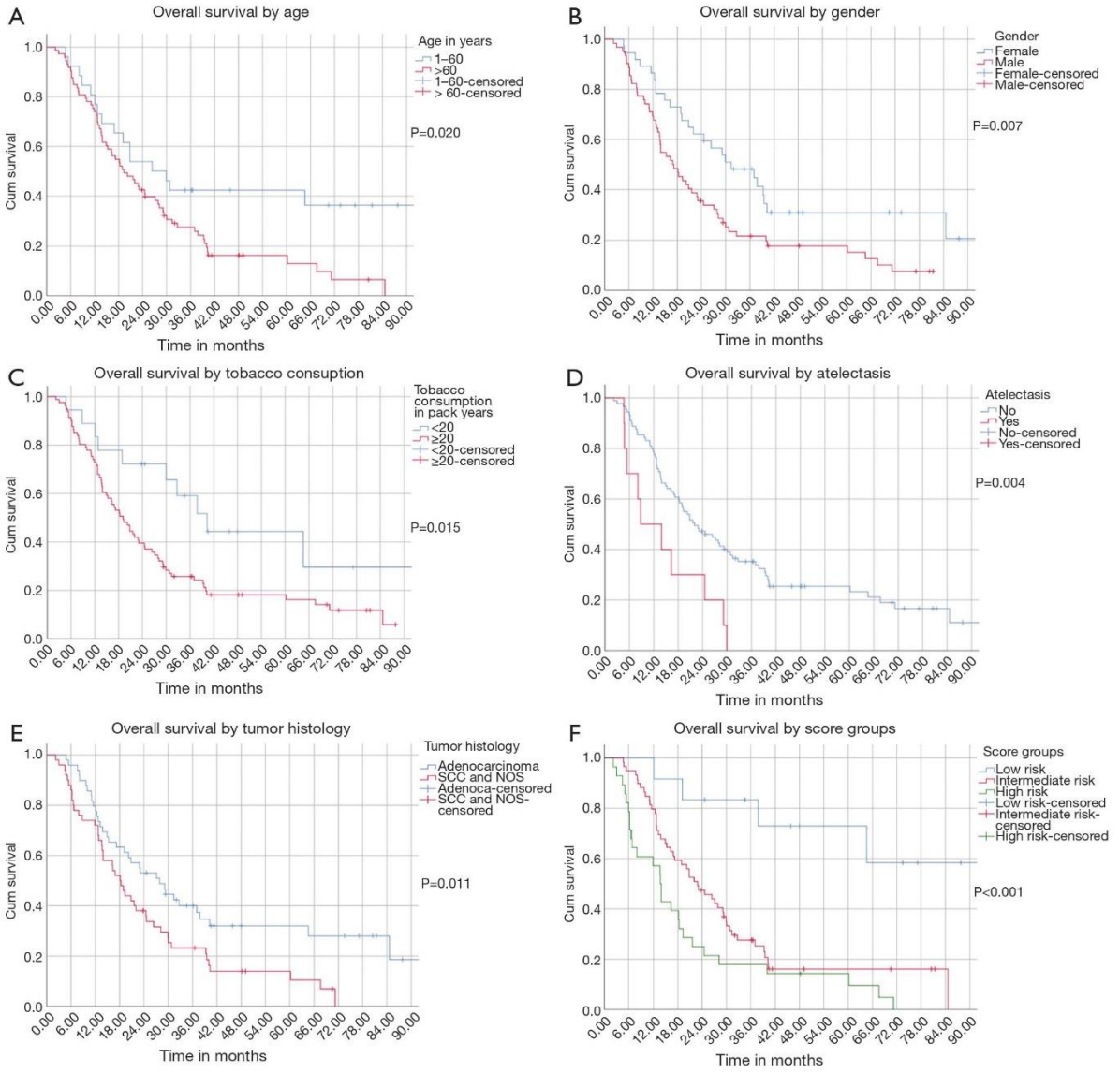

Figure 2 Overall survival (OS) by (A) age, (B) gender, (C) tobacco consumption, (D) atelectasis, (E) tumor histology, (F) score groups.

Validation in own prospective cohort

Median overall survival was not reached in the prospective validation cohort, median follow-up was 18 months (range: 5–30 months). Tumor related atelectasis was diagnosed in 11 (24%) of patients. One-year survival was 45% for them compared to 96% for patients without atelectasis (P=0.003). The majority of 76% were male patients, 1-year survival was 78% for male and 100% for female patients (P=0.064). Sixty-four percent of patients were older than 60 years at initial diagnosis with no difference in 1-year survival observed compared to those younger (P=0.999). The majority of 34 (76%) patients had smoked more than 20 PY, 1-year survival was 83% *vs.* 89% for those with less than 20 PY (P=0.518). For SCC and NOS (19 patients; 64%) *vs.* Adenocarcinoma (16 patients; 36%) no significant

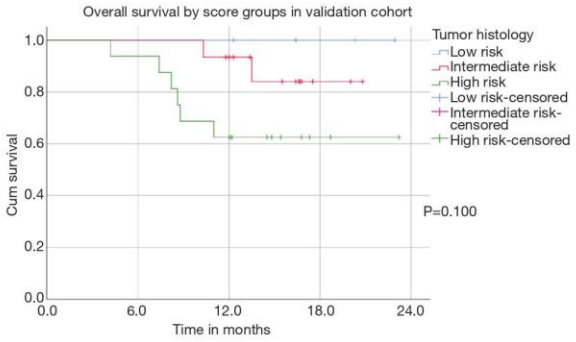

Figure 3 Overall survival in the validation cohort by score groups.

differences in 1-year survival could be detected wit 81% *vs.* 92% respectively (P=0.598).

According to the score four (11%) patients were sorted to the low risk, 15 patients (43%) to the intermediate and 16 (46%) patients to the high risk. One-year survival was 83% for all patients, 100% for the low risk, 94% for the intermediate risk and 70% for the high-risk subgroup (P=0.100). Median EFS after the first day of CRT was 12.6 months for all patients 15.1, 12.2 and 5.9 months for the low, intermediate and high-risk subgroups respectively (P=0.257) (*Figure 3*).

Discussion

In inoperable stage III NSCLC, multimodal therapy will eventually transition from universal approach based on the motto "one size fits all" to the tailoring of treatment algorithm according to principal patient and tumor characteristics. Heterogeneity of stage III disease remains a challenge, has a direct impact on patient prognosis and is responsible for controversial results in prospective studies concerning treatment escalation. The scaling of heterogeneity is necessary to optimize development of multimodal approach regarding radiation dose prescription, consolidation with checkpoint inhibitors etc.

In this study, we report on a simple score for patients with good ECOG-PS and inoperable stage III NSCLC treated with CRT. The score is generated on basis of comprehensive analysis of patient- and tumor-related factors and to be easily applied. The score consists of five basic parameters that will be evaluated before starting multimodal therapy in any case. Therefore, it does not lead to a further delay before start of treatment or accrue costs if applied. We decided to use rounded cut-offs for age and PY, as well as one point for each parameter in the score, to keep it easy to calculate and usable in clinical routine.

Defined low, intermediate and high-risk subgroups demonstrated remarkable differences in event-free and overall survival even though there were no significant differences according to ECOG-PS, tumor stage and applied multimodal treatment. Patients with inoperable stage III NSCLC and a low-risk had an excellent prognosis with estimated 2- and 3-year survival rates of 83% and 67%, respectively. In contrast, outcome in the high-risk patients was dismal despite adequate therapy with a median survival of 13.7 months and 2-/3-year survival rates of only 25% and 18%. A prospective score validation with 1 year of follow-up and 45 patients did deliver a trend for differing survival between the risk subgroups. One-year survival ranged from 70% in the high to 100% in the low risk patients.

Importantly, patients included in the present analysis were treated at a high-volume tertiary cancer center. All diagnostic procedures including pathology and comprehensive imaging were performed at the same institution. There was a very high rate of initial ^{18}F-FDG PET/CT (94%) in the analyzed cohort. In all cases, the decision to treat with CRT was confirmed by a multidisciplinary tumor-board.

The provided score has demonstrated how different patient prognosis in inoperable stage III NSCLC treated with multimodal approach could be. The event-free and overall survival in the low-risk subgroup was significantly better compared to historical data reported in the RTOG 0617 (21), GILT (22) and PROCLAIM (23) trials. Furthermore, survival of the low-risk subgroup was very similar to the data reported by Eberhardt *et al.* in the ESPATUE trial (24). However, multimodal approach in the ESPATUE was more intensive and included obligatory induction chemotherapy and accelerated radiation treatment protocol. Correspondingly, the rate of non-hematological severe toxicity was significantly higher compared to our present results.

Hallqvist *et al.* recently reported an excellent and similar with our low-risk subgroup survival in the conventional concurrent CRT arm (total dose of 68 Gy) of a randomized phase II study in patients with good PS and inoperable stage III NSCLC (25). The study, however, revealed a highly negative effect of dose escalation (up to 84 Gy) on patient survival in the experimental arm and was prematurely terminated.

Additionally, the achieved survival in our low-risk subgroup is in accordance with recently reported data from

Dieleman *et al.* in stage III patients with ECOG 0–2 treated with concurrent daily low-dose cisplatin and moderate hypofractionated (2.75 Gy per fraction to total dose of 66 Gy) thoracic irradiation (26). The authors stated that the treated population consisted of fit patients but exact data on ECOG-PS was missing. The reported rates of severe toxicity, first of all esophagitis were higher compared to our results. Iqbal *et al.* are following a similar approach with moderate hypofractionation concurrent CRT (55 Gy in 20 daily fractions concurrently with split-dose cisplatin vinorelbine chemotherapy) with promising results but slightly increased toxicity (27).

In contrast, conventional multimodal approach in patients with intermediate and, especially, high-risk needs further improvements. Whilst achieved survival for the intermediate risk cohort was principally in accordance with historical results, prognosis of the high-risk patients was very poor and more comparable with prognosis usually seen in metastatic disease. Patients with a high-risk score therefore represent the most challenging subgroup. Accumulation of patient- and treatment-related risk factors impede intensification of multimodal therapy.

In 1999, Movsas *et al.* has already reported on a potential negative survival impact of tumor histology and patient age based on the analysis of six prospective RTOG studies dedicated to treatment intensification (28). Analysis of 491 stage IIIA–B NSCLC patients treated with concurrent chemoradiation therapy published by Zhou *et al.* also revealed squamous cell histology as a strong local failure predictor (29).

This data suggests that patients with a high-risk score can benefit from a change of treatment paradigm, for example from conventionally fractionated thoracic irradiation to moderate hypofractionated concepts applied concurrently with chemotherapy.

Data reported from Dielemann *et al.* for patients treated concurrently with low-dose cisplatin and moderate hypofractionated thoracic irradiation seemed promising (26). The next step could also be the integration of checkpoint inhibition in the multimodal approach to moderate tumor immune surveillance, perhaps to further improve survival of intermediate or low risk patients. The pilot study of neo-adjuvant PD1-inhibition with nivolumab in resectable NSCLC was very promising with a major pathological response occurring in 45% of resected tumors after only two infusions of nivolumab (30). Initial survival data from the NICOLAS phase II trial investigating feasibility of concurrent chemoradioimmunotherapy with nivolumab in stage III NSCLC patients with ECOG 0–1 are also awaited and can potentially confirm a positive effect of concurrent and consolidation checkpoint inhibition on patient outcome (31). The recently published PACIFIC trial reported a historically best progression-free survival in patients with good PS and inoperable stage III NSCLC treated with CRT followed by consolidation treatment with Durvalumab (32).

It is important to consider the limitations of the present study. The score was based on comprehensive analysis of the follow-up data of 99 consecutive patients with good performance status, who completed initial diagnostic and staging procedures as well as multimodal therapy at a single high-volume university medical center. Hence, the next step will be validation of this heterogeneity score in external independent cohorts.

In summary, we present a simple score for inoperable stage III NSCLC patients with good PS treated with multimodal therapy. This score has identified remarkable overall survival differences after completion of CRT and suggested a need for further tailoring of the multimodal approach. The score has revealed an excellent long-term outcome of the low-risk patients but confirmed that utmost efforts are required to improve OS of patients in the high-risk subgroup.

Conclusions

In the present study we developed a simple score for inoperable stage III NSCLC patients with good performance status receiving CRT. The scaling of heterogeneity in stage III is necessary to further optimize a multimodal treatment.

Defined low, intermediate and high-risk score subgroups demonstrated remarkable differences in event-free and overall survival even though there were no significant differences according to ECOG-PS, tumor stage and applied treatment.

The score may aid physicians to infer patient clinical outcomes and optimize everyday decision-making.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All patients gave express written informed consent. This retrospective analysis is in compliance with the principles of the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of the Ludwig Maximilian University of Munich (No. 17-230). The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

How much primary tumor metabolic volume reduction is required to improve outcome in stage III NSCLC after chemoradiotherapy? A single-centre experience

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Abstract

Purpose We analysed a correlation between pre- to post-treatment primary tumour metabolic volume (PT-MV) reduction on 18F-FDG-PET/CT and survival in non-small cell lung cancer (NSCLC) patients treated with chemoradiotherapy (CRT).

Methods Sixty consecutive patients with NSCLC stage IIIA-B (UICC 7th edition), treated with chemoradiotherapy, who underwent 18F-FDG-PET/CT at the same institution before and 6 weeks after treatment, were analysed. Different metabolic response values were investigated on their correlation with survival parameters: complete response (100% PT-MV reduction); major response (80–99% PT-MV reduction); moderate response (50–79% PT-MV reduction); minor response (1–49% PT-MV reduction) and non-response (no change or increase in uptake).

Results From 60 patients, 52 (87%) had repeat PET/CT scans 6 weeks after completion of CRT. Complete metabolic response (CR) was reached in ten (17%), whereas major and moderate metabolic responses occurred in 16 (27%) and 15 (25%) patients, respectively. Four patients (7%) had minor metabolic response. Non-response was documented in seven patients (12%). Median overall survival (MS) for the entire cohort was 17 months (95% CI: 11.9–22.1 months). MS according to the different metabolic response values was as follows: 34 months (95% CI: 0–84.1); 22 months (95% CI: 14.2–29.8); 12 months (95% CI: 0.4–23.6); 11 months (95% CI: 0.2–21.8) and 17 months in patients with complete, major, moderate, minor and non-response (95% CI: 6.7–27.3), respectively ($p = 0.008$).

Olarn Roengvoraphoj and Chukwuka Eze contributed equally to this work.

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On multivariate analysis, significant predictors of survival included ECOG performance status ($p = 0.035$, HR 0.49, 95% CI: 0.25–0.95) as well as complete and major metabolic response as a continuous variable with PT-MV reduction of at least 80% ($p = 0.021$, HR 0.36, 95% CI: 0.15–0.86). Moderate metabolic response did not correlate with improved outcome ($p = 0.522$).
Conclusions In this homogeneous locally-advanced NSCLC single-centre patient cohort, a PT-MV reduction of at least 80% (complete and major metabolic response) following CRT was necessary to significantly improve patient outcome.

Keywords Chemoradiotherapy · Metabolic response · NSCLC · Primary tumour metabolic volume · Overall survival

Introduction

The standard treatment for inoperable, locally advanced NSCLC is concurrent chemoradiotherapy (CRT) applied with curative intent to a total radiation dose of at least 60 Gy [1]. In NSCLC, 18F-FDG-PET/CT has displaced conventional CT imaging in patient initial staging, treatment monitoring and follow-up [2]. Furthermore, 18F-FDG-PET/CT was also shown to be suitable for exact evaluation of remission status after primary multimodal treatment [3, 4].

Remission status after CRT is an important predictive of survival outcomes [2–4]. Patients with complete remission after CRT have significantly better survival compared to other subgroups [4]. Furthermore, residual metabolic tumour volume after definitive treatment could further determine prognosis [4]. There are various methods to evaluate metabolic remission status on PET/CT using various parameters, e.g., standardised uptake values, total lesion glycolysis (TLG) and metabolic tumour volume (MTV). However, the time to perform the PET/CT scan and the analysed tumour structures (primary tumour and/or lymph node) are variable. Pöttgen et al. analysed a prognostic role of tumour response using percentage of standardised uptake value remaining (%SUV remaining) after induction chemotherapy [5]. Ohri et al. reported that 30-month cumulative incidence rates of local progression were 32% for lesions with residual MTV > 25 cm^3 vs. with 5% for lesions with MTV < 25 cm^3 [6]. Mattoli et al. observed a correlation of SUVmax with overall survival and found that early responders after two cycles of induction chemotherapy had better PFS and OS than early non-responders [7].

Additionally, Wald et al. analysed tumor response assessment by kilo-voltage cone-beam-CT during concurrent CRT and found that higher relative volume loss between fractions 11 and 21 correlated significantly with improved PFS [8]. Our previous analysis demonstrated that pre-treatment PT-MV < 63 cm^3 and post-treatment PT-MV < 25 cm^3, as well as an at least 15% reduction in mid- to post-PT-MV significantly improved OS [4].

The aim of the present single-centre study was to investigate extensively the prognostic value of the pre- to post-treatment PT-MV reduction on 18F-FDG-PET/CT in a homogeneous patient cohort with inoperable stage III NSCLC treated with definitive chemoradiotherapy.

Patients and methods

Patients

Sixty consecutive patients [47 males (78.3%) and 13 females (21.7%)] with histologically confirmed NSCLC stage IIIA/B (UICC 7th Edition) and treated with definitive chemoradiotherapy at our centre, were analysed. Initial staging included bronchoscopy with biopsy, contrast-enhanced MRI of the brain and first 18F-FDG-PET/CT. A second 18F-FDG-PET/CT was performed 6 weeks after CRT. All patients provided written informed consent prior to treatment commencement. Thirty-five patients (58%) were treated in multi-centre clinical trials: nine patients in BROCAT study CTRT 99/97 [9], ten patients in InCoDor [10] and 16 patients in GILT [11]. This single-centre analysis was approved by the institutional review board.

Multimodality treatment

All patients received CRT with curative intent. Forty-one patients (68%) received concurrent CRT, whilst 19 (32%) received sequential CRT. The majority of patients received chemotherapy consisting of cisplatin and navelbine [11]. All patients received CT-based three-dimensional conformal radiotherapy delivered on a linac with megavoltage capability (6–15 MV) using a coplanar multiple field technique. The median applied total dose of thoracic irradiation (TRT) was 66 Gy (range 50–68 Gy). Elective nodal irradiation (ENI) was allowed to a total dose of 45–50 Gy and covered the involved mediastinal and corresponding adjoining lymph drainage stations.

18F-FDG-PET/CT

The 18F-FDG-PET-CT scans were performed prior to thoracic radiotherapy, and 6 weeks following radiotherapy at the same institution. There was no difference in timing of the PET/CT scan for those receiving concurrent vs. sequential CRT. Emission scans were initiated 60 min after intravenous administration of 18F-FDG. After acquisition of PET data, whole body CT scans were acquired after intravenous injection of 120 ml of iodinated contrast. PT-MV was chosen as a

parameter and was generated as per Huang et al. [12]. A threshold of 50% was used for calculating PT-MV. Different values of PT-MV reduction were analysed for correlation with PFS and OS.

Definition of metabolic response values according to the single-centre experience

Complete metabolic response was defined as a 100% reduction of PT-MV. Major metabolic response was documented when 80 to 99% reduction of PT-MV after CRT was achieved. A moderate metabolic response required 50 to 79% reduction of PT-MV. Patients with 1 to 49% PT-MV reduction and stable disease and/or increase in tumor uptake were categorised as minor and metabolic non-responders, respectively (see Table 1). In parallel, PERCIST criteria were also used for response evaluation [13].

Statistics

Statistical analysis was performed using IBM SPSS software version 24 (IBM, New York, USA). The median follow-up was 132 months (range: 46–218 months). Overall and progression-free survival were calculated from the date of initial pathological diagnosis. The estimation was performed using the Kaplan–Meier method and log-rank test. Different patient- and treatment-related parameters, including survival in subgroups according to the achieved metabolic response were compared for statistical significance by the log-rank test. Variables showing significant association ($p < 0.05$, log-rank test) with overall survival end point on univariate analysis were included in a multivariate model.

Table 2 Patient and treatment characteristics

Parameters	N (%)
Sex	
- Male	47 (78.3%)
- Female	13 (21.7%)
Age	
- Mean (range)	62 (50–78)
Histology	
- Adenocarcinoma	20(33.3%)
- Squamous cell carcinoma	32(53.3%)
- Large-cell carcinoma	7(11.7%)
- Not otherwise specified	1(1.7%)
Chemoradiotherapy	
- Sequential	19(31.7%)
- Concurrent	41(68.3%)
Platin-based chemotherapy	
- Yes	53(88.3%)
- No	7(11.7%)
Radiotherapy dose	
- <60 Gy	6(10%)
- 60–66 Gy	37(61.7%)
- >66 Gy	17(28.3%)
18F-FDG-PET/CT	
- Pre-treatment	60(100%)
- Post-treatment	52(56.67%)
Metabolic response after CRT (PT-MV reduction)	
- Complete (100% PT-MV reduction)	10 (16.7%)
- Major (80–99% PT-MV reduction)	16 (26.7%)
- Moderate (50–79% PT-MV reduction)	15 (25%)
- Minor (1–49% PT-MV reduction)	4(6.7%)
- Non-Response (No change, Increase in PT-MV)	7(11.7%)

Results

Patient and treatment characteristics

The patient and treatment characteristic are summarised in Table 2. Of the 60 patients treated, 47 (78%) were men and 13 (22%) were women. The median age was 62 years (range: 50–78). Median performance status according to ECOG for the entire cohort was 1. The percentage of patients with T1, T2, T3, T4 disease were 0 (0%), 6 (10%), 20 (33%), and 34 (57%), respectively, whereas N0, N1, N2 and

Table 1 Metabolic response according to single-centre experience

Metabolic response	According PERCIST	Metabolic response	According to single-centre experience
Complete remission (CR)	100% reduction	Complete metabolic response	100% PT-MV reduction
Partial remission (PR)	>30% reduction	Major metabolic response	80%–99% PT-MV reduction
Stable disease (SD)	Not CR, PR or PD	Moderate metabolic response	50%–79% PT-MV reduction
Progressive disease (PD)	30% increase in uptake	Minor metabolic response	1%–49% PT-MV reduction
		Non-response	No change, Increase in tumour uptake

N3 disease was present in eight (13%), three (5%), 29 (48%) and 20 (33%) patients, respectively. Platinum-based chemotherapy was administered in 53 patients (88%). Seven patients (12%) did not receive platinum-based chemotherapy due to renal failure. The median radiation total dose delivered was 66 Gy (range: 50–68 Gy). Thirty-seven patients (62%) received a total dose in the range of 60–66 Gy, while the rest of the patient cohort received a total dose less than 60 Gy ($n = 6$, 10%) and more than 66 Gy ($n = 17$, 28%), respectively.

Evaluation of PT-MV reduction after chemoradiotherapy

From 60 patients, who underwent 18F-FDG-PET/CT in treatment position prior to therapy, 52 (87%) had repeat PET/CT scans 6 weeks after completion of CRT to evaluate for percentage reduction of PT-MV. Eight patients (13%) did not receive repeat PET/CT scans due to high blood sugar levels or patient's decision to decline repeat imaging. According to single-centre metabolic response values, complete response was reached in ten (16.7%), whereas major and moderate responses occurred in 16 (26.7%) and 15 (25%) patients, respectively. Four patients (6.7%) had minor metabolic remission. Non-response was documented in seven patients (11.7%). There was no significant difference in achieved metabolic response between patients treated within different multicentre trials compared to the rest of the cohort (log-rank test, $p = 0.8$).

According to PERCIST criteria, complete remission was achieved in ten (16.7%) patients. Thirty-one (51.7%) had a partial remission whereas seven (11.7%) and four (6.7%) patients had stable and progressive disease, respectively.

Metabolic response status, progression-free and overall survival

MS for the entire cohort (60 patients) was 17 months (95% CI: 11.9–22.1 months). There was no significant difference in survival between concurrent and sequential CRT (17 vs. 13 months, respectively, $p = 0.87$, log-rank test). However, an OS benefit for patients with ECOG 0–1 compared to ECOG 2 ensued (23 vs. 13 months, respectively, $p = 0.002$, log-rank test).

According to the single-centre metabolic response scale, MS in terms of complete/major/moderate/minor and metabolic non-response subgroups was 34 (95% CI: 0–84.1 months)/22 (95% CI: 14.2–29.8 months)/12 (95% CI: 0.4–23.6 months)/11 (95% CI: 0.2–21.8 months) and 17 (95% CI: 6.7–27.3 months) months, respectively ($p = 0.008$, log-rank test) (Fig. 1). On univariate analysis, complete metabolic response was the best survival predictor ($p = 0.005$, log-rank test); major and moderate metabolic responses also correlated significantly with overall survival with p values of 0.02 and 0.04, respectively. According to PERCIST cut-offs, complete metabolic responders ($n = 10$) with no residual PT-MV after CRT achieved a MS of 34 (95% CI: 0–84 months) vs. 16 months (95% CI: 11–21 months) observed in the rest of the treated cohort ($p = 0.003$, log-rank test). Corresponding survival data in the partial, stable and progressive disease subgroups are shown in Table 3.

Median PFS for the entire cohort was 15 months (95% CI: 8.1–21.9 months). PFS was significantly superior in the complete metabolic responders (51 months) compared to the major (15 months); moderate (18 months); minor (7 months) and metabolic non-responders (8 months), respectively ($p = 0.008$, log-rank test) (Fig. 1). On univariate analysis, complete metabolic response was the only potential predictor of PFS ($p = 0.009$, log-rank test).

A multivariate analysis was performed to evaluate PT-MV reduction after CRT and its association with overall survival. According to the univariate analysis, ECOG status, complete and major metabolic response as a continuous variable and moderate metabolic response were investigated. Significant predictors of overall survival included ECOG 0 ($p = 0.035$, HR 0.49, 95% CI: 0.25–0.95) and PT-MV reduction >80% (complete and major metabolic responders) ($p = 0.021$, HR 0.36, 95% CI: 0.15–0.86–4.31). Moderate metabolic response showed no significant impact on patient outcome ($p = 0.522$, HR 0.75, 95% CI: 0.30–1.83) (see Table 4).

Discussion

The aim of this single-centre study was to analyse extensively the prognostic value of the PT-MV reduction in patients with inoperable stage III NSCLC after CRT. Our main finding was that at least 80% PT-MV reduction (major and complete metabolic response) was required to significantly improve long-term patient outcome. Importantly, patients with complete metabolic response (100% PT-MV reduction) had remarkable prognosis with a 5-year survival rate of 40%. Additionally, the remarkable PFS was reached in this patient subgroup with 3- and 5-year rates of 50 and 42%, respectively.

Concurrent platinum-based CRT to a total dose of at least 60 Gy is an actual treatment standard in inoperable stage III NSCLC [14]. Patients treated with concurrent CRT with curative intent achieve a median survival of 15 to 25 months and a 5-year survival rate of 10 to 25%, respectively [11, 15, 16]. In the last decade, continuous optimisation of multimodal treatment protocols did not lead to significant survival benefit. Based on data from RTOG 0617, dose escalation of TRT still remains questionable [17]. Furthermore, no randomised trial till date has demonstrated improved survival for chemotherapy-based induction and/or consolidation [11, 18,

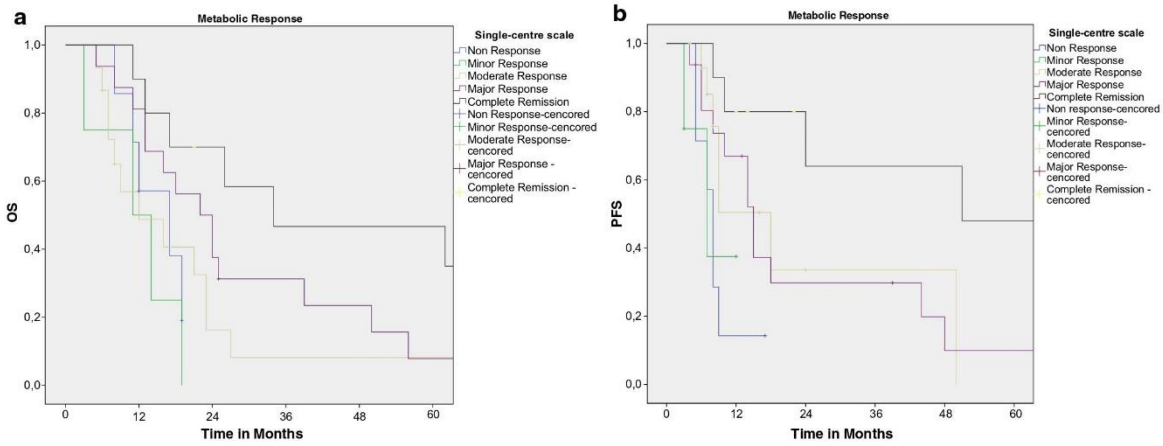

Fig. 1 OS and PFS according to single-centre analysis ($p = 0.008$ and $p = 0.009$, log-rank test)

19]. A recently published phase III study (PACIFIC trial) demonstrated consolidation with the PD-L1 inhibitor durvalumab for 48 weeks after concurrent CRT significantly improved PFS. Overall survival data is still pending and eagerly awaited [20]. Importantly, most patients (98%) in the PACIFIC trial had a substantial macroscopic tumour burden prior to starting consolidation with durvalumab. The subgroup analysis based on achieved remission status per RECIST demonstrated survival benefit in both groups of patients with partial remission and stable disease. Nevertheless, the efficacy of the PD-L1 inhibitor could potentially vary according to the residual tumour status after CRT. This relevant aspect of the PACIFIC trial needs further investigation.

Based on the present data, survival benefit of consolidation therapy in patients with complete metabolic response after CRT may be limited. Our previous analysis has shown that patients with significant residual metabolic tumor (PT-MV >25 cm^3) after CRT had significantly worse outcome compared to complete metabolic responders[4]. Based on this data, we can suppose that patients with major and moderate metabolic responses after CRT could be the best candidates for consolidation treatment with immune checkpoint inhibitors. Based on a previous publication from Huang et al., SUV and MTV changes in the course of multimodal treatment could be considered as imaging predictive markers of treatment response [12]. However, this hypothesis needs further validation in a prospective setting.

Nowadays, there is no eligible predictive imaging marker for comprehensive characterisation of treatment response to immunotherapy in NSCLC. The results of the PACIFIC trial has drawn attention to the fact that new imaging evaluation models in addition to RECIST criteria are necessary for the exact evaluation of the efficacy and duration of immunotherapy, especially in the consolidation setting. Unusual morphological response patterns, including delayed radiographic responses, are often associated with checkpoint inhibitors. PT-MV evaluated at different time points of multimodal treatment could be a plausible imaging candidate for these purposes. Based on our previous analysis, dynamic PT-MV changes during CRT may confer additional information for estimation of the risk of loco-regional progression and personalisation of consolidation therapy according to the achieved metabolic response.

An important aspect of the present study is the fact that achievement of minor to moderate metabolic response after CRT demonstrated no survival benefit compared to metabolic non-response. This finding points out the importance of registration and close analysis of the dynamic PT-MV changes in

Table 3 Median OS PERCIST vs. single-center classification

Metabolic response	Median OS in months (PERCIST) $P = 0.012$, log rank test	Metabolic response	Overall survival (our experience) $P = 0.008$, log rank test
Complete remission	34 months	Complete remission	34 months
Partial remission	18 months	Major response	22 months
Stable disease	14 months	Moderate response	12 months
Progressive disease	12 months	Minor response	11 months
		Non-response	17 months

Table 4 Multivariate Analysis

Parameter	*P* value	Hazard ratio	95% CI
ECOG 0	0.035	0.49	0.25–0.95
PT-MV reduction >80% (complete and major responder)	0.021	0.36	0.15–0.86
Moderate responder (PT-MV reduction 50–79%)	0.522	0.75	0.30–1.83

the course of multimodal treatment which could be considered for possible treatment adaptions. However, a limited number of patients per subgroup could have an impact on the statistical analysis. A large prospective study will be necessary to confirm our current results.

Further limitations of the present study are its retrospective design as well as tumour respiratory motion being a technical limitation of PT-MV assessment. However, a previous systematic review on this topic showed that there are major uncertainties in target volume delineation between 3-D and 4D-PET/CT and the clinical impact of 4D-PET/CT needs further clarification [21].

Conclusion

In this homogeneous locally-advanced NSCLC patient cohort treated with definitive CRT, achievement of complete and major metabolic response (PT-MV reduction of at least 80%) was required to significantly improve long-term patient outcome. This is the principal finding which may have an impact on the design of future prospective studies investigating an efficacy of consolidation treatment.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Disclosure None.

Ethical approval 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 later amendments or comparable ethical standards.

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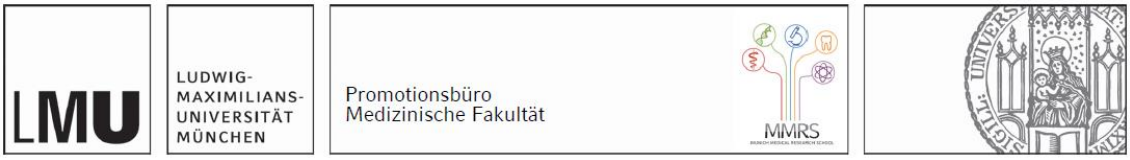
8. Affidavit



Eidesstattliche Versicherung

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Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

„Retrospektive Analyse von Patienten mit einem lokal-fortgeschrittenem nicht-kleinzelligen Lungenkarzinom die von 2006 bis 2016 mit einer primären Radiochemotherapie in der Klinik und Poliklinik für Strahlentherapie und Radioonkologie LMU behandelt wurden“

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München 21.07.2021 Julian Taugner

Ort, Datum Unterschrift Doktorandin bzw.
Doktorand

9. Lebenslauf

Julian Niklas Taugner

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Praktische Tätigkeit

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Weitere Kenntnisse

Sprachen:	English (C1-Niveau)
	Französisch (Grundlagen)

10. Publikationsliste (Stand 01.09.2020)

1. Roengvoraphoj O, Wijaya C, Eze C, Li M, Dantes M, **Taugner J**, Tufman A, Huber RM, Belka C, Manapov F.
   Analysis of primary tumor metabolic volume during chemoradiotherapy in locally advanced non-small cell lung cancer [published correction appears in Strahlenther Onkol. 2018 Mar 14;:]. Analyse des metabolischen Primärtumorvolumens im Verlauf der Radiochemotherapie bei lokal fortgeschrittenem nichtkleinzelligem Lungenkarzinom [published correction appears in Strahlenther Onkol. 2018 Mar 14;:]. *Strahlenther Onkol*. 2018;194(2):107-115. doi:10.1007/s00066-017-1229-3

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   How much primary tumor metabolic volume reduction is required to improve outcome in stage III NSCLC after chemoradiotherapy? A single-centre experience. *Eur J Nucl Med Mol Imaging*. 2018;45(12):2103-2109. doi:10.1007/s00259-018-4063-7

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   Survival score to characterize prognosis in inoperable stage III NSCLC after chemoradiotherapy. *Transl Lung Cancer Res*. 2019;8(5):593-604. doi:10.21037/tlcr.2019.09.19

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8. Gennen K, Käsmann L, **Taugner J**, Eze C, Karin M, Roengvoraphoj O, Neumann J, Tufman A, Orth M, Reu S, Belka C, Manapov F.
   Prognostic value of PD-L1 expression on tumor cells combined with CD8+ TIL density in

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Blood Parameters Demonstrating a Significant Survival Impact in Patients With Locally Advanced NSCLC Undergoing Definitive Chemoradiotherapy. *Anticancer Res*. 2020;40(4):2319-2322. doi:10.21873/anticanres.14198

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Pattern-of-failure and salvage treatment analysis after chemoradiotherapy for inoperable stage III non-small cell lung cancer. *Radiat Oncol*. 2020;15(1):148. Published 2020 Jun 9. doi:10.1186/s13014-020-01590-8

13. Käsmann L, Eze C, **Taugner J**, Roengvoraphoj O, Dantes M, Schmidt-Hegemann NS, Schiopu S, Belka C, Manapov F.
Chemoradioimmunotherapy of inoperable stage III non-small cell lung cancer: immunological rationale and current clinical trials establishing a novel multimodal strategy. *Radiat Oncol*. 2020;15(1):167. Published 2020 Jul 9. doi:10.1186/s13014-020-01595-3

11. Eigenanteil an Publikationen

11.1 Erstautorenschaft: Survival score to characterize prognosis in inoperable stage III NSCLC after chemoradiotherapy

Diese Arbeit wurde nahezu vollständig von mir erstellt: Die Datenerhebung erfolgte zum Großteil durch mich, Hilfe bei der Datenerhebung leisteten die Co-Autoren Kathrin Gennen, Monika Karin und Oleg Petruknov. Die Datenauswertung und Interpretation erfolgte ebenfalls durch mich, dabei standen die Co-Autoren Olarn Roengvoraphoj und Lukas Käsmann beratend zur Seite. Auch die Erstellung des Manuskriptes erfolgte durch mich mit Hilfe von Herrn Maurice Dantes und Chukwuka Eze. Die Co-Autoren Amanda Tufman, Claus Belka und Farkhad Manapov halfen bei der Erstellung der Diskussion und unterstützen mit wissenschaftlichen und konzeptionellen Ratschlägen. Das Lektorat erfolgte durch alle Autoren.

11.2 Co-Autorenschaft: How much primary tumor metabolic volume reduction is required to improve outcome in stage III NSCLC after chemoradiotherapy? A single-centre experience

Diese Arbeit wurde durch Herrn Olarn Roengvoraphoj konzipiert und erstellt. Große Teile der Datenerhebung erfolgten durch mich, zudem unterstützte ich den Erstautor bei der Erstellung des Manuskriptes und bei der Korrektur der finalen Fassung.