Kumulatives Habilitationsprojekt

zur Erlangung der Venia Legendi

für das Fach Strahlentherapie

vorgelegt von

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The evolving role of radiotherapy in the multimodal treatment of lung cancer

Kumulative Habilitationsschrift

zur Erlangung der Venia legendi im Fach

STRAHLENTHERAPIE

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1. List of Abbreviations

3D-CRT	3D conformal radiotherapy
[^{18}F]FDG PET/CT	^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography
ACH1	Achaete-scute homolog 1
ACC	Adenocarcinoma
AHRT	Accelerated hypofractionated radiotherapy
AJCC	American Joint Committee on Cancer
Approx.	Approximately
BED	Biologically effective dose
BM	Brain metastasis
BMFS	Brain-metastasis free survival
BMs	Brain metastases
cc	Cubic centimeter
CCI	Charlson Comorbidity Index
cCRT	Concurrent chemoradiation
CNS	Central nervous system
CT	Computed tomography
CRT	Chemoradiation
CTCAE	Common Terminology Criteria for Adverse Events version 5.0
DCB	Durable clinical benefit
DEGRO	German Society for Radiation Oncology
DLCO-SB	Single-breath diffusing capacity of the lung for carbon monoxide
Dmax	Maximum dose
Dmean	Mean dose
DMFS	Distant metastasis-free survival
ECOG	Eastern Cooperative Oncology Group
ES	Extensive stage
EVx	Percentage of normal esophagus volume receiving x Gy or more [%]
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
Fx/fx	Fraction
Gy	Gray

hypoRT	Hypofractionated radiotherapy
HVx	Percentage of normal heart volume receiving x Gy or more [%]
irAE	immunotherapy-related adverse events
IST	Interval of Simultaneous Treatment
IASLC	International Association for the Study of Lung Cancer
ICI	Immune checkpoint inhibitor
IMRT	Intensity modulated radiotherapy
LC	Local control
LS	Limited stage
LTOT	Long-term oxygen therapy
MED	Mean esophageal dose [Gy]
MHD	Mean heart dose [Gy]
MLD	Mean lung dose [Gy]
mmol/min/kPa	millimoles per minute per kilopascal
MRgRT	MR-guided radiotherapy
MTV	Metabolic tumor volume
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NEUROD1	Neurogenic differentiation 1
NOS	Tumors not otherwise specified
NSCLC	Non-small cell lung cancer
OS	Overall survival
OTT	Overall treatment time
PCI	Prophylactic cranial irradiation
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
POU2F3	POU Class 2 Homeobox 3
PS	Performance status
PT-MV	primary tumor metabolic volume
PTV	Planning target volume
RB	Retinoblastoma protein
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group

RV	Residual volume
SCC	Squamous cell carcinoma
SCLC	Small-cell lung cancer
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results
SoC	Standard of care
SUVmax	Maximum Standardized Uptake Value
TLC	Total lung capacity
TLG	Total lesion glycolysis
tMTV	
TNM	Tumor, node, metastasis
TP53	Tumor protein P53
TRT	Thoracic radiotherapy
TTP	Time to progression
VALSG	Veterans Affairs Lung Study Group
VC	Vital capacity
VMAT	Volumetric modulated arc therapy
Vx	Percentage of normal lung volume receiving x Gy or more [%]
YAP1	yes-associated protein 1

2. Introduction

Lung cancer is the leading cause of cancer mortality worldwide, accounting for more deaths than breast, prostate colorectal, and brain cancers combined. (Siegel et al. 2022) Non-small cell lung cancer (NSCLC) is the most common malignancy of the lung, accounting for approximately 85% of all lung tumors while small-cell lung cancer (SCLC) accounts for about 13% of cases. (Siegel et al. 2022)

In 2020, an estimated 228,820 new cases of lung neoplasms (116,300 in men and 112,520 in women) will be diagnosed in the USA leading to an estimated cancer mortality of 135,720 (72,500 in men and 63,220 in women). (Siegel, Miller, and Jemal 2020)

2.1. Small-cell lung cancer (SCLC)

2.1.1. General aspects

Small-cell lung cancer (SCLC) is an aggressive and highly recalcitrant disease that accounts for about 15% of all bronchogenic carcinomas. Its prevalence has decreased over recent decades due to the introduction of tobacco cessation programs and a decrease in smoking. For untreated patients, the prognosis is dismal in the order of 2-4 months. (Ettinger et al. 2020) At diagnosis, approximately one-third of patients present with limited-stage (LS) disease. Patients with tumors that have spread beyond the supraclavicular region are defined as having extensive-stage disease (ES).

Although SCLC initially responds well to chemotherapy and radiotherapy, there is a high propensity for relapse after first-line treatment including to the central nervous system (CNS) and approximately 10% remain disease-free after 2 years. (Petty and Paz-Ares 2023) At initial diagnosis, >10% of SCLC patients have brain metastases (BMs); >50% will develop BM within 2 years and remarkably BMs are detected in up to 80% of all patients at autopsy. (Manapov et al. 2018)

2.1.2. Pathology

SCLC is a neuroendocrine tumor associated with paraneoplastic syndromes and diagnosis is primarily based on histological appearance by light microscopy, showing dense sheets of small cells with neuroendocrine differentiation. A characteristic feature is necrosis, a substantially elevated mitotic count, and a high proliferation index (Ki67) also indicating rapid cell proliferation and propensity for early metastasis. (Borczuk AC, Chan JKC, Cooper WA, Dacic S, Kerr KM, Lantuejoul S, Marx A, Nicholson AG, Scagliotti GV, Thompson LDR, Travis WD, Tsao MS 2021; Petty and Paz-Ares 2023) Most SCLCs express the neuroendocrine markers CD45, CD56, chromogranin, and synaptophysin; fewer than 10% of SCLCs are negative for all neuroendocrine markers.(Borczuk AC, Chan JKC, Cooper WA, Dacic S, Kerr KM, Lantuejoul S, Marx A, Nicholson AG, Scagliotti GV, Thompson LDR, Travis WD, Tsao MS 2021) In recent years, insights into the biological characteristics and pathophysiology (genomic landscape, transcriptomics, immunologic characteristics) of SCLC have been gained with nearly ubiquitous biallelic inactivation of 2 key tumor suppressor genes described: tumor protein P53 (TP53) in approximately (approx.) 75%-90% of tumors and retinoblastoma protein (RB1) in approx. 60%-90% of tumors. (Petty and Paz-Ares 2023) However, oncogenic driver mutations susceptible to tyrosine kinase inhibitors or most other targeted therapies are lacking. (Gazdar, Bunn, and Minna 2017; Petty and Paz-Ares 2023) Subclassification of SCLC based on the expression of 4 key transcription regulators has been proposed: ASCL1 (Achaete-scute homolog 1)-high (SCLC-A), Neurogenic differentiation 1 (NEUROD1)-high (SCLC-N), POU2F3 (POU Class 2 Homeobox 3)-high (SCLC-P), and YAP1 (yes-associated protein 1)-high (SCLC-Y). (Petty and Paz-Ares 2023)

2.1.3. Prognosis and Survival

Historically, SCLC has been classified according to the Veterans Affairs Lung Study Group (VALSG) into LS-SCLC and ES-SCLC with LS defined as tumors confined to the hemithorax of

origin, the mediastinum, or the supraclavicular regions that could be safely encompassed in a two-dimensional radiation field (Murray et al. 1993; Zelen 1973), whereas the consensus report of the International Association for the Study of Lung Cancer (IASLC) in 1989 proposed a modification of the VALSG classification, recommending LS should constitute all non-metastatic disease stages which correspond to stages I-III, and ES-SCLC corresponds to metastatic or stage IV disease. (Micke et al. 2002; Stahel et al. 1989) In the contemporary era, staging according to the tumor, node, and metastasis (TNM)-staging is recommended. (Goldstraw et al. 2016)

Patients with LS-SCLC have a superior prognosis compared to ES-SCLC. Initial studies had reported a median survival of 16-24 months and a 5-year survival of 14% with the combined-modality treatment comprising chemotherapy, thoracic radiotherapy (TRT), and prophylactic cranial irradiation (PCI). (Ettinger et al. 2020) More recently, slightly improved survival outcomes have been observed with the use of more modern radiotherapy techniques and dose-escalation strategies. (Bogart et al. 2023; Faivre-Finn et al. 2017; Grønberg et al. 2021) Furthermore, the addition of TRT to chemotherapy in LS-SCLC is considered the standard of care (SoC) and associated with an absolute survival benefit of approximately 5% over chemotherapy alone (Ettinger et al. 2020) and the preponderance of evidence in favor of early TRT (with the first or second cycle of chemotherapy). (Ettinger et al. 2020)

PCI has been shown to prevent central nervous system failure in patients with good performance status and favorable response following primary chemoradiation. PCI is still widely considered the standard of care in LS-SCLC. However, this is the subject of more intense debate.

2.1.4. Staging

Staging procedures are essential to discern differences in outcome based on disease confined to the thorax amenable to radiotherapy, chemotherapy, and surgical resection. Initial staging for lung cancer generally consists of

- A thorough physical examination
- Routine blood workup
- A contrast-enhanced computed tomographic (CT) scan of the chest and upper abdomen
- A radionuclide bone scan/bone scintigraphy
- A contrast-enhanced brain magnetic resonance imaging (MRI) scan or CT
- A whole-body ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography - [^{18}F]FDG PET/CT - scan is also widely used as an initial staging tool. In this case, a bone scan can be potentially omitted.

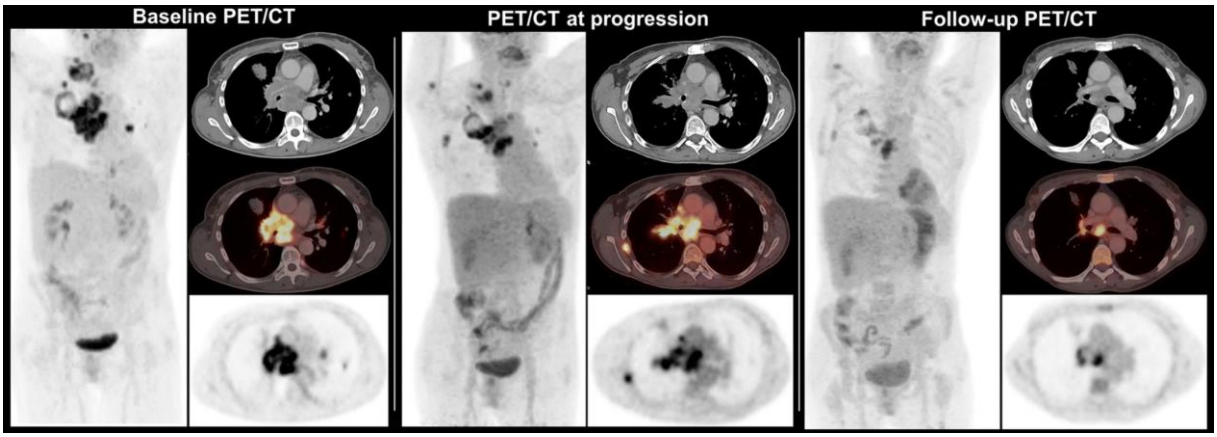


Figure 1: Baseline and follow-up [^{18}F]FDG PET/CT of a 49-year-old patient with lung cancer cT2b cN3 M0 (TNM 8th edition) with progressive disease (rib metastasis) 2 months after initiation of combined systemic therapy (Figure and caption adapted from Eze et al. (Eze et al. 2021))

2.1.5. First-line Treatment overview for LS-SCLC

After extensive workup, surgery as part of a multimodal treatment approach may be considered for patients with stages I-II disease (cT1-2N0). (Dingemans et al. 2021)

Historically, a meta-analysis of trials comparing chemotherapy alone versus chemotherapy combined with TRT in LS-SCLC demonstrated superior outcomes in the combination arm. (Pignon et al. 1992) The landmark Intergroup 0096 study demonstrated significantly improved survival with twice-daily (45 Gy) compared to once-daily TRT (45 Gy) concurrently with cisplatin and etoposide. (Turrisi et al. 1999) However, the open-label phase 3, randomized CONVERT trial demonstrated a numerical improvement in 2-year survival for twice-daily (45 Gy) RT vs. once-daily RT (66 Gy in 33 fractions), 56% vs. 51%. Since the trial was designed to show the superiority of once-daily TRT, the authors concluded that twice-daily TRT remains SoC, but the results suggested that once-daily RT (66 Gy) may be an alternative regimen. More recently, an open-label phase 2 randomized trial demonstrated significantly improved survival with higher-dose twice-daily TRT (60 Gy in 40 fractions) vs. standard-dose twice-daily TRT (45 Gy in 30 fractions). (Grønberg et al. 2021) A further phase 3, randomized North American Study CALGB 30610 (Alliance)/Radiation Therapy Oncology Group (RTOG) 0538 investigated the superiority of once-daily vs. twice-daily TRT. Median survival was 28.5 months vs. 30.1 months in the twice-daily vs. once-daily treatment arm, respectively.(Bogart et al. 2023) Furthermore, the preponderance of evidence favors early TRT (with the first or second cycle of chemotherapy). (Ettinger et al. 2020)

2.1.6. Prophylactic Cranial Irradiation (PCI)

Based on level A1 evidence, PCI is recommended in LS-SCLC patients with good performance status and favorable response after chemoradiation. Patients without extracranial failure have a 50-60% risk of developing CNS failure within 2-3 years after treatment commencement. The risk of brain failure can be halved with the use of PCI. (Aupérin et al. 1999) However, since its proposal for SCLC in 1973 and recommendation in 1999, PCI has been a contentious issue as data emanating from ES-SCLC studies in the contemporary Magnetic resonance imaging (MRI) era and ubiquity of comprehensive brain imaging which

was lacking in previous studies suggest equipoise of PCI and comprehensive brain surveillance. To further clarify this issue, particularly in LS-SCLC, several studies have been initiated. (Chu and Zhu 2023)

3. Overview of manuscripts

3.1 Small cell lung cancer

3.1.1. The evolving role of radiotherapy in the management of small cell lung cancer

Eze C, Roengvoraphoj O, Dantes M, Abdo R, Käsmann L, Schmidt-Hegemann NS, Belka C, Manapov F. Prophylactic Cranial Irradiation for Patients with Small Cell Lung Cancer in Germany: Pattern of Care Survey. Anticancer Res. 2018 Sep;38(9):5261-5265. doi: 10.21873/anticanres.12851. PMID: 30194176. Anticancer Research (IF: 1.865)

Following the controversies regarding PCI, a nationwide survey was conducted to investigate the pattern of care regarding the application of PCI in Germany. Despite its recognized benefits, the use of PCI varies widely due to differing medical practices and guidelines across regions and institutions. The objective of this study was to assess the current patterns of PCI use, identify factors influencing its application, and highlight the variations in practice among healthcare providers in Germany.

To this effect, Radiation oncology institutions in Germany were surveyed via an anonymous online questionnaire sent by e-mail to member institutions of the German Society for Radiation Oncology (DEGRO). The survey included questions about the frequency of PCI use, patient selection criteria, treatment protocols, and perceived barriers to the implementation of PCI. The responses were analyzed to identify trends and discrepancies in the application of PCI. A 29% response rate was achieved. The survey included a substantial number of tertiary referral hospitals in particular academic medical centers (high-volume centers) treating 50-100 lung cancer patients per annum. Most respondents,

in the order of 97%, recommended PCI in LS-SCLC and 67% in ES-SCLC. Eighty-eight percent of all responders recommended a PCI total dose of 30 Gy in 15 fractions (fx). Overall, 11% and 38% of respondents applied PCI simultaneously with chemo- and TRT, respectively. A quarter of respondents offered hippocampal avoidance and routinely performed serial follow-up brain imaging.

The results of the survey revealed significant variations in the use of PCI among different institutions. While some healthcare providers routinely administered PCI to eligible SCLC patients, others were more conservative in their approach. Factors influencing the decision to use PCI included the stage of cancer, the overall health of the patient, and the presence of any contraindications. Additionally, institutional protocols and the availability of resources played a crucial role in determining the frequency and manner of PCI applications.

In conclusion, the study provides valuable insights into the current practices associated with the use of PCI for small-cell lung cancer patients in Germany. By identifying the variations in PCI applications, the research emphasizes the importance of harmonizing standardized guidelines and improving education among healthcare providers. This would help to optimize the use of PCI, thereby improving the outcomes and quality of care for patients with SCLC.

Eze C, Roengvoraphoj O, Manapov F.
Prophylactic Cranial Irradiation in Resected Early-Stage Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2017 Jul 1;98(3):612-614. doi: 10.1016/j.ijrobp.2017.03.002. Epub 2017 Mar 8. PMID: 28581402.
International Journal of Radiation Oncology, Biology, Physics (IF: 5.554)

Eze C, Roengvoraphoj O, Manapov F. Prophylactic Cranial Irradiation in Resected Small Cell Lung Cancer: Comprehensive Staging, Adjuvant Chemotherapy, and Strict Stratification of Pathological Stage Play a Role. J Thorac Oncol. 2017 Sep;12(9):e137-e138. doi: 10.1016/j.jtho.2017.03.021. PMID: 28838711.
J Thorac Oncol (IF: 10.336)

Previous studies have indicated that patients with stage I (T1-2N0M0) SCLC generally experience more favorable outcomes, with 5-year survival rates around 50%. (Schreiber et al. 2010; Yu et al. 2010) According to the National Comprehensive Cancer Network (NCCN) guidelines, surgery should be considered only after thorough staging, including comprehensive brain imaging with MRI and exclusion of lymph node involvement using CT scans, PET-CT scans, or endobronchial ultrasound and/or mediastinoscopy for enlarged nodes. Post-surgery, it is recommended that patients receive 4 cycles of adjuvant chemotherapy based on various analyses. (Ettinger et al. 2020) The only prospective randomized study on this topic focused on limited-disease SCLC, confirming diagnosis via bronchoscopy, thus excluding patients with peripheral nodules and normal bronchoscopy results. In this study, only 19% of participants had clinical stage I disease. Those who responded to 5 cycles of cyclophosphamide, doxorubicin, and vincristine were randomized to either thoracotomy with thoracic and cranial irradiation or to receive only thoracic and cranial irradiation. The study found no survival benefit from pulmonary resection, nor did it affect the pattern of relapse. (Lad et al. 1994)

Further analyses of the Surveillance, Epidemiology, and End Results (SEER) database suggest that surgery, especially lobectomy, might be beneficial for some patients with localized disease. However, these studies are limited by selection bias. (Schreiber et al. 2010; Yu et al. 2010) Therefore, in the absence of randomized studies, the standard treatment remains chemoradiotherapy, except for a select group of patients.

The role of PCI in this subset of patients is also under scrutiny. The NCCN recommends PCI for all patients who have undergone complete resection. (Ettinger et al. 2020) However, the efficacy of PCI in pathologic stage I (p-stage I) SCLC is debated due to reports of relatively low brain relapse rates. While Le Péchoux et al reviewed PCI in lung cancer (Le Péchoux et al. 2016), Knisely et al raised concerns about the interpretation of these findings for p-stage I patients. (Knisely et al. 2016)

A National Cancer Database analysis, which is the largest pooled data analysis on adjuvant treatment after surgery for pT1-2N0M0 SCLC, provides further insights. This analysis included 954 resected

patients who were categorized based on the type of adjuvant therapy they received: 37.1% received chemotherapy alone, 19.9% received chemoradiation, 10.9% received cranial irradiation, and 2.3% received radiation alone. Compared to surgery alone, adjuvant chemotherapy with cranial radiation (hazard ratio, 0.52) or without radiation (hazard ratio, 0.78) showed improved survival. (Yang et al. 2016) However, there are several issues with this analysis. Preoperative T- and N-status were unknown for 45% and 44.1% of patients, respectively, and post-surgery lymph nodes were not examined in 9.5% of cases. Furthermore, the differentiation between p-stage I and II disease was problematic due to clinical staging based on the American Joint Committee on Cancer 6th and 7th editions. Stage I included T1-2N0M0 in the 6th edition, but the 7th edition included T2b-3N0-1M0 tumors, potentially incorporating patients with worse prognoses. Additionally, it is unclear whether comprehensive brain imaging was performed before surgery and cranial irradiation. There is a possibility that some of the 104 patients who received cranial irradiation may have already had brain metastases.

Ichinose et al. reviewed the incidence of BMs in 45 patients after complete remission, finding rates of 15%, 20%, 53%, and 80% for stages I, II, IIIA, and IIIB, respectively, without PCI. (Ichinose et al. 1989) Recent studies have questioned the need for PCI in resected p-stage I disease. Gong et al. found a 6% incidence of BM in stage I and 29% in stages II/III, despite omitting PCI. (Gong et al. 2013) Another analysis found no significant survival benefit or increased BM risk between PCI and non-PCI groups in p-stage I disease. (Xu et al. 2016) Ozawa et al. compared 29 patients with PCI to 95 without it, finding no significant differences in survival or BM incidence. The low incidence of BM in the non-PCI group may be due to a higher proportion of stage I patients. (Ozawa et al. 2015)

Given the difficulty of conducting a well-powered prospective study on this issue, the available data must be interpreted cautiously. If a surgical approach is chosen for clinical stage I disease, comprehensive staging with MRI and exclusion of lymph node involvement should be performed. Our previous study confirmed a survival benefit of PCI in patients who underwent comprehensive staging with cranial MRI. (Eze et al. 2016) Future revisions of national and international guidelines should

address the role of PCI in this context.

Evaluating the neurotoxicity of PCI is challenging due to various confounding factors, including disease progression, PCI dose and fractionation, concurrent chemotherapy, and patient characteristics. Although randomized trials have not shown significant neurologic sequelae, recent debates continue on this topic. (Le Péchoux et al. 2016) Based on the current evidence, PCI may be omitted in resected p-stage I patients if cranial MRI is available. Future guidelines should address this issue more thoroughly.

Eze C*, Roengvoraphoj O*, Niyazi M, Hildebrandt G, Fietkau R, Belka C, Manapov F. Treatment Response and Prophylactic Cranial Irradiation Are Prognostic Factors in a Real-life Limited-disease Small-cell Lung Cancer Patient Cohort Comprehensively Staged With Cranial Magnetic Resonance Imaging. Clin Lung Cancer. 2017 Jul;18(4):e243-e249. doi: 10.1016/j.cllc.2016.11.005. Epub 2016 Nov 21. PMID: 28065620. Clinical Lung Cancer (IF: 4.204)

In LS-SCLC, CRT followed by PCI is the standard of care. However, endorsement of PCI and its incorporation into national and international guidelines was largely based on a meta-analysis of studies conducted before the universal adoption of contrast-enhanced brain magnetic resonance imaging (MRI) which showed improvement in patient survival outcomes following PCI. (Aupérin et al. 1999) In 2008, a study demonstrated a superior detection rate of MRI vs. computed tomography (CT). (Seute et al. 2008) In the same year, another group was the first to report on the role of repeat MRI following primary CRT and before the start of PCI in a small cohort of LS-SCLC patients i.e. MRI for initial staging before CRT and after CRT before PCI. Interestingly, in 13/40 who were initially negative on initial MRI, brain metastasis (BM) was detected on repeat MRI and was a negative prognosticator. (Manapov, Klautke, and Fietkau 2008)

Thus, PCI has previously been proven to decrease the incidence of BMs with a modest improvement in survival albeit in the pre-MRI era. (Aupérin et al. 1999) To confirm these findings, the impact of PCI was investigated in 184 LS-SCLC patients treated with CRT and

its association with TTP, BMFS, and OS. In total 152 (83%) patients responded to treatment (partial or complete remission) and 71/152 responders received PCI. Metachronous BMs were detected in 16/71 (23%) and 42/113 (37%) in the PCI and Non-PCI group, respectively. Median OS was 26 vs. 14 vs. 9 months in responders with PCI, responders without PCI, and non-responders, respectively. A similar outcome was also observed for TTP and BMFS. On multivariate analysis, PCI was associated with OS (HR = 1.899; $p < 0.0001$) and TTP (HR = 2.164; $p = 0.001$) after adjustment for other prognostic factors.

Manapov F*, **Eze C***, Niyazi M, Roengvoraphoj O, Li M, Hegemann NS, Hildebrandt G, Fietkau R, Belka C.
Investigating a Correlation between Chemoradiotherapy Schedule Parameters and Overall Survival in a real-life LD SCLC Patient Cohort. J Cancer. 2016 Oct 17;7(14):2012-2017. doi: 10.7150/jca.16741. PMID: 27877216; PMCID: PMC5118664.
Journal of Cancer (IF: 2.916)

Manapov F, Niyazi M, Gerum S, Roengvoraphoj O, **Eze C**, Li M, Hildebrandt G, Fietkau R, Klautke G, Belka C. Evaluation of the role of remission status in a heterogeneous limited disease small-cell lung cancer patient cohort treated with definitive chemoradiotherapy. BMC Cancer. 2016 Mar 14;16:216. doi: 10.1186/s12885-016-2245-x. PMID: 26975407; PMCID: PMC4791754.
BMC Cancer (IF: 3.288)

A detailed investigation was conducted to evaluate the impact of concurrent chemoradiation (CRT) schedule parameters on outcomes in a real-life cohort of patients with limited-stage small cell lung cancer (LS-SCLC) from two university hospitals. This analysis included 182 patients, focusing on the influence of various schedule parameters of primary multimodal treatment. Notably, only 4% of patients received early hyperfractionated accelerated concurrent CRT per Turrisi et al. (Turrisi et al. 1999) Prophylactic cranial irradiation was administered to patients who achieved complete or partial remission after CRT. To better understand the role of the concurrent treatment phase, a new

parameter, Interval of Simultaneous Treatment (IST), was introduced. IST measured the number of days during which radiotherapy and chemotherapy were administered concurrently, including weekends and intervals between chemotherapy cycles.

All 182 patients completed primary CRT, with the vast majority (96%) following the conventional CRT protocol, which included a total radiation dose of at least 50 Gy (range: 50 – 66 Gy). The median duration of chemotherapy was 128 days for concurrent treatment and 93 days for sequential treatment, while the median duration of thoracic irradiation was 43 days. IST values of 30, 35, 42, and 49 days were reviewed, with an IST of 35 days proposed as the optimal cutoff for further analysis. This interval encompassed at least two completed chemotherapy cycles and was relevant for both accelerated and conventional thoracic irradiation.

Based on IST, patients were categorized into three subgroups: IST 0 (sequential CRT) with 111 patients (61%), IST > 0 and < 35 (short dose-dense concurrent phase) with 20 patients (11%), and IST > 35 (prolonged concurrent phase) with 51 patients (28%). The median survival for the entire cohort was 534 days, with no significant difference between concurrent and sequential treatments (589 days vs. 533 days, respectively). However, the IST > 0 and < 35 subgroup showed a trend toward prolonged overall survival, with a median of 1169 days compared to 533 days and 448 days for the IST 0 and IST > 35 subgroups, respectively ($p = 0.109$). The short dose-dense concurrent phase (IST > 0 and < 35 days) demonstrated nearly double the overall survival compared to the other subgroups. In the 71 patients treated exclusively with concurrent CRT, the survival benefit in the IST > 0 and < 35 subgroup was statistically significant in both univariate ($p = 0.021$) and multivariate analyses (HR 0.38; $p = 0.039$). No survival benefit was observed between sequential CRT (IST > 0) and prolonged concurrent phase CRT (IST > 35 days).

In summary, the study found that the duration of the concurrent phase, specifically IST, was linked to patient outcomes, with the short dose-dense concurrent phase (IST > 0 and < 35 days) identified as optimal for planning definitive CRT.

A further analysis examined the impact of primary tumor response after CRT on patient outcomes. Patient subgroups were categorized based on remission status - complete response, partial response, or non-response (stable or progressive disease) - and compared across different survival parameters. Of the 184 patients who completed primary multimodal treatment, 65 (35%) achieved complete remission, 77 (42%) had partial remission, and 37 (20%) had non-response, with remission status unvalidated in 5 (3%) patients. Median overall survival was 21.8 months for complete responders, 14.9 months for partial responders, and 11.5 months for non-responders ($p < 0.001$). The same trend was observed for time to progression and distant metastasis-free survival. Multivariate analysis showed that complete responders had significantly better overall survival compared to non-responders and a trend toward improved time to progression (HR 1.48; $p = 0.1$) and distant metastasis-free survival (HR 1.63; $p = 0.06$) compared to partial responders. This study highlighted the significant correlation between remission status after CRT and patient survival, with complete responders showing notable advantages in overall survival and distant control.

Roengvoraphoj O*, **Eze C***, Niyazi M, Li M, Hildebrandt G, Fietkau R, Belka C, Manapov F.
Prognostic role of patient gender in limited-disease small-cell lung cancer treated with chemoradiotherapy. Strahlenther Onkol. 2017 Feb;193(2):150-155. English. doi: 10.1007/s00066-016-1073-x. Epub 2016 Nov 16. PMID: 27853828.
Strahlentherapie und Onkologie (IF: 2.735)

A SEER database analysis by Lally et al. reported a 5-year OS rate of 14% for females compared to 11% for males. (Lally et al. 2009)

This retrospective analyzed the prognostic value of patient gender in a large, heterogeneous series of individuals treated with definitive CRT and defined its association with different survival parameters.

In previous studies, patient gender was postulated to be a prognostic factor for outcomes in LS-SCLC. In this analysis, we investigated this association using data from a bi-institutional

cohort of 179 LS-SCLC patients treated with CRT from 1999 to 2012. We examined the impact of gender on time to progression (TTP), local control (LC), brain metastasis-free survival (BMFS), distant metastasis-free survival (DMFS), and overall survival (OS).

We found that median OS was significantly associated with gender: 20 months for female patients and 14 months for male patients (p=0.021). This association remained significant after adjusting for other factors in a multivariate analysis (HR 1.38; p=0.04). This was also true for gender subgroups classified according to remission status following primary CRT. Additionally, there was a significant difference in median OS between genders for patients receiving PCI. However, males had a higher incidence of metachronous brain failure (40/110 in males vs. 18/69 in females), resulting in significantly longer BMFS in females. No correlation between gender and TTP, LC, or DMFS was detected.

3.1.2. Summary and Discussion

In 1999, Aupérin and colleagues established the role of prophylactic cranial irradiation (PCI) in small cell lung cancer (SCLC) for complete responders based on seven randomized clinical trials conducted between 1977 and 1995. At the initial diagnosis, only a minority of participants had extensive disease. (Aupérin et al. 1999) In 2007, the European Organisation for Research and Treatment of Cancer published a trial endorsing PCI for extensive-stage (ES)-SCLC. (Slotman et al. 2007) However, these studies were conducted before brain magnetic resonance imaging became routine for staging SCLC. Critics argue that the moderate but significant survival benefit of PCI may be due to the eradication of subclinical brain metastases.

A previous phase 3 trial by Takahashi and colleagues failed to show a survival benefit of PCI compared to observation in ES-SCLC patients who underwent comprehensive MRI surveillance and treatment of occult BMs.(Takahashi et al. 2017) This has fueled the debate

on PCI within the thoracic oncology community. Comprehensive brain staging in LS-SCLC is crucial, as highlighted by a single-center analysis where 33% of LS-SCLC complete responders developed subclinical brain relapse detected on a second MRI scan before PCI. The median survival for these patients was poor. (Manapov et al. 2008) A Japanese trial by Ozawa et al. analyzed records from four cancer centers and found no survival benefit from PCI, though the study was underpowered with only 29 patients in the PCI group. (Ozawa et al. 2015)

Surveys have reported general care patterns for SCLC. (Jain et al. 2016) In a 2016 US survey, 90.5% of respondents recommended a second MRI after chemotherapy before PCI for ES-SCLC patients. (Jain et al. 2016) Similarly, a German survey conducted by our group showed that 88% of radiation oncology facilities performed a second brain imaging before PCI. Despite limited data, this strategy is widely accepted in the management of SCLC.

The universal adoption of comprehensive brain imaging will personalize the role of PCI in SCLC, defining patient subgroups that benefit most. To assess these subgroups and the true prophylactic role of PCI, key issues need addressing. The primary goal of PCI - whether to decrease symptomatic and/or occult BM incidence - must be defined. Studies have shown significant differences in BM incidence depending on the TNM stage, suggesting a shift from the Veterans Administration Lung Study Group classification to the Union for International Cancer Control classification. This shift will help identify SCLC patient subgroups with an increased BM risk who might benefit from PCI. (Goldstraw et al. 2016)

The link between preventing intracranial relapse and overall survival in SCLC is complex, as isolated brain relapse is rare and can be managed with stereotactic radiosurgery. Systematic analyses of relapse patterns in previous trials are needed. The extent of recurrence and the presence of symptoms are critical for overall survival. Separate analyses of intracranial and extracranial progression-free survival will provide insights and influence PCI decision-

making. Takahashi's trial remains the only randomized study on comprehensive MRI surveillance in ES-SCLC patients treated with PCI, highlighting varying brain relapse rates but lacking detailed recurrence pattern data. (Takahashi et al. 2017)

The toxic effects of PCI could be mitigated by adopting hippocampal avoidance and neuroprotectants. (Manapov et al. 2018) Ongoing phase 2 and 3 trials on hippocampal-sparing PCI will provide data on neuropsychological outcomes, quality of life, and intracranial relapse rates. The timing of PCI application (early vs. late) also affects treatment efficacy and should be considered.

In conclusion, PCI remains the standard of care for LS-SCLC (T1-4, N0-3). However, omitting PCI in resected p-stage I disease could be discussed if active MRI surveillance and access to salvage radiotherapy, particularly stereotactic radiosurgery, are readily available. For ES-SCLC, considering conflicting data, active MRI surveillance can be considered. MRI before and after primary treatment, every three months should be conducted to identify patients with occult BMs for early salvage radiotherapy. Future prospective studies will help define high-risk patient subgroups most likely to benefit from PCI.

3.2. Non-small cell lung cancer (NSCLC)

3.2.1. The evolving role of radiotherapy in the management of non-small cell lung cancer

At the time of diagnosis, most patients with NSCLC present with locally advanced or metastatic disease associated with 5-year relative survival rates of 31% and 5%, respectively. (Goldstraw et al. 2016; Siegel et al. 2020) In patients with inoperable stage III disease, platinum-based CRT followed by consolidation immune checkpoint inhibition with the PD-L1 inhibitor durvalumab is the new standard of care. (Antonia et al. 2019) In the metastatic setting, nivolumab was the first drug approved by the U.S. Food and Drug Administration (FDA) in 2015 for advanced or metastatic NSCLC in the second-line setting.

Later that year, pembrolizumab was granted accelerated approval in the second line. Atezolizumab was also added to the repertoire in the second-line setting for PD-L1 unselected patients the following year and shortly after, pembrolizumab was the first drug approved in the first-line treatment for non-oncogene addicted patients with PD-L1 tumor proportion score (TPS) ≥ 50% and expansion of this indication in 2019 to include patients with PD-L1 positive tumors based on the KEYNOTE-042 trial. (Ettinger et al. 2020)

PD-L1 expression can be either constitutive or induced in many tumors to promote cancer immune evasion. In an attempt to combat this adaptive immune resistance, combinations with chemotherapy and anti-angiogenic agents have also received FDA approval. (Ettinger et al. 2020) Recent additions to this armamentarium are nivolumab plus ipilimumab, approved on May 15, 2020, for first-line treatment of non-oncogene addicted PD-L1 positive mNSCLC (Hellmann et al. 2019) and atezolizumab, approved on May 18, 2020 in the first-line for mNSCLC with PD-L1 ≥ 50% of tumor cells or PD-L1 tumor-infiltrating immune cells covering ≥ 10% of the tumor area and no EGFR or ALK genomic tumor aberrations. (Spigel et al. 2019)

3.2.2. Accelerated hypofractionated radiotherapy in patients with poor prognostic factors

Eze C, Taugner J, Roengvoraphoj O, Schmidt-Hegemann NS, Käsmann L, Wijaya C, Belka C, Manapov F. Initial report on feasibility of PET/CT-based image-guided moderate hypofractionated thoracic irradiation in node-positive non-small cell lung cancer patients with poor prognostic factors and strongly diminished lung function: a retrospective analysis. Radiat Oncol. 2019 Sep 4;14(1):163. doi: 10.1186/s13014-019-1304-2. PMID: 31484542; PMCID: PMC6727570.
Radiation Oncology (IF: 2.895)

Concurrent platinum-based CRT to a dose of 60-66 Gy followed by consolidation PD-L1 inhibition with durvalumab is the standard of care for patients with inoperable stage III

disease. (Antonia et al. 2019) However, a large portion of patients are unable to tolerate concurrent CRT due to poor prognostic factors e.g. Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, etc., and are thus referred for palliative treatment or best supportive care. (Burdett et al. 2008)

Accelerated hypofractionated radiotherapy (AHRT) is an adopted strategy to improve patient outcomes owing to a higher biologically effective dose (BED) for larger fractions and shorter overall treatment time leading to reduced repopulation of tumor cells. (Fowler and Chappell 2000) Indeed, the regimen of 55 Gy/20 fx is the most widely used schedule in the United Kingdom. (Prewett et al. 2012) Several prospective studies have reported on AHRT without concurrent chemotherapy in stage III NSCLC demonstrating feasibility. (Cannon et al. 2013; Iqbal et al. 2019; Parisi et al. 2019; Zhu et al. 2011) However, these studies included patients with favorable performance status. In addition, 2 systematic reviews have reported on the feasibility of palliative and radical-intent moderate hypofractionated radiotherapy with doses ranging from 45 Gy/15 fx to 10 Gy/1 fx and 45 Gy/15 fx to 75 Gy/28 fx, respectively. (Kaster et al. 2015; Lester et al. 2006)

In this analysis, we retrospectively analyzed the data of eight highly selected and closely monitored patients with highly diminished pulmonary function: forced expiratory volume in 1 second (FEV1) ≤ 1.0 L and/or Single-breath diffusing capacity of the lung for carbon monoxide (DLCO-SB) ≤ 40% and/or on long-term oxygen therapy (LTOT) treated with hypofractionated radiotherapy (hypoRT). At a median follow-up of 29.4 months, the median PFS and OS were 19 and 34.3 months, respectively. Importantly, there was no case of grade 2+ radiation pneumonitis. Four patients developed grade 2 radiation esophagitis. In an otherwise patient cohort with a miserable prognosis, our protocol demonstrated feasibility.

Eze C, Taugner J, Schmidt-Hegemann NS, et al. Feasibility of hypofractionated radiotherapy in inoperable node-positive NSCLC patients with poor prognostic factors and limited pulmonary reserve: a prospective observational study. *Acta Oncol*. 2021;60(8):1074-1078. doi:10.1080/0284186X.2021.1941244
Acta Oncologica (IF: 4.3)

This study reports on a prospective cohort of high-risk patients with poor performance status and compromised pulmonary function treated with hypoRT. Data from 20 patients with node-positive stage IIB(N1)/III NSCLC treated between August 2017 and March 2020 were analyzed. Patients were discussed at a multidisciplinary tumor board and referred for hypoRT. Eligibility included proven NSCLC, age ≥ 18 years, ECOG performance status (PS) ≥ 2, inoperable node-positive stage IIB-III disease, FEV1 ≤ 1.0 L, DLCO-SB ≤ 40%, or on long-term oxygen therapy. Exclusion criteria were concurrent chemotherapy and previous thoracic radiotherapy. All patients underwent PET/CT, MRI of the brain, and pulmonary function tests.

Radiotherapy was delivered using volumetric modulated arc therapy (VMAT) with 3.0 Gy fractions to a dose of 45.0–48.0 Gy. Patients were monitored for toxicity and followed up with regular assessments and imaging studies. The study observed grade 1-2 esophagitis and pneumonitis, with one case of grade 3 pneumonitis. Treatment responses included 20% complete remission, 65% partial remission/stable disease, and 15% progressive disease. The median progression-free survival (PFS) was 8.4 months, and the median overall survival was 16.1 months. An exploratory analysis found no significant effect of induction systemic therapy on PFS or OS.

This study demonstrates the feasibility and favorable outcomes of moderate hypofractionated hypoRT in high-risk NSCLC patients with poor PS and diminished

pulmonary function, suggesting a promising treatment pathway for this distinct patient cohort.

Eze C, Guggenberger JE, Schmidt-Hegemann NS, et al.
Pooled analysis on image-guided moderately hypofractionated thoracic irradiation in inoperable node-positive/recurrent patients with non-small cell lung cancer with poor prognostic factors and severely limited pulmonary function and reserve. *Cancer*. 2022;128(12):2358-2366. doi:10.1002/cncr.34201
Cancer (IF: 6.2)

Kenndoff S, Nieto A, Guggenberger J…**Eze C**
Dosimetric predictors of acute radiation pneumonitis and esophagitis in hypofractionated thoracic irradiation of non-small cell lung cancer patients with poor prognostic factors: Dosimetric predictors of acute radiation pneumonitis and esophagitis following hypofractionation in NSCLC. *Adv Radiat Oncol*. Published online November 14, 2024. oi:10.1016/j.adro.2024.101682
Advances in Radiation Oncology (IF: 2.2)

Zinn AB, Kenndoff S, Holzgreve A…**Eze C**
Prognostic significance of pretreatment PET parameters in inoperable, node-positive NSCLC patients with poor prognostic factors undergoing hypofractionated radiotherapy: a single-institution retrospective study. *EJNMMI Rep.* 2024;8(1):32. Published 2024 Oct 8. doi:10.1186/s41824-024-00220-w
European Journal of Nuclear Medicine and Molecular Imaging Reports (IF: 1.7)

Non-small cell lung cancer remains the leading cause of cancer-related deaths worldwide. (Sung et al. 2021) The standard of care for inoperable, node-positive stage IIB(N1)/III NSCLC constitutes consolidation with the PD-L1 inhibitor durvalumab following concurrent chemoradiation (CRT). (Antonia et al. 2018) However, the pivotal trial that established that established this approach involved patients with favorable baseline performance status. For those with poor prognostic factors - such as frailty, poor baseline performance status, or

multiple comorbidities - concurrent CRT is often unsuitable. These patients are typically referred to palliative radiotherapy or best supportive care.(Yusuf et al. 2020)

Accelerated hypofractionated radiotherapy (AHRT) offers an alternative, delivering higher biologically effective doses (BED) while reducing the overall treatment duration. This approach aims to minimize tumor cell repopulation. (Fowler and Chappell 2000) Previous studies on AHRT for locally advanced NSCLC have included both favorable and unfavorable risk factor patients. (Amini et al. 2012; Cannon et al. 2013; Parisi et al. 2019; Pollom et al. 2016; Valeriani et al. 2019; Westover et al. 2015; Zhu et al. 2011) Recently, the first randomized trial evaluating AHRT in patients with poor performance status was published. (Iyengar et al. 2021) Nonetheless, there is a knowledge gap regarding its effectiveness in a subset of patients with severe pulmonary impairment (FEV1 ≤ 1L and/or DLCO-SB ≤ 40% predicted and/or on LTOT). In the abovementioned publications, we analyzed all patients treated at our institution with this concept spanning multiple publications from 2014 onwards. In this pooled analysis, 47 patients were analyzed (Patient treatment characteristics are shown in Table 1)

Table 1: Patient and treatment characteristics (adapted from Eze et al. Cancer 2022)

	Number (%)
Total	**47 (100)**
Age	
Median (years)	72 (52.2-88)
Mean (SD)	71.9 (8.6)
Age > 70 years	
Yes	27 (57.4)
No	20 (42.6)
Gender	
Male	27 (57.4)
Female	20 (42.6)
T category	
Tx	8 (17)
T1	1 (2.1)
T2	8 (17)
T3	13 (27.7)
T4	17 (36.2)
N category	
N1	9 (19.1)

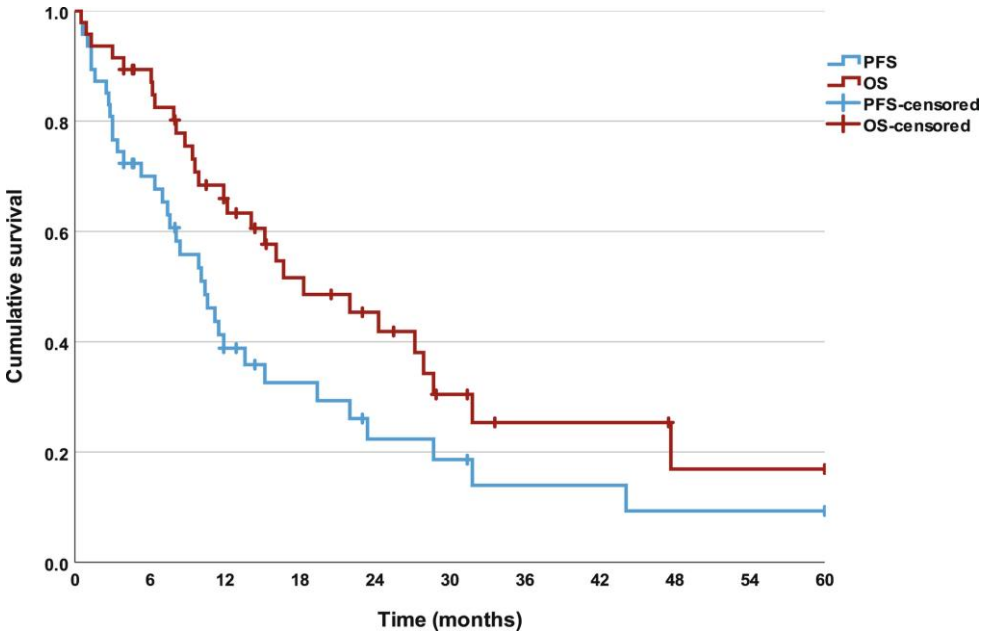
N2	24 (51.1)
N3	14 (29.8)
Stage	
IIB	2 (4.3)
IIIA	8 (17)
IIIB	17 (36.2)
IIIC	12 (25.5)
Recurrent (stage III)	8 (17)
CCI	
4-6	30 (63.8)
≥7	17 (36.2)
Staging PET-CT	
Yes	42 (89.4)
No	5 (10.8)
Radiotherapy modality	
3D-CRT	6 (12.8%)
IMRT/VMAT	41 (87.2%)
PTV (cc)	
Median [range]	315.4 [83.4-1174.1cc]
Mean (SD)	410.8 (267.1)
Histology	
SCC	20 (42.6)
ACC	22 (46.8)
NOS	5 (10.6)
Induction systemic therapy	
Yes	19 (40.4)
No	28 (59.6)
Salvage systemic therapy	
Yes	10 (21.3)
No	37 (78.7)
Baseline FEV1	
Median (L) [range]	1.17 [0.69-2.84]
Mean (L) [SD]	1.28 [0.5]
Median (%) [range]	47.5 [27.9-96.4]
Mean (%) [SD]	51 [17.1]
Vital Capacity	
Median (L) [range]	2.34 [1.23-3.74]
Mean (L) [SD]	2.25 [0.64]
Median (%) [range]	67.8 [33-110]
Mean (%) [SD]	67.7 [14]
Baseline DLCO-SB	
Median (mmol/min/kPa)	2.59 [1-4.7]

Mean (mmol/min/kPa) [SD]	2.7 (0.88)
Median (%) predicted [range]	35 [13.3-69]
Mean (%) [SD]	34.51 [10.46]
LTOT	
Yes	18 (39.3)

Abbreviations: 3D-CRT= Three dimensional conformal radiation therapy; ACC= Adenocarcinoma; cc= cubic centimeter; CCI= Charlson Comorbidity Index; DLCO-SB= single-breath diffusing capacity of the lung for carbon monoxide; ECOG-PS= Eastern Cooperative Oncology Group Performance Status; FEV1= forced expiratory volume in 1 second; IMRT = Intensity modulated radiation therapy; LTOT= long-term oxygen therapy; mmol/min/kPa= millimoles per minute per kilopascal; NOS= not otherwise specified; PET/CT= positron emission tomography/computed tomography; PTV= planning target volume; RT= Radiotherapy; SCC= squamous cell carcinoma; SD= standard deviation; VMAT= volumetric modulated arc therapy

Between 2014 and 2021, 47 patients with a median age of 72 years were treated. At baseline the median FEV1 was 1.17 L, vital capacity was 2.34 L and DLCO-SB was 35% predicted. The mean and median planning target volumes were 410.8cc and 315.4cc, respectively.

With a median follow-up of 28.9 months after hypofractionated radiotherapy, the median progression-free survival and overall survival were 10.4 months and 18.3 months (Figure 2), respectively. The 6- and 12-month PFS/OS rates were 70%/89.4% and 38.8%/66% (Figure 2), respectively. Treatment was well tolerated, with only one instance each of grade 3 pneumonitis and esophagitis. No grade 3+ adverse event was observed.



Cancer, Volume: 128, Issue: 12, Pages: 2358-2366, First published: 13 April 2022, DOI: (10.1002/cncr.34201)

In further analyses, clinical and dosimetric analyses of clinical and dosimetric predictors of esophagitis and pneumonitis were investigated.

Dosimetric parameters such as mean lung dose (MLD), mean heart dose (MHD) and mean esophageal dose (MED) were analyzed, along with the percentage of lung, heart, and esophageal volumes receiving specific radiation doses. Acute radiation esophagitis and pneumonitis events were evaluated within 3 months and 6 months post-treatment, respectively. Statistical analyses indicated that higher MLD, percentage of normal lung volume receiving 10 Gy (V10), and 18 Gy (V18) are associated with an increased risk of pneumonitis, while higher V5 and V10 values in the contralateral lung also pose a risk. The maximum dose (Dmax) was found to be a significant predictor of esophagitis, with the percentage of normal esophagus volume receiving 5 Gy (EV5) and 40 Gy (EV40) potentially associated with esophagitis onset. Although MLD and Dmax emerged as significant predictors, the study's small sample size limits the depth of the conclusions, warranting further research with larger cohorts to optimize treatment planning and outcomes.

Additionally, the role of [^{18}F]FDG PET/CT in this distinct patient cohort was also analyzed. The analysis aimed to assess the prognostic value of pretreatment positron emission tomography (PET) parameters in high-risk patients undergoing hypofractionated radiotherapy. A retrospective analysis of 42/47 patients was conducted. Clinical, treatment-related, and [^{18}F]FDG PET-based parameters were correlated with PFS and OS. After a median follow-up of 47.1 months, the median PFS and OS were 11.5 months and 24.3 months, respectively. Significant predictors of PFS included salvage systemic treatment, SUVmax, and tMTV, while ECOG-PS, histology, and tMTV were significant for OS. Multivariable analysis identified SUVmax as a significant predictor for PFS and ECOG-PS for

OS, with tMTV approaching significance. The high tMTV group had a median PFS of 5.3 months compared to 15.2 months in the low tMTV group, and a median OS of 14.1 months compared to 33.5 months for lower tMTV. These findings suggest that pretreatment PET parameters, especially tMTV, are promising prognostic indicators for NSCLC patients undergoing hypofractionated radiotherapy, highlighting their potential as biomarkers for patient stratification.

Eze C, Lombardo E, Nierer L, et al.
MR-guided radiotherapy in node-positive non-small cell lung cancer and severely limited pulmonary reserve: a report proposing a new clinical pathway for the management of high-risk patients. *Radiat Oncol*. 2022;17(1):43. Published 2022 Feb 24. doi:10.1186/s13014-022-02011-8
Radiation Oncology (IF: 3.6)

Furthermore, we investigated the role of online MR-guided radiotherapy (MRgRT) - a significant advancement in radiation oncology - offering enhanced real-time tumor visualization, adaptive planning for anatomical changes, and improved motion management. Drawing from our previous experience with conventional linear accelerators, MRgRT in high-risk patients. Theoretically, the use of online soft-tissue visualization and gating capabilities reduces uncertainty in radiotherapy delivery, potentially supporting dose-escalation strategies, in a further technical report, the tumor motion and breathing curve analyses for a patient with node-positive stage IIB(N1) NSCLC and severely compromised pulmonary function treated in a prospective observational study using moderately hypofractionated MR-guided radiotherapy (MRgRT). The patient's pulmonary function was significantly impaired, with total lung capacity (TLC) at 8.78L/132% predicted, residual volume (RV) at 6.35L/271% predicted, vital capacity (VC) max at 2.43L/58% predicted, FEV1 at 1.19L/38% predicted, and DLCO-SB corrected for hemoglobin at 2.76

mmol/min/kPa/30% predicted. Treatment was delivered with the MRIdian system (Viewray Inc, Oakwood, USA) to a total dose of 48.0 Gy over 16 daily fractions.

The treatment was well tolerated without significant toxicity, and the first follow-up imaging at three months post-radiotherapy showed partial remission. This case is notable for the patient's severely compromised pulmonary function and represents the first published instance of using online MR-guided accelerated hypofractionated radiotherapy for primary node-positive NSCLC, proposing a clinical pathway for managing high-risk patients.

3.2.2.1. Summary and Discussion

In summary, we report our long-term experience in managing patients with locally advanced or recurrent node-positive NSCLC and severely compromised lung function, who were ineligible for definitive concurrent chemoradiation. The findings provide a clinical pathway for managing these high-risk patients. Unlike other studies on hypofractionated radiotherapy (RT), our analyses included patients with severely limited pulmonary function, with all treated patients having an FEV1 ≤ 1.0 L, DLCO-SB ≤40%, and/or being on long-term oxygen therapy (LTOT). The mean FEV1 and DLCO were significantly lower in our study (51% and 34.5%, respectively) compared to other studies.

Most patients (60%) were enrolled prospectively, and the majority (78.7%) did not receive any salvage systemic treatment after radiotherapy, which was not a significant predictor for progression-free survival or overall survival in multivariate analysis. ECOG-PS and planning target volume (PTV) were significant prognosticators for OS, while PTV was borderline significant for PFS. Patients had a median age of 72 years, a high Charlson Comorbidity Index, and advanced disease stages (IIIA, IIIB, IIIC, and regional nodal recurrence).

Our results compare favorably to other studies. With a median follow-up of 28.9 months, the median PFS was 10.4 months, and the 6- and 12-month PFS rates were 70% and 38.8%. The median OS was 18.3 months, with 6- and 12-month OS rates of 89.4% and 66%. Treatment was well tolerated, with only one case each of grade 3 pneumonitis and esophagitis and no greater than grade 3 acute adverse events. Most patients (79%) had baseline dyspnea, and post-radiotherapy pulmonary function tests (PFTs) showed only a nonsignificant decline in DLCO-SB.

Locoregional relapse occurred in 38.3% of patients, consistent with another radiotherapy-alone series. While dose escalation has been considered to improve local control, randomized trials have not demonstrated a survival benefit in unresectable stage III NSCLC treated with concurrent chemoradiation. (Bradley et al. 2020) The use of immune checkpoint inhibitors is a promising strategy, supported by trials like PACIFIC and real-world data showing improved locoregional control and patient outcomes. (Antonia et al. 2018; Spigel et al. 2022; Wang et al. 2022)

There are some limitations to our analyses, including being conducted at a single tertiary cancer center and potential selection bias in the retrospective cohort. Despite these limitations, the results reflect the feasibility of safely and effectively treating inoperable node-positive NSCLC in patients with poor performance status and severely limited lung function using individualized moderately hypofractionated radiotherapy. Recruitment for an updated institutional protocol on a magnetic resonance-guided radiotherapy treatment platform is ongoing, which may enable isotoxic dose-escalation strategies. In conclusion, the survival rates achieved for this multimorbid patient group were encouraging.

3.2.3. The role of [^{18}F]FDG PET/CT in the management of non-small cell lung cancer

Roengvoraphoj O*, **Eze C***, Wijaya C, Dantes M, Taugner J, Tufman A, Huber RM, Bartenstein P, Belka C, Manapov F.

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 Nov;45(12):2103-2109. doi: 10.1007/s00259-018-4063-7. Epub 2018 Jun 6. PMID: 29876620.

European Journal of Nuclear Medicine and Molecular Imaging (IF: 7.182)

The changes in metabolic activity following (C)RT can be observed earlier than morphologic changes on CT scans and metabolic changes characterized by PET-metrics: Maximum Standardized Uptake Value (SUVmax), Metabolic tumor volume (MTV), Total lesion glycolysis (TLG) during or shortly after treatment have been identified as prognosticators for disease recurrence and survival. (Cremonesi et al. 2017; van Diessen et al. 2020; Gensheimer et al. 2017; Machtay et al. 2013; Ohri et al. 2017; Usmanij et al. 2013) An association of residual MTV at a cutoff of 25cm^3 with tumor local control was identified (Ohri et al. 2017) and corroboration of these findings was previously published by our group.

In this analysis, a correlation between pre- to post-treatment primary tumor metabolic volume (PT-MV) reduction on [^{18}F]FDG PET/CT and survival NSCLC patients following CRT. Sixty consecutive patients with NSCLC stage IIIA-B (UICC 7th edition were assessed before and 6 weeks after treatment. Various metabolic response values were investigated on their correlation with survival parameters: Median overall survival for the entire cohort was 17 months. Median OS was 34 months, 12 months, and 11 months in patients with complete, moderate, and minor responses, respectively (p=0.008). On multivariate analysis after adjustment for other factors, complete and major metabolic response as a continuous variable with PT-MV reduction of at least 80% remained a significant prognosticator.

Eze C, Schmidt-Hegemann NS, Sawicki LM, et al.
PET/CT imaging for evaluation of multimodal treatment efficacy and toxicity in advanced NSCLC-current state and future directions. *Eur J Nucl Med Mol Imaging*. 2021;48(12):3975-3989. doi:10.1007/s00259-021-05211-8
Eur J Nucl Mol Imaging (IF: 10.057)

Manapov F, Eze C, Holzgreve A, et al.
PET/CT for Target Delineation of Lung Cancer Before Radiation Therapy. *Semin Nucl Med*. 2022;52(6):673-680. doi:10.1053/j.semnuclmed.2022.05.003
Seminars in Nuclear Medicine (IF: 4.9)

In the abovementioned reviews, the role of [^{18}F]FDG PET/CT imaging in assessing the effectiveness and side effects of combined treatments for advanced non-small cell lung cancer (NSCLC) was evaluated. PET/CT is instrumental in evaluating tumor response to therapy, monitoring disease progression, and detecting treatment-related toxicities. It provides comprehensive insights into both anatomical and metabolic changes in tumors. In addition, PET/CT is pertinent for assessing the success of multimodal treatment approaches by showing changes in the metabolic activity of tumors, which often precede anatomical changes. Additionally, PET/CT helps in identifying adverse effects of treatments early, enabling timely intervention to manage and mitigate side effects.

Advances in imaging technology and the integration of artificial intelligence are expected to improve diagnostic accuracy and personalized treatment planning. Overall, PET/CT imaging stands out as a powerful tool in the management of advanced NSCLC, offering a detailed evaluation of treatment efficacy and safety, with promising potential for future advancements.

Holzgreve A, Taugner J, Käsmann L…, Eze C*, Unterrainer M*, Manapov F*
Metabolic patterns on [^{18}F]FDG PET/CT in patients with unresectable stage III NSCLC undergoing chemoradiotherapy±durvalumab maintenance treatment. *Eur J Nucl Med Mol Imaging*. 2023;50(8):2466-2476. doi:10.1007/s00259-023-06192-6
Eur J Nucl Mol Imaging (IF: 8.6)

The purpose of this study was to evaluate metabolic changes in tumors and secondary lymphoid organs in patients with unresectable stage III NSCLC receiving durvalumab maintenance treatment after chemoradiotherapy (CRT), compared to those undergoing CRT alone. The study included 43 patients with [^{18}F]FDG PET/CT scans before and after standard CRT; 16 of these patients received durvalumab before the second PET/CT scan. Tumor and lymphoid organ uptake were compared between patients receiving CRT alone and those receiving both CRT and durvalumab (CRT-IO).

Initial uptake characteristics were similar between the two groups. However, significant differences were observed under durvalumab treatment: there was a greater reduction in tumor uptake intensity in the CRT-IO group compared to CRT alone, with a median decrease in SUVmax of –70.0% vs. –24.8% ($p = 0.009$). Conversely, spleen uptake increased in the CRT-IO group while it decreased in the CRT group (median + 12.5% vs. –4.4%, $p = 0.029$). Overall survival was significantly longer in the CRT-IO group, with fewer events of progression or death.

Additionally, PET/CT scans showed a higher proportion of findings suggestive of immunotherapy-related adverse events (irAE) in the CRT-IO group (12/16) compared to the CRT group (8/27), with a p-value of 0.005. In conclusion, durvalumab maintenance after CRT leads to distinct metabolic changes in tumors and increased splenic metabolism, along with a higher incidence of irAE findings on PET/CT, correlating with significantly prolonged survival. Further survival analysis will be conducted as more clinical events occur.

3.2.3.1. Summary and Discussion

Pre-treatment FDG-PET parameters have proven to be reliable prognostic indicators for outcomes and survival in advanced NSCLC. (Chin et al. 2018; Seban et al. 2020) While SUVmax is commonly used to assess treatment response, metrics such as MTV, tMTV, and TLG are considered the most robust prognostic factors during initial staging. Multiple studies have established a link between these parameters and patient outcomes. (Chin et al. 2018; Seban et al. 2020) For instance, a connection has been noted between high TMTV and poor inflammatory status, leading to a worse prognosis and lack of durable clinical benefit (DCB). (Seban et al. 2020) Another study demonstrated that radiomic features from baseline pre-treatment FDG PET/CT scans can accurately identify patients likely to achieve DCB. However, these parameters are not yet uniformly applied in clinical practice. (Mu et al. 2019)

Changes in metabolic activity after (C)RT can be detected earlier with PET than morphological changes on CT scans. PET metrics such as SUVmax, MTV, and TLG, measured during or shortly after treatment, have been identified as prognostic biomarkers for disease recurrence and survival. (Cremonesi et al. 2017; van Diessen et al. 2019; Gensheimer et al. 2017; Machtay et al. 2013; Ohri et al. 2017; Roengvoraphoj et al. 2017; Unterrainer et al. 2020; Usmanij et al. 2013) Studies have found that a residual MTV cutoff of 25 cm^3 is associated with local tumor control (Ohri et al. 2017), reinforcing the prognostic value of pre-treatment primary tumor MTV, reduction in mid- to post-treatment MTV, and the correlation between post-treatment MTV and patient outcomes by our research group across multiple studies. (Roengvoraphoj et al. 2017, 2018)

4. References

Amini, Arya, Steven H. Lin, Caimiao Wei, Pamela Allen, James D. Cox, and Ritsuko Komaki. 2012. "Accelerated Hypofractionated Radiation Therapy Compared to Conventionally Fractionated Radiation Therapy for the Treatment of Inoperable Non-Small Cell Lung Cancer." *Radiation Oncology* 7(1):33.

Antonia, Scott J., Augusto Villegas, Davey Daniel, David Vicente, Shuji Murakami, Rina Hui, Takayasu Kurata, Alberto Chiappori, Ki H. Lee, Maike de Wit, Byoung C. Cho, Maryam Bourhaba, Xavier Quantin, Takaaki Tokito, Tarek Mekhail, David Planchard, Young-Chul Kim, Christos S. Karapetis, Sandrine Hiret, Gyula Ostoros, Kaoru Kubota, Jhanelle E. Gray, Luis Paz-Ares, Javier de Castro Carpeño, Corinne Faivre-Finn, Martin Reck, Johan Vansteenkiste, David R. Spigel, Catherine Wadsworth, Giovanni Melillo, Maria Taboada, Phillip A. Dennis, and Mustafa Özgüroğlu. 2018. "Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC." *New England Journal of Medicine* 379(24):2342–50.

Antonia, Scott J., Augusto Villegas, Davey Daniel, David Vicente, Shuji Murakami, Rina Hui, Takayasu Kurata, Alberto Chiappori, Ki H. Lee, Maike de Wit, Byoung C. Cho, Maryam Bourhaba, Xavier Quantin, Takaaki Tokito, Tarek Mekhail, David Planchard, Young-Chul Kim, Christos S. Karapetis, Sandrine Hiret, Gyula Ostoros, Kaoru Kubota, Jhanelle E. Gray, Luis Paz-Ares, Javier de Castro Carpeño, Corinne Faivre-Finn, Martin Reck, Johan Vansteenkiste, David R. Spigel, Catherine Wadsworth, Giovanni Melillo, Maria Taboada, Phillip A. Dennis, and Mustafa Özgüroğlu. 2019. *Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC | NEJM*. Vol. 379. Massachusetts Medical Society.

Aupérin, A., R. Arriagada, J. P. Pignon, C. Le Péchoux, A. Gregor, R. J. Stephens, P. E. Kristjansen, B. E. Johnson, H. Ueoka, H. Wagner, and J. Aisner. 1999. "Prophylactic Cranial Irradiation for Patients with Small-Cell Lung Cancer in Complete Remission." *The New England Journal of Medicine* 341(7):476–84.

Bogart, Jeffrey, Xiaofei Wang, Gregory Masters, Junheng Gao, Ritsuko Komaki, Laurie E. Gaspar, John Heymach, James Bonner, Charles Kuzma, Saiama Waqar, William Petty, Thomas E. Stinchcombe, Jeffrey D. Bradley, and Everett Vokes. 2023. "High-Dose Once-Daily Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer: CALGB 30610 (Alliance)/RTOG 0538." *Journal of Clinical Oncology*.

Borczuk AC, Chan JKC, Cooper WA, Dacic S, Kerr KM, Lantuejoul S, Marx A, Nicholson AG, Scagliotti GV, Thompson LDR, Travis WD, Tsao MS, Yatabe Y. 2021. *Thoracic Tumours*. Vol. 2th. edited by L. Dilani, W. Valerie A., W. Beiko, and C. lan A. International Agency for Research on Cancer (lARC).

Bradley, Jeffrey D., Chen Hu, Ritsuko R. Komaki, Gregory A. Masters, George R. Blumenschein, Steven E. Schild, Jeffrey A. Bogart, Kenneth M. Forster, Anthony M. Magliocco, Vivek S. Kavadi, Samir Narayan, Puneeth Iyengar, Clifford G. Robinson, Raymond B. Wynn, Christopher D. Koprowski, Michael R. Olson, Joanne Meng, Rebecca Paulus, Walter J. Curran, and Hak Choy. 2020. "Long-Term Results of NRG Oncology RTOG 0617: Standard-versus High-Dose Chemoradiotherapy with or without Cetuximab for Unresectable Stage III Non-Small-Cell Lung Cancer." *Journal of Clinical Oncology* 38(7):706–14.

Burdett, Sarah, S. Burdett, R. Stephens, L. Stewart, J. Tierney, A. Auperin, T. Le Chevalier, C. Le Pechoux, J. P. Pignon, R. Arriagada, J. Higgins, D. Johnson, J. Van Meerbeeck, M. Parmar, R. Souhami, D. Bell, G. Cartei, Y. Cormier, M. Cullen, P. Ganz, C. Gridelli, S. Kaasa, E. Quoix, E. Rapp, L. Seymour, S. Spiro, N. Thatcher, D. Tummarello, C. Williams, and I. Williamson. 2008. "Chemotherapy in Addition to Supportive Care Improves Survival in Advanced Non-Small-Cell Lung Cancer: A Systematic Review and Meta-

Analysis of Individual Patient Data from 16 Randomized Controlled Trials." *Journal of Clinical Oncology* 26(28):4617–25.

Cannon, Donald M., Minesh P. Mehta, Jarrod B. Adkison, Deepak Khuntia, Anne M. Traynor, Wolfgang A. Tomé, Richard J. Chappell, Ranjini Tolakanahalli, Pranshu Mohindra, Søren M. Bentzen, and George M. Cannon. 2013. "Dose-Limiting Toxicity after Hypofractionated Dose-Escalated Radiotherapy in Non-Small-Cell Lung Cancer." *Journal of Clinical Oncology* 31(34):4343–48.

Chin, Alexander L., Kiran A. Kumar, Haiwei H. Guo, Peter G. Maxim, Heather Wakelee, Joel W. Neal, Maximillian Diehn, Billy W. Loo, and Michael F. Gensheimer. 2018. "Prognostic Value of Pretreatment FDG-PET Parameters in High-Dose Image-Guided Radiotherapy for Oligometastatic Non–Small-Cell Lung Cancer." *Clinical Lung Cancer* 19(5):e581–88.

Chu, Xiao and Zhengfei Zhu. 2023. "Prophylactic Cranial Irradiation in Small Cell Lung Cancer: An Update." *Current Opinion in Oncology* 35(1):61–67.

Cremonesi, Marta, Laura Gilardi, Mahila Esmeralda Ferrari, Gaia Piperno, Laura Lavinia Travaini, Robert Timmerman, Francesca Botta, Guido Baroni, Chiara Maria Grana, Sara Ronchi, Delia Ciardo, Barbara Alicja Jereczek-Fossa, Cristina Garibaldi, and Roberto Orecchia. 2017. "Role of Interim 18F-FDG-PET/CT for the Early Prediction of Clinical Outcomes of Non-Small Cell Lung Cancer (NSCLC) during Radiotherapy or Chemo-Radiotherapy. A Systematic Review." *European Journal of Nuclear Medicine and Molecular Imaging* 44(11):1915–27.

van Diessen, J. N. A., M. La Fontaine, M. M. van den Heuvel, E. van Werkhoven, I. Walraven, W. V Vogel, J. S. A. Belderbos, and J. J. Sonke. 2020. "Local and Regional Treatment Response by (18)FDG-PET-CT-Scans 4weeks after Concurrent Hypofractionated Chemoradiotherapy in Locally Advanced NSCLC." *Radiother Oncol* 143:30–36.

van Diessen, Judi N. A., Matthew La Fontaine, Michel M. van den Heuvel, Erik van Werkhoven, Iris Walraven, Wouter V. Vogel, José S. A. Belderbos, and Jan Jakob Sonke. 2019. "Local and Regional Treatment Response by 18FDG-PET-CT-Scans 4 weeks after Concurrent Hypofractionated Chemoradiotherapy in Locally Advanced NSCLC." *Radiotherapy and Oncology* 143:30–36.

Dingemans, A. M. C., M. Früh, A. Ardizzoni, B. Besse, C. Faivre-Finn, L. E. Hendriks, S. Lantuejoul, S. Peters, N. Reguart, C. M. Rudin, D. De Ruysscher, P. E. Van Schil, J. Vansteenkiste, and M. Reck. 2021. "Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up☆." *Annals of Oncology* 32(7):839–53.

Ettinger, David S., Douglas E. Wood, Vice Chair, Dara L. Aisner, Wallace Akerley, Jessica R. Bauman, Ankit Bharat, Robert H. Lurie, Debora S. Bruno, Joe Y. Chang, Lucian R. Chirieac, Thomas A. D, Thomas J. Dilling, Michael Dobelbower, Scott Gettinger, Ramaswamy Govindan, Matthew A. Gubens, Mark Hennon, Leora Horn, Rudy P. Lackner, Michael Lanuti, Ticiana A. Leal, Jules Lin, Billy W. Loo, Renato G. Martins, Erminia Massarelli, Gregory A. Otterson, Sandip P. Patel, Gregory J. Riely, Steven E. Schild, Theresa A. Shapiro, Aditi P. Singh, James Stevenson, Alda Tam ϕ, Kurt W. Tauer, St Jude, Stephen C. Yang, NCCN Kristina Gregory, and Ocn Miranda Hughes. 2020. *National Comprehensive Cancer Network. NSCLC (Version 3.2020). Https://Www.Nccn.Org/Professionals/Physician_gls/Pdf/Nscl.Pdf. Accessed April 30, 2020.*

Eze, Chukwuka, Olarn Roengvoraphoj, Maximilian Niyazi, Guido Hildebrandt, Rainer Fietkau, Claus Belka, Farkhad Manapov. 2016. "Treatment Response and Prophylactic Cranial Irradiation Are Prognostic Factors in a Real-Life Limited-Disease Small-Cell Lung Cancer Patient Cohort Comprehensively Staged With Cranial Magnetic Resonance Imaging." *Clinical Lung Cancer* 0(0):4539–44.

Eze, Chukwuka, Nina Sophie Schmidt-Hegemann, Lino Morris Sawicki, Julian Kirchner, Olarn Roengvoraphoj, Lukas Käsmann, Lena M. Mittlmeier, Wolfgang G. Kunz, Amanda Tufman, Julien Dinkel, Jens Ricke, Claus Belka, Farkhad Manapov, and Marcus Unterrainer. 2021. "PET/CT Imaging for Evaluation of Multimodal Treatment Efficacy and Toxicity in Advanced NSCLC—Current State and Future Directions." *European Journal of Nuclear Medicine and Molecular Imaging* 1–15.

Faivre-Finn, Corinne, Michael Snee, Linda Ashcroft, Wiebke Appel, Fabrice Barlesi, Adityanarayan Bhatnagar, Andrea Bezjak, Felipe Cardenal, Pierre Fournel, Susan Harden, Cecile Le Pechoux, Rhona McMenemin, Nazia Mohammed, Mary O'Brien, Jason Pantarotto, Veerle Surmont, Jan P. Van Meerbeeck, Penella J. Woll, Paul Lorigan, and Fiona Blackhall. 2017. "Concurrent Once-Daily versus Twice-Daily Chemoradiotherapy in Patients with Limited-Stage Small-Cell Lung Cancer (CONVERT): An Open-Label, Phase 3, Randomised, Superiority Trial." *The Lancet Oncology* 18(8):1116–25.

Fowler, J. F. and R. Chappell. 2000. "Non-Small Cell Lung Tumors Repopulate Rapidly during Radiation Therapy [2]." *International Journal of Radiation Oncology Biology Physics* 46(2):516–17.

Gazdar, Adi F., Paul A. Bunn, and John D. Minna. 2017. "Small-Cell Lung Cancer: What We Know, What We Need to Know and the Path Forward." *Nature Reviews Cancer* nrc.2017.87.

Gensheimer, Michael F., Julian C. Hong, Christine Chang-Halpenny, Hui Zhu, Neville C. W. Eclov, Jacqueline To, James D. Murphy, Heather A. Wakelee, Joel W. Neal, Quynh Thu Le, Wendy Y. Hara, Andrew Quon, Peter G. Maxim, Edward E. Graves, Michael R. Olson, Maximilian Diehn, and Billy W. Loo. 2017. "Mid-Radiotherapy PET/CT for Prognostication and Detection of Early Progression in Patients with Stage III Non-Small Cell Lung Cancer." *Radiotherapy and Oncology* 125(2):338–43.

Goldstraw, Peter, Kari Chansky, John Crowley, Ramon Rami-Porta, Hisao Asamura, Wilfried E.E. Eberhardt, Andrew G. Nicholson, Patti Groome, Alan Mitchell, Vanessa Bolejack, David Ball, David G. Beer, Ricardo Beyruti, Frank Detterbeck, Wilfried Ernst Erich Eberhardt, John Edwards, Françoise Galateau-Sallé, Dorothy Giroux, Fergus Gleeson, James Huang, Catherine Kennedy, Jhingook Kim, Young Tae Kim, Laura Kingsbury, Haruhiko Kondo, Mark Krasnik, Kaoru Kubota, Antoon Lerut, Gustavo Lyons, Mirella Marino, Edith M. Marom, J. Van Meerbeeck, Takashi Nakano, Anna Nowak, Michael Peake, Thomas Rice, Kenneth Rosenzweig, Enrico Ruffini, Valerie Rusch, Nagahiro Saijo, Paul Van Schil, Jean Paul Sculier, Lynn Shemanski, Kelly Stratton, Kenji Suzuki, Yuji Tachimori, Charles F. Thomas, William Travis, Ming S. Tsao, Andrew Turrisi, Johan Vansteenkiste, Hirokazu Watanabe, Yi Long Wu, Paul Baas, Jeremy Erasmus, Seiki Hasegawa, Kouki Inai, Kemp Kernstine, Hedy Kindler, Lee Krug, Kristiaan Nackaerts, Harvey Pass, David Rice, Conrad Falkson, Pier Luigi Filosso, Giuseppe Giaccone, Kazuya Kondo, Marco Lucchi, Meinoshin Okumura, Eugene Blackstone, F. Abad Cavaco, E. Ansótegui Barrera, J. Abal Arca, I. Parente Lamelas, A. Arnau Obrer, R. Guijarro Jorge, G. K. Bascom, A. I. Blanco Orozco, M. González Castro, M. G. Blum, D. Chimondeguy, V. Cvijanovic, S. Defranchi, B. De Olaiz Navarro, I. Escobar Campuzano, I. Macía Vidueira, E. Fernández Araujo, F. Andreo García, K. M. Fong, G. Francisco Corral, S. Cerezo González, J. Freixinet Gilart, L. García Arangüena, S. García Barajas, P. Girard, T. Goksel, M. T. González Budiño, G. González Casaurrán, J. A. Gullón Blanco, J. Hernández Hernández, H. Hernández Rodríguez, J. Herrero Collantes, M. Iglesias Heras, J. M. Izquierdo Elena, E. Jakobsen, S. Kostas, P. León Atance, A. Núñez Ares, M. Liao, M. Losanovscky, G. Lyons, R. Magaroles, L. De Esteban Júlvez, M. Mariñán Gorospe, B. McCaughan, C. Kennedy, R. Melchor Íñiguez, L. Miravet Sorribes, S. Naranjo Gozalo, C. Álvarez De Arriba, M. Núñez Delgado, J. Padilla Alarcón, J. C. Peñalver Cuesta, J. S. Park,

H. Pass, M. J. Pavón Fernández, M. Rosenberg, V. Rusch, J. S. Sánchez De Cos Escuín, A. Saura Vinuesa, T. E. Strand, M. Serra Mitjans, D. Subotic, S. Swisher, R. Terra, C. Thomas, K. Tournoy, P. Van Schil, M. Velasquez, Y. L. Wu, and K. Yokoi. 2016. "The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer." *Journal of Thoracic Oncology* 11(1):39–51.

Gong, Linlin, Q. I. Wang, Lujun Zhao, Zhiyong Yuan, Ruijian Li, and Ping Wang. 2013. "Factors Affecting the Risk of Brain Metastasis in Small Cell Lung Cancer With Surgery: Is Prophylactic Cranial Irradiation Necessary for Stage I-III Disease?" *International Journal of Radiation Oncology*Biology*Physics* 85(1):196–200.

Grønberg, Bjørn Henning, Kristin Toftaker Killingberg, Øystein Fløtten, Odd Terje Brustugun, Kjersti Hornslien, Tesfaye Madebo, Seppo Wang Langer, Tine Schytte, Jan Nyman, Signe Risum, Georgios Tsakonas, Jens Engleson, and Tarje Onsøien Halvorsen. 2021. "High-Dose versus Standard-Dose Twice-Daily Thoracic Radiotherapy for Patients with Limited Stage Small-Cell Lung Cancer: An Open-Label, Randomised, Phase 2 Trial." *The Lancet. Oncology* 22(3):321–31.

Hellmann, Matthew D., Luis Paz-Ares, Reyes Bernabe Caro, Bogdan Zurawski, Sang-We Kim, Enric Carcereny Costa, Keunchil Park, Aurelia Alexandru, Lorena Lupinacci, Emmanuel de la Mora Jimenez, Hiroshi Sakai, Istvan Albert, Alain Vergnenegre, Solange Peters, Konstantinos Syrigos, Fabrice Barlesi, Martin Reck, Hossein Borghaei, Julie R. Brahmer, Kenneth J. O'Byrne, William J. Geese, Prabhu Bhagavatheeswaran, Sridhar K. Rabindran, Ravi S. Kasinathan, Faith E. Nathan, and Suresh S. Ramalingam. 2019. "Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer." *New England Journal of Medicine* 381(21):2020–31.

Ichinose, Y., N. Hara, M. Ohta, A. Motohiro, K. Hata, and K. Yagawa. 1989. "Brain Metastases in Patients with Limited Small Cell Lung Cancer Achieving Complete Remission. Correlation with TNM Staging." *Chest* 96(6):1332–35.

Iqbal, M. S., G. Vashisht, R. McMenemin, P. Atherton, F. McDonald, T. Simmons, A. Bradshaw, J. Kovarik, H. Turnbull, L. Dodd, P. Mulvenna, and A. Greystoke. 2019. "Hypofractionated Concomitant Chemoradiation in Inoperable Locally Advanced Non-Small Cell Lung Cancer: A Report on 100 Patients and a Systematic Review." *Clinical Oncology* 31(2):e1–10.

Iyengar, Puneeth, Elizabeth Zhang-Velten, Laurence Court, Kenneth Westover, Yulong Yan, Mu-Han Lin, Zhenyu Xiong, Mehul Patel, Douglas Rivera, Joe Chang, Mark Saunders, Anand Shivnani, Andrew Lee, Randall Hughes, David Gerber, Jonathan Dowell, Ang Gao, John Heinzerling, Ying Li, Chul Ahn, Hak Choy, and Robert Timmerman. 2021. "Accelerated Hypofractionated Image-Guided vs Conventional Radiotherapy for Patients With Stage II/III Non–Small Cell Lung Cancer and Poor Performance Status: A Randomized Clinical Trial." *JAMA Oncology*.

Jain, Aditya, Jia Luo, Yiyi Chen, Mark A. Henderson, Charles R. Thomas, and Timur Mitin. 2016. "Current Patterns of Care for Patients with Extensive-Stage SCLC: Survey of U.S. Radiation Oncologists on Their Recommendations Regarding Prophylactic Cranial Irradiation." *Journal of Thoracic Oncology* 11(8):1305–10.

Kaster, Tyler S., Brian Yaremko, David A. Palma, and George B. Rodrigues. 2015. "Radical-Intent Hypofractionated Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer: A Systematic Review of the Literature." *Clinical Lung Cancer* 16(2):71–79.

Knisely, Jonathan, Rajiv Sharma, Anuj Goenka, Aditya Halthore, C. Le Pechoux, A. Sun, BJ Slotman, et al., L. Gong, QI Wang, L. Zhao, Z. Yuan, R. Li, P. Wang, H. Zhu, Y. Bi, A. Han, et al., R. Tsuchiya, K. Suzuki, Y. Ichinose, et al., A. Sun, K. Bae, EM Gore, and et al. 2016. *PCI in Resected Small-Cell Lung Cancer*. Vol. 17. Elsevier.

Lad, Thomas, Steven Piantadosi, Paul Thomas, David Payne, John Ruckdeschel, and Giuseppe Giaccone. 1994. “A Prospective Randomized Trial to Determine the Benefit of Surgical Resection of Residual Disease Following Response of Small Cell Lung Cancer to Combination Chemotherapy.” *Chest* 106:320S-323S.

Lally, Brian E., Ann M. Geiger, James J. Urbanic, Jerome M. Butler, Stacy Wentworth, Michael C. Perry, Lynn D. Wilson, Janet K. Horton, Frank C. Detterbeck, Antonius A. Miller, Charles R. Thomas, and A. William Blackstock. 2009. “Trends in the Outcomes for Patients with Limited Stage Small Cell Lung Cancer: An Analysis of the Surveillance, Epidemiology, and End Results Database.” *Lung Cancer* 64(2):226–31.

Lester, Jason F., Fergus Macbeth, Elizabeth Toy, and Bernadette Coles. 2006. “Palliative Radiotherapy Regimens for Non-Small Cell Lung Cancer.” in *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd.

Machtay, M., F. Duan, B. A. Siegel, B. S. Snyder, J. J. Gorelick, J. S. Reddin, R. Munden, D. W. Johnson, L. H. Wilf, A. DeNittis, N. Sherwin, K. H. Cho, S. K. Kim, G. Videtic, D. R. Neumann, R. Komaki, H. Macapinlac, J. D. Bradley, and A. Alavi. 2013. “Prediction of Survival by [18F]Fluorodeoxyglucose Positron Emission Tomography in Patients with Locally Advanced Non-Small-Cell Lung Cancer Undergoing Definitive Chemoradiation Therapy: Results of the ACRIN 6668/RTOG 0235 Trial.” *J Clin Oncol* 31(30):3823–30.

Manapov, Farkhad, Lukas Käsmann, Olarn Roengvoraphoj, Maurice Dantes, Nina Sophie Schmidt-Hegemann, Claus Belka, and Chukwuka Eze. 2018. “Prophylactic Cranial Irradiation in Small-Cell Lung Cancer: Update on Patient Selection, Efficacy and Outcomes.” *Lung Cancer (Auckland, N.Z.)* 9:49–55.

Manapov, Farkhat, Gunther Klautke, and Rainer Fietkau. 2008. “Prevalence of Brain Metastases Immediately before Prophylactic Cranial Irradiation in Limited Disease Small Cell Lung Cancer Patients with Complete Remission to Chemoradiotherapy: A Single Institution Experience.” *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer* 3(6):652–55.

Micke, Patrick, Andreas Faldum, Tsegay Metz, Kai-Michael Beeh, Fernando Bittinger, Jan-Georg Hengstler, and Roland Buhl. 2002. “Staging Small Cell Lung Cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer--What Limits Limited Disease?” *Lung Cancer (Amsterdam, Netherlands)* 37(3):271–76.

Mu, Wei, Ilke Tunali, Jhanelle E. Gray, Jin Qi, Matthew B. Schabath, and Robert J. Gillies. 2019. “Radiomics of 18F-FDG PET/CT Images Predicts Clinical Benefit of Advanced NSCLC Patients to Checkpoint Blockade Immunotherapy.” *European Journal of Nuclear Medicine and Molecular Imaging*.

Murray, N., P. Coy, J. L. Pater, I. Hodson, A. Arnold, B. C. Zee, D. Payne, E. C. Kostashuk, W. K. Evans, P. Dixon, A. Sadura, R. Feld, M. Levitt, R. Wierzbicki, J. Ayoub, J. A. Maroun, and K. S. Wilson. 1993. “Importance of Timing for Thoracic Irradiation in the Combined Modality Treatment of Limited-Stage Small-Cell Lung Cancer.” *Journal of Clinical Oncology* 11(2):336–44.

Ohri, Nitin, William R. Bodner, Balazs Halmos, Haiying Cheng, Roman Perez-Soler, Steven M. Keller, Shalom Kalnicki, and Madhur Garg. 2017. “18F-Fluorodeoxyglucose/Positron Emission Tomography Predicts Patterns of Failure After Definitive Chemoradiation Therapy for Locally Advanced Non-Small Cell Lung Cancer.” *International Journal of Radiation Oncology Biology Physics* 97(2):372–80.

Ozawa, Yuichi, Minako Omae, Masato Fujii, Takashi Matsui, Masato Kato, Shinya Sagisaka, Kazuhiro Asada, Masato Karayama, Toshihiro Shirai, Kazumasa Yasuda, Yutaro Nakamura, Naoki Inui, Kazunari Yamada, Koshi Yokomura, and Takafumi Suda. 2015. “Management of Brain Metastasis with Magnetic Resonance Imaging and Stereotactic

Irradiation Attenuated Benefits of Prophylactic Cranial Irradiation in Patients with Limited-Stage Small Cell Lung Cancer." *BMC Cancer* 15:589.

Parisi, Elisabetta, Giovenzio Genestreti, Anna Sarnelli, Giulia Ghigi, Donatella Arpa, Marco Angelo Burgio, Giampaolo Gavelli, Alice Rossi, Emanuela Scarpi, Manuela Monti, Anna Tesei, Rolando Polico, and Antonino Romeo. 2019. "Accelerated Hypofractionated Radiotherapy plus Chemotherapy for Inoperable Locally Advanced Non-Small-Cell Lung Cancer: Final Results of a Prospective Phase-II Trial with a Long-Term Follow-Up." *Radiation Oncology* 14(1).

Le Péchoux, Cecile, Alexander Sun, Ben J. Slotman, Dirk De Ruysscher, José S. A. Belderbos, and Elizabeth M. Gore. 2016. "Prophylactic Cranial Irradiation for Patients with Lung Cancer." *The Lancet Oncology* 17(7).

Petty, W. Jeffrey and Luis Paz-Ares. 2023. "Emerging Strategies for the Treatment of Small Cell Lung Cancer: A Review." *JAMA Oncology* 9(3):419–29.

Pignon, Jean-Pierre, Rodrigo Arriagada, Daniel C. Ihde, David H. Johnson, Michael C. Perry, Robert L. Souhami, Ola Brodin, Rudolf A. Joss, Merrill S. Kies, Bernard Lebeau, Taisuke Onoshi, Kell Østerlind, Martin H. N. Tattersall, and Henry Wagner. 1992. "A Meta-Analysis of Thoracic Radiotherapy for Small-Cell Lung Cancer." *New England Journal of Medicine* 327(23):1618–24.

Pollom, Erqi L., Yushen Qian, Ben Y. Durkee, Rie von Eyben, Peter G. Maxim, David B. Shultz, Michael Gensheimer, Maximilian Diehn, and Billy W. Loo. 2016. "Hypofractionated Intensity-Modulated Radiotherapy for Patients With Non–Small-Cell Lung Cancer." *Clinical Lung Cancer* 17(6):588–94.

Prewett, S. L., S. Aslam, M. V. Williams, and D. Gilligan. 2012. "The Management of Lung Cancer: A UK Survey of Oncologists." *Clinical Oncology* 24(6):402–9.

Roengvoraphoj, O., C. Wijaya, C. Eze, M. Li, M. Dantes, J. Taugner, A. Tufman, R. M. Huber, C. Belka, and F. Manapov. 2017. "Analysis of Primary Tumor Metabolic Volume during Chemoradiotherapy in Locally Advanced Non-Small Cell Lung Cancer." *Strahlentherapie Und Onkologie*.

Roengvoraphoj, Olarn, Chukwuka Eze, Cherylina Wijaya, Maurice Dantes, Julian Taugner, Amanda Tufman, Rudolf Maria R. M. Huber, Peter Bartenstein, Claus Belka, and Farkhad Manapov. 2018. "How Much Primary Tumor Metabolic Volume Reduction Is Required to Improve Outcome in Stage III NSCLC after Chemoradiotherapy? A Single-Centre Experience." *European Journal of Nuclear Medicine and Molecular Imaging* 45(12):2103–9.

Schreiber, David, Justin Rineer, Jeremy Weedon, Dan Vongtama, Angela Wortham, Anne Kim, Peter Han, Kwang Choi, and Marvin Rotman. 2010. "Survival Outcomes with the Use of Surgery in Limited-Stage Small Cell Lung Cancer." *Cancer* 116(5):1350–57.

Seban, Romain-David, Laura Mezquita, Arnaud Berenbaum, Laurent Dercle, Angela Botticella, Cécile Le Pechoux, Caroline Caramella, Eric Deutsch, Serena Grimaldi, Julien Adam, Samy Ammari, David Planchard, Sophie Leboulleux, Benjamin Besse, and Benjamin Besse BenjaminBESSE. 2020. "Baseline Metabolic Tumor Burden on FDG PET/CT Scans Predicts Outcome in Advanced NSCLC Patients Treated with Immune Checkpoint Inhibitors." *European Journal of Nuclear Medicine and Molecular Imaging* 47:1147–57.

Seute, Tatjana, Pieter Leffers, Guul P. M. ten Velde, and Albert Twijnstra. 2008. "Detection of Brain Metastases from Small Cell Lung Cancer." *Cancer* 112(8):1827–34.

Siegel, Rebecca L., Kimberly D. Miller, Hannah E. Fuchs, and Ahmedin Jemal. 2022. "Cancer Statistics, 2022." *CA: A Cancer Journal for Clinicians* 72(1):7–33.

Siegel, Rebecca L., Kimberly D. Miller, and Ahmedin Jemal. 2020. "Cancer Statistics, 2020." *CA: A Cancer Journal for Clinicians* 70(1):7–30.

Slotman, Ben, Corinne Faivre-Finn, Gijs Kramer, Elaine Rankin, Michael Snee, Matthew Hatton, Pieter Postmus, Laurence Collette, Elena Musat, Suresh Senan, and EORTC Radiation Oncology Group and Lung Cancer Group. 2007. "Prophylactic Cranial Irradiation in Extensive Small-Cell Lung Cancer." *New England Journal of Medicine* 357(7):664–72.

Spigel, D., F. de Marinis, G. Giaccone, N. Reinmuth, A. Vergnenegre, C. H. Barrios, M. Morise, E. Felip, Z. G. Andric, S. Geater, M. Özgüroğlu, S. Mocci, M. McCleland, I. Enquist, K. M. Komatsubara, Y. Deng, H. Kuriki, X. Wen, J. Jassem, and R. S. Herbst. 2019. "LBA78 - IMpower110: Interim Overall Survival (OS) Analysis of a Phase III Study of Atezolizumab (Atezo) vs Platinum-Based Chemotherapy (Chemo) as First-Line (1L) Treatment (Tx) in PD-L1–Selected NSCLC." *Annals of Oncology* 30:v915.

Spigel, David R., Corinne Faivre-Finn, Jhanelle E. Gray, David Vicente, David Planchard, Luis Paz-Ares, Johan F. Vansteenkiste, Marina C. Garassino, Rina Hui, Xavier Quantin, Andreas Rimner, Yi-Long Wu, Mustafa Özgüroğlu, Ki H. Lee, Terufumi Kato, Maike de Wit, Takayasu Kurata, Martin Reck, Byoung C. Cho, Suresh Senan, Jarushka Naidoo, Helen Mann, Michael Newton, Piruntha Thiyagarajah, and Scott J. Antonia. 2022. "Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer." *Journal of Clinical Oncology* 40(12):1301–11.

Stahel, Rolf A., Robert Ginsberg, Klaus Havemann, Fred R. Hirsch, Daniel C. Ihde, Jacek Jassem, Karl Karrer, L. Herbert Maurer, Kell Osterlind, and Paul Van Houtte. 1989. "Staging and Prognostic Factors in Small Cell Lung Cancer: A Consensus Report." *Lung Cancer* 5(4–6):119–26.

Sung, Hyuna, Jacques Ferlay, Rebecca L. Siegel, Mathieu Laversanne, Isabelle Soerjomataram, Ahmedin Jemal, and Freddie Bray. 2021. "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries." *CA: A Cancer Journal for Clinicians* 71(3):209–49.

Takahashi, Toshiaki, Takeharu Yamanaka, Takashi Seto, Hideyuki Harada, Hiroshi Nokihara, Hideo Saka, Makoto Nishio, Hiroyasu Kaneda, Koichi Takayama, Osamu Ishimoto, Koji Takeda, Hiroshige Yoshioka, Motoko Tachihara, Hiroshi Sakai, Koichi Goto, and Nobuyuki Yamamoto. 2017. "Prophylactic Cranial Irradiation versus Observation in Patients with Extensive-Disease Small-Cell Lung Cancer: A Multicentre, Randomised, Open-Label, Phase 3 Trial." *The Lancet Oncology* 18(5):663–71.

Turrisi, Andrew T., Kyungmann Kim, Ronald Blum, William T. Sause, Robert B. Livingston, Ritsuko Komaki, Henry Wagner, Seena Aisner, and David H. Johnson. 1999. "Twice-Daily Compared with Once-Daily Thoracic Radiotherapy in Limited Small-Cell Lung Cancer Treated Concurrently with Cisplatin and Etoposide." *The New England Journal of Medicine* 340(4):265–71.

Unterrainer, M., C. Eze, H. Ilhan, S. Marschner, O. Roengvoraphoj, N. S. Schmidt-Hegemann, F. Walter, W. G. Kunz, P. Munck Af Rosenschöld, R. Jeraj, N. L. Albert, A. L. Grosu, M. Niyazi, P. Bartenstein, and C. Belka. 2020. "Recent Advances of PET Imaging in Clinical Radiation Oncology." *Radiation Oncology* 15(1):1–15.

Usmanij, E. A., L. F. de Geus-Oei, E. G. Troost, L. Peters-Bax, E. H. van der Heijden, J. H. Kaanders, W. J. Oyen, O. C. Schuurbiers, and J. Bussink. 2013. "18F-FDG PET Early Response Evaluation of Locally Advanced Non-Small Cell Lung Cancer Treated with Concomitant Chemoradiotherapy." *J Nucl Med* 54(9):1528–34.

Valeriani, Maurizio, Luca Marinelli, Luca Nicosia, Chiara Reverberi, Vitaliana De Sanctis, Davide Mollo, and Mattia Falchetto Osti. 2019. "Locally Advanced Inoperable Primary or Recurrent Non-Small Cell Lung Cancer Treated with 4-Week Hypofractionated Radiation Therapy (3 Gy/Fraction)." *Radiologia Medica* 124(12):1324–32.

Wang, Yu, Tao Zhang, Yilin Huang, Wei Li, Jingjing Zhao, Yin Yang, Canjun Li, Luhua Wang,

and Nan Bi. 2022. “Real-World Safety and Efficacy of Consolidation Durvalumab After Chemoradiation Therapy for Stage III Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis.” *International Journal of Radiation Oncology, Biology, Physics* 112(5):1154–64.

Westover, Kenneth D., Billy W. Loo, David E. Gerber, Puneeth Iyengar, Hak Choy, Maximilian Diehn, Randy Hughes, Joan Schiller, Jonathan Dowell, Zabi Wardak, David Sher, Alana Christie, Xian Jin Xie, Irma Corona, Akanksha Sharma, Margaret E. Wadsworth, and Robert Timmerman. 2015. “Precision Hypofractionated Radiation Therapy in Poor Performing Patients with Non-Small Cell Lung Cancer: Phase 1 Dose Escalation Trial.” *International Journal of Radiation Oncology Biology Physics* 93(1):72–81.

Xu, Jianlin, Haitang Yang, Xiaolong Fu, Bo Jin, Yuqing Lou, Yanwei Zhang, Xueyan Zhang, Hua Zhong, Huimin Wang, Dan Wu, and Baohui Han. 2016. “Prophylactic Cranial Irradiation for Patients with Surgically Resected Small Cell Lung Cancer.” *Journal of Thoracic Oncology*.

Yang, Chi-Fu Jeffrey, Derek Y. Chan, Paul J. Speicher, Brian C. Gulack, Xiaofei Wang, Matthew G. Hartwig, Mark W. Onaitis, Betty C. Tong, Thomas A. D’Amico, Mark F. Berry, and David H. Harpole. 2016. “Role of Adjuvant Therapy in a Population-Based Cohort of Patients With Early-Stage Small-Cell Lung Cancer.” *Journal of Clinical Oncology* 34(10):1057–64.

Yu, James B., Roy H. Decker, Frank C. Detterbeck, and Lynn D. Wilson. 2010. “Surveillance Epidemiology and End Results Evaluation of the Role of Surgery for Stage I Small Cell Lung Cancer.” *Journal of Thoracic Oncology* 5(2):215–19.

Yusuf, Dimas, Ryan N. Walton, Manjusha Hurry, Christie Farrer, D. Gwyn Bebb, and Winson Y. Cheung. 2020. “Population-Based Treatment Patterns and Outcomes for Stage III Non-Small Cell Lung Cancer Patients: A Real-World Evidence Study.” *American Journal of Clinical Oncology: Cancer Clinical Trials*.

Zelen, M. 1973. “Keynote Address on Biostatistics and Data Retrieval.” *CANCER CHEMOTHER.REP.* 4(2).

Zhu, Zheng Fei, Min Fan, Kai Liang Wu, Kuai Le Zhao, Huan Jun Yang, Gui Yuan Chen, Guo Liang Jiang, Li Juan Wang, Sen Zhao, and Xiao Long Fu. 2011. “A Phase II Trial of Accelerated Hypofractionated Three-Dimensional Conformal Radiation Therapy in Locally Advanced Non-Small Cell Lung Cancer.” *Radiotherapy and Oncology* 98(3):304–8.

5. Own Bibliography

Eze C, Roengvoraphoj O, Dantes M, Abdo R, Käsmann L, Schmidt-Hegemann NS, Belka C, Manapov F. Prophylactic Cranial Irradiation for Patients with Small Cell Lung Cancer in Germany: Pattern of Care Survey. Anticancer Res. 2018 Sep;38(9):5261-5265. doi: 10.21873/anticanres.12851. PMID: 30194176.

Eze C, Roengvoraphoj O, Manapov F. Prophylactic Cranial Irradiation in Resected Early-Stage Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2017 Jul 1;98(3):612-614. doi: 10.1016/j.ijrobp.2017.03.002. Epub 2017 Mar 8. PMID: 28581402.

Eze C, Roengvoraphoj O, Manapov F. Prophylactic Cranial Irradiation in Resected Small Cell Lung Cancer: Comprehensive Staging, Adjuvant Chemotherapy, and Strict Stratification of Pathological Stage Play a Role. J Thorac Oncol. 2017 Sep;12(9):e137-e138. doi: 10.1016/j.jtho.2017.03.021. PMID: 28838711.

Eze C*, Roengvoraphoj O*, Niyazi M, Hildebrandt G, Fietkau R, Belka C, Manapov F. Treatment Response and Prophylactic Cranial Irradiation Are Prognostic Factors in a Real-life Limited-disease Small-cell Lung Cancer Patient Cohort Comprehensively Staged With Cranial Magnetic Resonance Imaging. Clin Lung Cancer. 2017 Jul;18(4):e243-e249. doi: 10.1016/j.cllc.2016.11.005. Epub 2016 Nov 21. PMID: 28065620.

Manapov F*, **Eze C***, Niyazi M, Roengvoraphoj O, Li M, Hegemann NS, Hildebrandt G, Fietkau R, Belka C. Investigating a Correlation between Chemoradiotherapy Schedule Parameters and Overall Survival in a real-life LD SCLC Patient Cohort. J Cancer. 2016 Oct 17;7(14):2012-2017. doi: 10.7150/jca.16741. PMID: 27877216; PMCID: PMC5118664.

Manapov F, Niyazi M, Gerum S, Roengvoraphoj O, **Eze C**, Li M, Hildebrandt G, Fietkau R, Klautke G, Belka C. Evaluation of the role of remission status in a heterogeneous limited disease small-cell lung cancer patient cohort treated with definitive chemoradiotherapy. BMC Cancer. 2016 Mar 14;16:216. doi: 10.1186/s12885-016-2245-x. PMID: 26975407; PMCID: PMC4791754.

Roengvoraphoj O*, **Eze C***, Niyazi M, Li M, Hildebrandt G, Fietkau R, Belka C, Manapov F. Prognostic role of patient gender in limited-disease small-cell lung cancer treated with chemoradiotherapy. Strahlenther Onkol. 2017 Feb;193(2):150-155. English. doi: 10.1007/s00066-016-1073-x. Epub 2016 Nov 16. PMID: 27853828.

Eze C, Taugner J, Roengvoraphoj O, Schmidt-Hegemann NS, Käsmann L, Wijaya C, Belka C, Manapov F. Initial report on feasibility of PET/CT-based image-guided moderate hypofractionated thoracic irradiation in node-positive non-small cell lung Cancer patients with poor prognostic factors and strongly diminished lung function: a retrospective analysis. Radiat Oncol. 2019 Sep 4;14(1):163. doi: 10.1186/s13014-019-1304-2. PMID: 31484542; PMCID: PMC6727570.

Eze C, Taugner J, Schmidt-Hegemann NS, Käsmann L, Guggenberger JE, Roengvoraphoj O, Dantes M, Gjika A, Li M, Belka C, Manapov F. Feasibility of hypofractionated radiotherapy in inoperable node-positive NSCLC patients with poor prognostic factors and limited pulmonary reserve: a prospective observational study. Acta Oncol. 2021 Aug;60(8):1074-1078. doi: 10.1080/0284186X.2021.1941244. Epub 2021 Jun 22. PMID: 34155956.

Eze C, Guggenberger JE, Schmidt-Hegemann NS, Kenndoff S, Taugner J, Käsmann L, Schönecker S, Flörsch B, Li M, Belka C, Manapov F. Pooled analysis on image-guided moderately hypofractionated thoracic irradiation in inoperable node-positive/recurrent patients with non-small cell lung cancer with poor prognostic factors and severely limited pulmonary function and reserve. Cancer. 2022 Jun 15;128(12):2358-2366. doi: 10.1002/cncr.34201. Epub 2022 Apr 13. PMID: 35417563.

Kenndoff S, Nieto A, Guggenberger JE, Taugner J, Mansoorian S, Käsmann L, Schmidt-Hegemann NS, Manapov F, Belka C, **Eze C**. Dosimetric predictors of acute radiation pneumonitis and esophagitis in hypofractionated thoracic irradiation of non-small cell lung cancer patients with poor prognostic factors: Dosimetric predictors of acute radiation pneumonitis and esophagitis following hypofractionation in NSCLC. Adv Radiat Oncol. Published online November 14, 2024. doi:10.1016/j.adro.2024.101682

Zinn AB, Kenndoff S, Holzgreve A, Käsmann L, Guggenberger JE, Hering S, Mansoorian S, Schmidt-Hegemann NS, Reinmuth N, Tufman A, Dinkel J, Manapov F, Belka C, **Eze C**. Prognostic significance of pretreatment PET parameters in inoperable, node-positive NSCLC patients with poor prognostic factors undergoing hypofractionated radiotherapy: a single-institution retrospective study. EJNMMI Rep. 2024 Oct 8;8(1):32. doi: 10.1186/s41824-024-00220-w. PMID: 39375264; PMCID: PMC11458843.

Eze C, Lombardo E, Nierer L, Xiong Y, Niyazi M, Belka C, Manapov F, Corradini S. MR-guided radiotherapy in node-positive non-small cell lung cancer and severely limited pulmonary reserve: a report proposing a new clinical pathway for the management of high-risk patients. Radiat Oncol. 2022 Feb 24;17(1):43. doi: 10.1186/s13014-022-02011-8. PMID: 35209922; PMCID: PMC8876180.

Roengvoraphoj O*, **Eze C***, Wijaya C, Dantes M, Taugner J, Tufman A, Huber RM, Bartenstein P, Belka C, Manapov F. 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 Nov;45(12):2103-2109. doi: 10.1007/s00259-018-4063-7. Epub 2018 Jun 6. PMID: 29876620.

Eze C, Schmidt-Hegemann NS, Sawicki LM, Kirchner J, Roengvoraphoj O, Käsmann L, Mittlmeier LM, Kunz WG, Tufman A, Dinkel J, Ricke J, Belka C, Manapov F, Unterrainer M. PET/CT imaging for evaluation of multimodal treatment efficacy and toxicity in advanced NSCLC-current state and future directions. Eur J Nucl Med Mol Imaging. 2021 Nov;48(12):3975-3989. doi: 10.1007/s00259-021-05211-8. Epub 2021 Mar 24. PMID: 33760957; PMCID: PMC8484219.

Manapov F, **Eze C**, Holzgreve A, Käsmann L, Nieto A, Taugner J, Unterrainer M. PET/CT for Target Delineation of Lung Cancer Before Radiation Therapy. Semin Nucl Med. 2022 Nov;52(6):673-680. doi: 10.1053/j.semnuclmed.2022.05.003. Epub 2022 Jun 30. PMID: 35781392.

Holzgreve A, Taugner J, Käsmann L, Müller P, Tufman A, Reinmuth N, Li M, Winkelmann M, Unterrainer LM, Nieto AE, Bartenstein P, Kunz WG, Ricke J, Belka C, **Eze C***, Unterrainer M*, Manapov F*. Metabolic patterns on [18F]FDG PET/CT in patients with unresectable stage III NSCLC undergoing chemoradiotherapy ± durvalumab maintenance treatment. Eur J Nucl Med Mol Imaging. 2023 Jul;50(8):2466-2476. doi: 10.1007/s00259-023-06192-6. Epub 2023 Mar 23. PMID: 36951991; PMCID: PMC10250493.

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