Title

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Authors

Liu, Kevin X
Sierra-Davidson, Kailan
Tyan, Kevin
et al.

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Surgical complications and clinical outcomes after dose-escalated trimodality therapy for non-small cell lung cancer in the era of intensity-modulated radiotherapy

Kevin X. Liu, MD, DPhil[*,1], **Kailan Sierra-Davidson, MD, DPhil**[*,2], **Kevin Tyan, BA**[3], **Lawrence T. Orlina, CMD**[1], **J. Paul Marcoux, MD**[5], **Benjamin H. Kann, MD**[1], **David Kozono, MD, PhD**[1], **Raymond H. Mak, MD**[1], **Abby White, DO**[4], **Lisa Singer, MD, PhD**[1,6]

[1]Department of Radiation Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States.

[2]Department of Surgery, Massachusetts General Hospital, Boston, MA, United States.

[3]Harvard Medical School, Boston, MA, United States

[4]Division of Thoracic Surgery, Brigham and Women's Hospital, Boston, Massachusetts, United States

[5]Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA.

[6]Department of Radiation Oncology, University of California, San Francisco, CA, United States.

Abstract

Background: Trimodality therapy (TMT) with preoperative chemoradiation followed by surgical resection is used for locally-advanced non-small-cell lung cancer (LA-NSCLC). Traditionally, preoperative radiation doses ≤54 Gy are used due to concerns regarding excess morbidity, but little is known about outcomes and toxicities after TMT with intensity-modulated radiotherapy (IMRT) to higher doses.

Methods: A retrospective analysis of patients who received planned TMT with IMRT for LA-NSCLC at Brigham and Women's Hospital/Dana-Farber Cancer Institute between 2008 and 2017 was performed. Clinical and treatment characteristics, pathologic response, and surgical toxicity

Co-corresponding authors: Kevin X. Liu, Department of Radiation Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Harvard Medical School, 450 Brookline Ave, Boston, MA 02215. kevin_liu@dfci.harvard.edu, Telephone: 617-632-3591; Lisa Singer, Department of Radiation Oncology, University of California, San Francisco, 505 Parnassus Ave, San Francisco, CA 94143. lisa.singer@ucsf.edu, Telephone: 415-353-8900.

*equally contributing first-authors

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were assessed. Kaplan-Meier method and log-rank test was used for survival outcomes. Cox proportional-hazards regression was used for multivariable analysis.

Results: Forty-six patients received less than definitive doses of <60 Gy and 30 patients received definitive doses ≥60 Gy. Surgical outcomes, pathologic complete response, and postoperative toxicity did not differ significantly between the groups. With median follow-up of 3.6 years (range: 0.4–11.4), three-year locoregional recurrence-free survival (78.0% vs. 68.3%, p=0.51) and overall survival (OS) (61.0% vs. 69.4%, p=0.32) was not significantly different between patients receiving <60 Gy and ≥60 Gy, respectively. On multivariable analysis, older age, clinical stage, and length of hospital stay (LOS) >7 days were associated with OS.

Conclusions: With IMRT, there was no increased rate of surgical complications in patients receiving higher doses of radiation. Survival outcomes or LOS did not differ based on radiation dose, but increased LOS was associated with worse OS. Larger prospective studies are needed to further examine outcomes after IMRT in patients with LA-NSCLC receiving TMT.

Keywords

non-small cell lung cancer; trimodality; radiation; intensity modulated radiotherapy; IMRT; radiation dose; surgical complication; survival

Introduction

Lung cancer remains the leading cause of cancer mortality in the United States and around the world [1]. Management of locally-advanced non-small cell lung cancer (LA-NSCLC) frequently includes a combined modality approach of chemoradiation (CRT). However, there is mixed evidence surrounding the role of trimodality therapy (TMT), which involves surgical resection after neoadjuvant CRT. Early phase II studies reported encouraging survival rates and supported feasibility of this approach [2, 3]. The phase III Intergroup 0139 trial demonstrated improved progression-free survival (PFS) and fewer local relapses with chemoradiation to 45 Gy followed by surgery compared to chemoradiation alone [4]. Although there was no difference in overall survival (OS), surgical morbidity and mortality were relatively high in this study which may have affected these outcomes [4].

While early studies investigating TMT eschewed high radiation doses to limit serious postoperative complications, including acute respiratory distress syndrome (ARDS) [2–6], subsequent studies have demonstrated safety of higher preoperative radiation doses ≥60 Gy [7–11]. The phase II Radiation Therapy Oncology Group (RTOG) 0229 trial reported a 63% rate of mediastinal nodal clearance (MNC) in patients receiving 61.2 Gy during neoadjuvant CRT, and patients with MNC had a significantly higher two-year OS of 75% compared to 52% for patients with residual nodal disease [12]. Vyfhuis and colleagues [13] found that TMT utilizing definitive doses ≥60 Gy significantly improved survival compared to planned and unplanned bimodality therapy, and patients achieving MNC had significantly longer OS compared with patients with residual nodal disease. MNC after CRT has been consistently identified as a strong predictor for improved outcomes in TMT [2, 12–16]. Limited preoperative radiation therapy doses (45–50.4 Gy) may have contributed to lower

rates of MNC in early studies of TMT [12, 13]; however, few studies have directly compared the impact of neoadjuvant radiation dose on outcomes after TMT [8, 17–20].

The advent of modern radiation planning techniques with IMRT has enabled optimization of conformal dose delivery while sparing normal tissues [21]. However, there is limited data regarding the role of IMRT in TMT. For example, in the study by Vyfhuis et al. [13], only 23.7% of patients received intensity-modulated radiation therapy (IMRT). We therefore performed a retrospective analysis of patients with LA-NSCLC at our institution treated with TMT using IMRT to investigate postoperative complications and clinical outcomes between patients receiving higher (≥60 Gy) or lower (<60 Gy) doses of CRT.

Methods

The study was approved by the Dana-Farber Cancer Institute Institutional Review Board. A retrospective review of medical records was performed for patients diagnosed with non-small cell lung cancer, receiving neoadjuvant chemoradiotherapy with IMRT between 2008 and 2017 for planned TMT. Patients were excluded if they had Stage IV disease at presentation, did not subsequently receive a surgical resection, or received hypofractionated radiotherapy or stereotactic body radiotherapy. Neoadjuvant radiation dose was selected based on surgeon preference (n=11 surgeons for <60 Gy cohort and n=8 surgeons for ≥60 Gy cohort).

Per institutional practice, tumor and involved nodes were contoured as gross tumor volume, with margin to account for respiratory motion (using 4D-CT when available) and additional margin for microscopic disease of 5–8mm, and margin for daily setup of 5mm for planning target volume. Eclipse (Varian Medical System, Palo Alto, CA, USA) was used for radiation planning. Normal organ dose constraints included: spinal cord (maximum dose <50 Gy); lungs (mean dose <17 Gy, V5 Gy <50%, V20 Gy <30%); heart (V45 Gy <30%, V50 Gy <20%). All patients received fixed field IMRT or volumetric arc therapy delivered using Varian iX or TrueBeam linear accelerators (Varian Medical System, Palo Alto, CA, USA), and daily cone-beam CT was used. Chemotherapy was selected by the medical oncologist and regimens included 2 cycles of cisplatin/etoposide (n=55), cisplatin/pemetrexed (n=2), carboplatin/etoposide (n=1), or carboplatin/pemetrexed (n=1); and weekly carboplatin/paclitaxel (n=17). The surgical procedure was determined by thoracic surgeons, and included bronchoscopy with or without thoracoscopy followed by a thoracotomy or video-assisted thoracoscopic surgery (VATS). The thoracic surgeons considered many factors, including extent of disease and the patient's pulmonary and functional status, in determining the extent of resection.

We collected data regarding clinical and treatment characteristics, including sex, age at diagnosis, race/ethnicity, smoking history and status, medical comorbidities (history of diabetes mellitus, peripheral vascular disease, or coronary artery disease), prior lung surgery, histology, clinical stage, utilization of PET/CT, mediastinoscopy and endobronchial ultrasound for staging, radiation dose, and surgical approach (thoracotomy or VATS). Clinical and pathological TNM staging was defined at time of data collection according to American Joint Committee on Cancer (AJCC) 8th edition [22]. Dosimetric parameters,

including esophagus V50 Gy, esophagus mean dose, heart V45 Gy, heart V50 Gy, lungs V5 Gy, lungs V20 Gy, and mean lung dose (MLD), were collected. Resection status was defined as R0 for complete resection and R1 for microscopic residual disease [23]. Postoperative data were collected for length of hospital stay, readmission within 30 days, disposition at discharge, and complications within 30 days after surgery, including cardiovascular events, post-operative infection, intensive care unit (ICU) admission, bronchopleural fistula, requirement for re-intubation, and packed red blood cell transfusion. Toxicity was defined according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.

Follow-up time was defined as time from diagnosis of non-small cell lung cancer. Surveillance after TMT were planned to include history and physical examination and CT chest with or without PET/CT at least every 3–6 months; however, the exact timing of imaging and follow-up appointments were determined by oncology providers in discussion with the patients based on indication, such as new symptoms requiring earlier evaluation. At the time of recurrence, a PET/CT and MRI brain with contrast was performed. OS was analyzed as time to death with censoring at last follow-up. Lung cancer-specific survival (LCCS) was defined as time to death due to lung cancer. Locoregional recurrence-free survival (LRRFS) was defined as time to disease progression or recurrence at the surgical margin, ipsilateral hemithorax (including ipsilateral pleural metastases), and/or regional lymph node basins (pulmonary, hilar, mediastinal, subcarinal, and supraclavicular nodes). Distant metastasis-free survival (DMFS) was defined as time to disease progression or recurrence in the contralateral lung, in distant lymph node basins or outside of the ipsilateral hemithorax.

Statistical analyses were performed using Stata 15© (Stata Corp, College Station, TX). For categorical variables, Fisher’s exact test or Chi-square tests were used for comparisons between groups. Survival analyses were performed using Kaplan-Meier method and log-rank test. For univariate and multivariable analyses, Cox proportional hazards regression analyses were used. Important clinical and treatment characteristics, including sex, age, clinical stage, and surgical approach, as well as variables with $p<0.05$ on univariate analysis were included in the multivariable model. P-value <0.05 denoted significance.

Results

We identified 76 patients who underwent planned TMT with IMRT for LA-NSCLC, with 46 receiving <60 Gy and 30 receiving ≥60 Gy (Supporting Table 1). Patient demographics and disease characteristics are summarized in Table 1. Both groups were similar in age, sex, race, smoking history, and medical comorbidities (Table 1). There was a significant difference in distribution of clinical N stage, with more cases of N0 and N3 disease in the higher dose group ($p=0.02$). The majority of patients in both groups had stage IIIA or IIIB disease, with one patient in the lower dose group with stage IIB disease and three patients in the higher dose group with stage IIIC disease ($p=0.14$).

The proportion of patients undergoing concurrent cisplatin or carboplatin and etoposide (71.7% vs. 76.7%) with radiation was not different between the lower and higher dose

groups, respectively (p=0.7911). Of note, only 1 patient was unable to complete 2 cycles of either cisplatin/carboplatin and etoposide or cisplatin/carboplatin and pemetrexed due to failure to thrive. For the 17 patients receiving concurrent weekly chemotherapy with radiation, patients received median 5 weeks (range 3–6) of carboplatin/paclitaxel.

Dosimetric parameters are summarized in Table 2. MLD was significantly higher in the higher dose group (16.7 Gy vs. 13.6 Gy, p=0.005), but there were no differences in lung V5 Gy or V20 Gy. Mean esophagus dose (24.2 vs. 20.2 Gy, p=0.03) and esophagus V50 Gy distribution (19.6% vs. 1.5%, p<0.0001) were also significantly higher in the higher dose group. We noted no differences in heart V45 Gy or V50 Gy between the two groups.

Surgical characteristics, outcomes, and complications are summarized in Table 3. The majority of patients received thoracotomy (80.3%). Notably, there was a greater delay between the end of radiation therapy and surgery in the higher dose group (median 55 days, range 21–148) compared to the lower dose group (41 days, range 4–96, p<0.0001). There was no significant difference in rates of nodal clearance (ypN0) and pCR between the two groups (Table 3). Length of stay (LOS) and postoperative complications including grade ≥ 3 cardiovascular events, grade ≥ 2 infection, ICU admission, and readmission within 30 days, did not differ significantly between the two groups. One patient who received ≥60 Gy developed a small peripheral bronchopleural fistula on postoperative day 10, which resolved with conservative management. Of note, one patient in the lower dose group (mean heart dose of 13.4 Gy, MLD of 13.9 Gy, lung V5 Gy of 46.7%) and two patients in the higher dose group (mean heart doses of 6.4–17.9 Gy, MLDs of 17.3–18.7 Gy, lungs V5 Gy of 55.8–56.7%) died in the hospital following surgery due to ARDS.

We analyzed clinical outcomes based on the dose of neoadjuvant CRT received during TMT (Fig. 1). Median follow-up was 3.6 years (range: 0.4–11.4) for the cohort. The 3-year OS rate was not significantly different between patients receiving >60 Gy vs. ≥60 Gy (69.4% vs. 61.0%, p=0.32, Fig. 1A). Similarly, LCCS (p=0.36, Fig. 1B), DMFS (p=0.48, Fig. 1C), and LRRFS (p=0.51, Fig. 1D) were not different between the two groups.

We next performed an analysis of parameters that were associated with OS (Table 4). Significant univariate predictors of OS included age at diagnosis (HR 1.05, 95% CI: 1.01–1.09, p=0.02), LOS >7 days (HR 3.49, 95% CI: 1.75–6.94, p<0.001), ICU admission (HR 2.37, 95% CI: 1.13–4.98, p=0.02), and MLD ≥17 Gy (HR 2.29, 95% CI: 1.13–4.66, p=0.02). We included other parameters in the multivariable model based on clinical relevance and significance on univariate analysis, including clinical stage IIIB/IIIC vs. IIB/IIIA (p=0.15), surgical approach (p=0.08), and postoperative grade ≥3 toxicity (p=0.07). On multivariable analysis, age at diagnosis (HR 1.07, 95% CI: 1.02–1.12, p<0.01), clinical stage IIIB/IIIC (HR 2.63, 95% CI: 1.49–4.65, p=0.001), and LOS >7 days (HR 5.31, 95% CI: 1.92–14.65, p=0.001) were independent predictors of OS.

Discussion

This study presents one of the largest cohorts of patients receiving IMRT in TMT for LA-NSCLC and provides analysis of dosimetric parameters, surgical complications, and

clinical outcomes between patients receiving higher doses (≥60 Gy) or lower doses (<60 Gy) of CRT. Importantly, we found that while patients in the higher dose group received increased radiation doses to the esophagus and lungs compared to the lower dose group, there were no significant differences in postoperative toxicity events or complications. However, higher doses of radiation did not translate to improved pCR, disease-free rates, or survival outcomes.

Our findings suggest that higher radiation doses during neoadjuvant CRT using IMRT are well-tolerated without increased postoperative complications or grade ≥2 toxicities despite statistically significant increases in esophagus V50 Gy (median 19.6% vs. 1.5%), esophagus mean dose (24.2 vs. 20.2 Gy), and lung mean dose (16.7 vs. 13.6 Gy). Patients in the higher dose group had significantly longer time to surgery, suggesting that higher radiation dose may require longer recovery. Two patients in the high dose group who suffered grade 5 toxicities after surgery due to ARDS had MLD >17 Gy. MLD ≥17 Gy was associated with worse OS on univariate analysis, but when accounting for other factors in the multivariable model, MLD ≥17 Gy no longer significantly correlated with OS, suggesting that other confounding factors, such as clinical stage or extent of disease, may contribute to OS and higher MLD. Previous studies have noted higher rates of post-operative complications after higher radiation doses [19, 20]; however, these studies did not include patients receiving IMRT. Delivery of more precise conformal doses while sparing adjacent organs may contribute to our finding that radiation dose did not influence post-operative complications [24, 25]. Retrospective studies have demonstrated lower rates of grade ≥3 pneumonitis and other pulmonary and esophageal toxicities with IMRT compared to 3D-conformal radiotherapy in LA-NSCLC [21, 25–29].

Our cohort's 3-year OS rates of 69.4% for the >60 Gy and 61% for the ≥60 Gy group are on the higher end of the range reported after TMT in the literature [4, 12, 13], and compare favorably to modern 3-year OS rates achieved by chemoradiation alone (26–43.6%) or by chemoradiation followed by durvalumab (56.7%) for Stage III, unresectable NSCLC [30–32]. Higher radiation doses did not improve pCR, nodal clearance, or survival outcomes in our cohort, building upon previous studies with similar findings after TMT [8, 18–20]. Seder et al. [20] found that higher radiation doses of 60 Gy did not improve pCR, MNC or OS compared to 45 Gy. Two other studies found that higher radiation dose (≥60 Gy) CRT improves pCR compared with lower radiation dose (<60 Gy), but there was no OS benefit [8, 19]. A large database study of 1,041 patients, of which only 1.3% received IMRT, analyzed outcomes based on high-dose (54–74 Gy), standard-dose (45–54 Gy), and low-dose (36–45 Gy) neoadjuvant CRT [18]. Despite superior MNC in the high-dose group, median OS was shorter compared to patients with standard-dose or low-dose CRT [18]. Our data further suggests extensive surgical resections may provide adequate local control and compensate for a lower neoadjuvant radiation dose (<60 Gy), which is not considered a curative dose in LA-NSCLC with chemoradiation alone. There may also be confounding by indication in the higher dose group, which featured a greater distribution of higher clinical stage disease including more patients with N3 and stage IIIB/IIIC disease. Of note, the three patients with IIIC disease per AJCC 8th edition staging were treated in the era of the AJCC 7th edition with Stage IIIB disease.

We found other clinical parameters that were associated with OS within our entire cohort. On multivariable analysis, increased age, advanced clinical stage, and increased LOS were significant predictors for OS. LOS >7 days (upper quartile) was associated with a 5-fold increased risk of mortality. Prolonged LOS is not well-studied in NSCLC. In general, LOS is used as a measure of postoperative outcomes in NSCLC and other cancers; however, some studies have shown that baseline patient characteristics may greatly contribute to the variance in LOS [33–35]. Interestingly, prolonged LOS has been found to be a significant predictor of OS following esophagectomy for esophageal cancer, and was thought to be related to delay of postoperative oncologic treatment and reduced administration of salvage therapy [36]. Thus, LOS may reflect a patient's ability to recover from a significant surgery, and predict tolerability of further therapy at the time of progression or recurrence. However, LOS may also be a reflection of preoperative comorbidity and baseline functional status and therefore it is challenging to conclude whether worse OS with longer hospital stays can be attributed to malignancy or to other comorbid conditions. Future studies are needed to elucidate the impact of LOS on outcomes and assess whether this may be an area of intervention.

While our study reports on one of the largest cohorts treated with IMRT during TMT and provides important insight on the effect of definitive radiation dose on outcomes, we acknowledge certain limitations of our analysis, including its retrospective nature in a single institution, a relatively small cohort, and limited records for some patients followed-up at their home institution after completion of treatment. Given 22.4% of patients had N0 disease at diagnosis, the rate of nodal downstaging is likely an overestimation. Other baseline clinical and treatment characteristics between the two groups may explain the lack of survival benefit with definitive doses of CRT. For example, more patients in the higher dose group had N3 disease, which may have adversely affected outcomes in the higher dose group. In addition, more patients in the higher dose group had stage IIIB/IIIC disease, and stage IIIB/IIIC disease was significantly associated with OS on multivariable analysis. In addition, the increased delay between end of radiation and surgery may have contributed to worse outcomes in the higher dose group, as a retrospective multivariable analysis controlling for radiation dose in TMT found significant decrement in OS for patients undergoing surgery later than 42 days after completing CRT [37]. However, time between end of radiation and surgery >45 days was not significantly associated with OS. While we did not find significant differences between dose groups in terms of postoperative toxicity incidence and grading, we were unable to assess radiation-specific toxicities prior to surgery. Finally, it is important to note that after the PACIFIC trial demonstrated improved PFS and OS, durvalumab has become the new standard of care for patients with unresectable LA-NSCLC who have not progressed after CRT [38, 39]. Given the benefit of durvalumab after chemoradiation, it is possible that patient selection for TMT has now changed and thus, we did not collect data after 2017. Furthermore, there may be additional survival benefit with adjuvant therapy following neoadjuvant treatment and surgery [40]. Future prospective studies should investigate the clinical utility of TMT in the context of advanced radiation therapy techniques, additional adjuvant therapy, or improved systemic therapies, such as durvalumab.

In conclusion, we demonstrate that in the era of IMRT, TMT with higher doses (≥60 Gy) for patients with LA-NSCLC does not increase surgical complications or postoperative toxicity compared to patients receiving lower doses (<60 Gy). However, while the dose of radiation using IMRT did not impact pathologic response or clinical outcomes, prolonged LOS was an independent predictor of survival. Given these findings, further prospective studies with larger cohorts are needed to further understand the benefit of IMRT and radiation dose for patients undergoing TMT for LA-NSCLC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

3D-CRT	three-dimensional conformal radiation therapy
AJCC	American Joint Committee on Cancer
ARDS	acute respiratory distress syndrome
CI	confidence interval
CRT	chemoradiation
CT	computed tomography
DMFS	Distant metastasis-free survival
EBUS	endobronchial ultrasound
Gy	Gray
HR	hazard ratio
ICU	intensive care unit
IMRT	intensity-modulated radiotherapy
LA	locally advanced
LCCS	lung cancer-specific survival
LOS	length of hospital stay
LRRFS	Locoregional recurrence-free survival
MLD	mean lung dose
MNC	mediastinal nodal clearance

NSCLC	non-small cell lung cancer
OS	overall survival
pCR	pathologic complete response
PET/CT	positron emission tomography/computed tomography
PFS	progression-free survival
RTOG	Radiation Therapy Oncology Group
TMT	trimodality therapy
VATS	video-assisted thoracoscopic surgery

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Highlights

- Little is known about outcomes and toxicities after preplanned trimodality therapy with IMRT to higher doses.
- Using IMRT, there was no difference in complications or overall survival for patients receiving <60 Gy and ≥60 Gy
- On univariate and multivariable analyses, increased length of hospital stay was significantly associated with worse overall survival

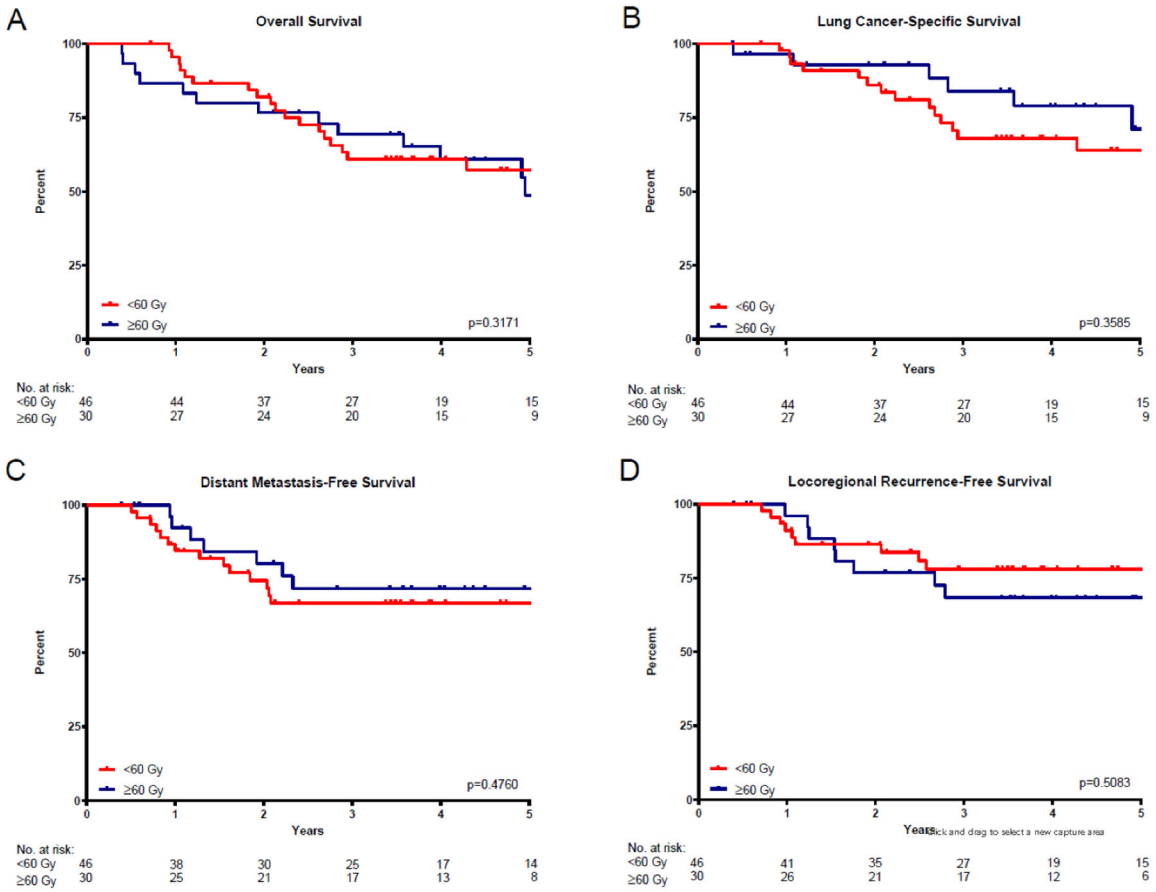

Figure 1. Survival outcomes for patients undergoing trimodality therapy receiving <60 Gy and ≥60 Gy using IMRT.

(A) Overall survival, (B) lung cancer-specific survival, (C) distant metastasis-free survival, and (D) locoregional recurrence-free survival for patients undergoing trimodality therapy receiving <60 Gy and ≥60 Gy using IMRT. Kaplan-Meier survival curves with log-rank test.

Table 1.

Demographic and clinical characteristics of patients receiving neoadjuvant chemoradiation with <60 Gy and ≥ 60 Gy

	Patients receiving <60 Gy, n (%) or median	Patients receiving ≥ 60 Gy, n (%) or median	P-value
Age at diagnosis (years)	62.1 (range: 44.6–81.3)	62.0 (range: 45.9–76.7)	0.78
Sex			
Female	24 (52.2%)	19 (63.3%)	0.37
Male	22 (47.8%)	11 (36.7%)	
Race			
Non-Hispanic White	45 (97.8%)	28 (93.3%)	0.56
Other	1 (2.2%)	2 (6.7%)	
Smoking History			
Never Smoker	4 (8.7%)	4 (13.3%)	0.80
Active Smoker	22 (47.8%)	15 (50.0%)	
Former Smoker	20 (43.5%)	11 (36.7%)	
History of diabetes mellitus			
Yes	3 (6.5%)	5 (16.7%)	0.25
No	43 (93.5%)	25 (83.3%)	
History of peripheral vascular disease			
Yes	8 (17.4%)	11 (36.7%)	0.10
No	38 (82.6%)	19 (63.3%)	
History of coronary artery disease			
Yes	6 (13.0%)	7 (23.3%)	0.35
No	40 (87.0%)	23 (76.7%)	
History of prior lung surgery			
Yes	6 (13.0%)	1 (3.3%)	0.23
No	40 (87.0%)	29 (96.7%)	
Histology			
Adenocarcinoma	32 (69.6%)	20 (66.7%)	0.91
Squamous cell carcinoma	12 (26.1%)	9 (30.0%)	
Other	2 (4.3%)	1 (3.3%)	
Clinical T stage			
1	8 (17.4%)	4 (13.3%)	0.49
2	12 (26.1%)	4 (13.3%)	
3	11 (23.9%)	10 (33.3%)	
4	15 (32.6%)	12 (40.0%)	
Clinical N stage			
0	8 (17.4%)	9 (30.0%)	0.02*
1	5 (10.9%)	2 (6.7%)	
2	32 (69.6%)	13 (43.3%)	
3	1 (2.2%)	6 (20.0%)	

	Patients receiving <60 Gy, n (%) or median	Patients receiving ≥ 60 Gy, n (%) or median	P-value
Clinical stage			
IIB	1 (2.2%)	0 (0.0%)	0.14
IIIA	30 (65.2%)	17 (56.7%)	
IIIB	15 (32.6%)	10 (33.3%)	
IIIC	0 (0.0%)	3 (10.0%)	
Staging PET/CT			
Yes	46 (100.0%)	29 (96.7%)	0.40
No	0 (0.0%)	1 (3.3%)	
Staging mediastinoscopy			
Yes	38 (82.6%)	22 (73.3%)	0.39
No	8 (17.4%)	8 (26.7%)	
Staging EBUS			
Yes	31 (67.4%)	18 (60.0%)	0.63
No	15 (32.6%)	12 (40.0%)	

Abbreviations: Gy, gray; PET/CT, positron emission tomography/computed tomography; EBUS, endobronchial ultrasound.

Table 2.

Dosimetric parameters for patients receiving neoadjuvant chemoradiation with <60 Gy and ≥ 60 Gy

	Patients receiving <60 Gy, median	Patients receiving ≥ 60 Gy, median	P-value
Esophagus V50 Gy (%)	1.5 (range: 0–34.3)	19.6 (range: 0–43.5)	<0.0001*
Esophagus mean (Gy)	20.2 (range: 4.1–42.0)	24.2 (range: 6.3–45.1)	0.03*
Heart V45 Gy (%)	3.6 (range: 0–36.9)	6.6 (range: 0–37.9)	0.13
Heart V50 Gy (%)	1.2 (range: 0–35.4)	4.9 (range: 0–24.3)	0.10
Lungs V5 Gy (%)	45.6 (range: 17.1–69.8)	51.7 (range: 10.9–73.0)	0.15
Lungs V20 Gy (%)	24.3 (range: 8.4–36.6)	28.1 (range: 5.1–36.6)	0.17
Lungs mean (Gy)	13.6 (range: 5–19.2)	16.7 (range: 3.2–21.9)	0.005*

Abbreviations: Gy, gray; V5 Gy, volume of organ at risk receiving 5 Gy; V20 Gy, volume of organ at risk receiving 20 Gy; V45 Gy, volume of organ at risk receiving 45 Gy; V50 Gy, volume of organ at risk receiving 50 Gy

Table 3.

Surgical characteristics and outcomes for patients receiving neoadjuvant chemoradiation with <60 Gy and ≥ 60 Gy

	Patients receiving <60 Gy, n (%) or median	Patients receiving ≥ 60 Gy, n (%) or median	P-value
Surgical approach			
Thoracotomy	35 (77.8%)	26 (86.7%)	0.38
VATS	10 (22.2%)	4 (13.3)	
Time from end of radiation to surgery (days)	41 (range: 4–96)	55 (21–148)	<0.0001*
Resection status			
R0	41 (91.1%)	28 (93.3%)	1.00
R1	4 (8.9%)	2 (6.7%)	
Complete pathologic response			
Yes	6 (13.0%)	5 (16.7%)	0.74
No	40 (87.0%)	25 (83.3%)	
ypT stage			
0	8 (17.4%)	8 (26.7%)	0.61
1	12 (26.1%)	10 (33.3%)	
2	16 (34.8%)	6 (20.0%)	
3	7 (15.2%)	5 (16.7%)	
4	3 (6.5%)	1 (3.3%)	
ypN stage			
0	31 (67.4%)	16 (53.3%)	0.36
1	3 (6.5%)	5 (16.7%)	
2	11 (23.9%)	7 (23.3%)	
3	0 (0.0%)	1 (3.3%)	
X	1 (2.2%)	1 (3.3%)	
Length of hospital stay	6 (range: 3–48)	6 (range: 3–20)	0.38
Post-operative toxicity			
Grade 2	7 (15.6%)	3 (10.0%)	0.77
Grade 3	10 (22.2%)	6 (20.0%)	
Grade 4	1 (2.2%)	0 (0.0%)	
Grade 5	1 (2.2%)	2 (6.7%)	
Grade ≥ 3 cardiovascular toxicity			
Yes	7 (15.6%)	4 (13.3%)	1.00
No	38 (84.4%)	26 (86.7%)	
Grade ≥ 2 post-operative infection			
Yes	7 (15.6%)	8 (26.7%)	0.26
No	38 (84.4%)	22 (73.3%)	
ICU admission			
Yes	10 (22.2%)	6 (20.0%)	1.00
No	35 (77.8%)	24 (80.0%)	

	Patients receiving <60 Gy, n (%) or median	Patients receiving ≥ 60 Gy, n (%) or median	P-value
Post-operative re-intubation			
Yes	4 (8.9%)	3 (10.0%)	1.00
No	41 (91.1%)	27 (90.0%)	
Post-operative packed red blood cell transfusion			
Yes	7 (15.9%)	3 (10.0%)	0.73
No	37 (84.1%)	27 (90.0%)	
Readmission within 30 days			
Yes	3 (6.7%)	6 (20.7%)	0.14
No	42 (93.3%)	23 (79.3%)	
Disposition			
Home	42 (93.3%)	25 (83.3%)	0.37
Rehab	2 (4.4%)	3 (10.0%)	
Died in hospital	1 (2.2%)	2 (6.7%)	

Abbreviations: Gy, gray; VATS, video-assisted thoracoscopic surgery; ICU, intensive care unit

Table 4.

Univariate and multivariable analyses for parameters associated with overall survival

	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Sex				
Female	Ref.		Ref.	
Male	1.23 (0.64–2.38)	0.53	1.15 (0.55–2.41)	0.71
Age at diagnosis (years) †	1.05 (1.01–1.09)	0.02 *	1.07 (1.02–1.12)	0.004 *
Race				
Non-Hispanic White	Ref.			
Other	0.68 (0.09–4.97)	0.70		
Histology				
Adenocarcinoma	Ref.			
Squamous cell carcinoma	1.13 (0.55–3.12)	0.75		
Other	1.65 (0.37–7.44)	0.51		
Clinical Stage				
IIB/IIIA	Ref.		Ref.	
IIIB/IIIC	1.63 (0.84–3.15)	0.15	2.63 (1.49–4.65)	0.001 *
Time from end of radiation to surgery				
≤ 45 days	Ref.			
>45 days	1.32 (0.69–2.56)	0.40		
Surgical approach				
Thoracotomy	Ref.		Ref.	
VATS	1.99 (0.91–4.36)	0.08	2.16 (0.92–5.08)	0.08
Complete Response				
No	Ref.			
Yes	0.54 (0.19–1.54)	0.25		
Length of stay (days) †	1.06 (1.02–1.10)	0.002 *		
Length of stay				
≤ 7 days	Ref.		Ref.	
>7 days	3.49 (1.75–6.94)	<0.001 *	5.31 (1.92–14.65)	0.001 *
ICU admission				
No	Ref.		Ref.	
Yes	2.37 (1.13–4.98)	0.02 *	0.79 (0.31–2.03)	0.62
Grade ≥ 3 toxicity				
No	Ref.		Ref.	
Yes	1.93 (0.96–3.87)	0.07	1.59 (0.65–3.87)	0.31
Radiation dose				
<60 Gy	Ref.			
≥ 60 Gy	1.41 (0.72–2.76)	0.32		

	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Heart V45				
<30%	Ref.			
≥ 30%	1.75 (0.41–7.39)	0.45		
Heart V50				
<20%	Ref.			
≥ 20%	1.09 (0.33–3.59)	0.89		
Lungs V5				
<50%	Ref.			
≥ 50%	1.34 (0.68–2.64)	0.41		
Lungs V20				
<30%	Ref.			
≥ 30%	1.67 (0.78–3.56)	0.19		
Mean lung dose				
<17 Gy	Ref.		Ref.	
≥ 17 Gy	2.29 (1.13–4.66)	0.02 *	1.47 (0.63–3.45)	0.37

† denotes continuous variable;

* denotes significance with p-value <0.05

Abbreviations: CI, confidence interval; HR, hazard ratio; VATS, video-assisted thoracoscopic surgery; ICU, intensive care unit