Journal Pre-proof

Dosimetry and Toxicity Comparison of Three-Dimensional Conformal Radiation Therapy and Intensity-Modulated Radiation Therapy in Locally Advanced Lung Cancer Across a Large Statewide Quality Collaborative

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PII: S0360-3016(25)00236-6
DOI: https://doi.org/10.1016/j.ijrobp.2025.03.007
Reference: ROB 29293

To appear in: *International Journal of Radiation Oncology, Biology, Physics*

Received date: 16 December 2024
Revised date: 17 February 2025
Accepted date: 2 March 2025

Please cite this article as: Steven G. Allen MD PhD , Caitlin A. Schonewolf MD , Matthew J. Schipper PhD , Huiying (Maggie) Yin MS , Peter A. Paximadis MD , Larry L. Kestin MD , Michael Dominello DO , Melissa Wilson MS , Martha M. Matuszak PhD , James A. Hayman MD MBA , Shruti Jolly MD MBA , on behalf of: Michigan Radiation Oncology Quality Consortium as part of the Blue Cross Blue Shield of Michigan and Blue Care Network of Michigan Value Partnerships Program, Dosimetry and Toxicity Comparison of Three-Dimensional Conformal Radiation Therapy and Intensity-Modulated Radiation Therapy in Locally Advanced Lung Cancer Across a Large Statewide Quality Collaborative, *International Journal of Radiation Oncology, Biology, Physics* (2025), doi: https://doi.org/10.1016/j.ijrobp.2025.03.007

Dosimetry and Toxicity Comparison of Three-Dimensional Conformal Radiation Therapy and Intensity-Modulated Radiation Therapy in Locally Advanced Lung Cancer Across a Large Statewide Quality Collaborative

Running Title:
3D-CRT vs IMRT dosimetry and toxicity in NSCLC

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Disclosures:
Authors report grant funding and/or salary support from Blue Cross Blue Shield of Michigan and Blue Care Network (Drs. Hayman, Jolly, Matuszak, Schipper; H.Yin); Varian Medical Systems (Dr. Matuszak); Consulting fees from Innovative Analytics (Dr. Schipper); Leadership or fiduciary role for Varian Medical Systems and AstraZeneca (Dr. Jolly); employment and stock options for DELFI Diagnostics (Dr. Schonewolf); and support for meeting attendance from AstraZeneca (Dr. Dominello).

Funding:
MROQC is financially supported by Blue Cross Blue Shield of Michigan and the Blue Care Network of Michigan as part of the BCBSM Value Partnerships Program

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Data Sharing Statement:
We are not authorized to share MROQC data. The data is individually owned by the member institutions of MROQC.

Abstract

Purpose/Objective(s): Use of intensity-modulated radiation therapy (IMRT) versus three-dimensional conformal external beam radiation therapy (3D-CRT) for definitive chemoradiation therapy (CRT) in locally advanced non-small cell lung cancer (LA-NSCLC) has been associated with decreased late pneumonitis, decreased high dose to the heart (itself associated with improved overall survival), and improved patient quality of life. In a statewide radiation oncology quality consortium, we sought to evaluate the impact of IMRT versus 3D-CRT treatment technique on dosimetry and toxicity.

Materials/Methods: From 2012 to 2022, 1746 LA-NSCLC patients meeting inclusion criteria underwent definitive RT (90% CRT) with either 3D-CRT (n=313) or IMRT (n=1433) and were enrolled in the [quality consortium] prospective, multicenter statewide initiative. Physician reported toxicity and patient reported outcomes (PROs) were collected during treatment through 6 months after RT and compared by treatment technique. Inverse probability of treatment weighting (IPTW) was used to account for differences in prognostic factors between IMRT and 3D-CRT patients.

Results: Compared with 3D-CRT patients, IMRT patients had significantly larger PTVs (median 386 cc vs 292 cc, p<0.0001) and were more likely to have Stage IIIB disease (34.3% vs 23.0%, p<0.0001). After adjustment using IPTW, treatment with IMRT compared to 3D-CRT reduced high dose to the lung (mean V30Gy 17.9% vs 19.2%, p=0.027) and heart (proportion with V40Gy≥20% 6.4% vs 15.3% p<0.0001). In logistic regression models using IPTW, through 6 months of early follow-up there were no significant differences between 3D-CRT and IMRT in rates of grade 2+ acute esophagitis (Odds Ratio = 1.02; 95% CI=0.73,1.42; p=0.91) and grade 2+ early pneumonitis (OR = 1.62; 95% CI:0.89, 2.96; p=0.11) or in likelihood of a clinically significant decline in PROs.

Conclusion: With late follow-up ongoing, the current study supports the continued preferential use of IMRT over 3D-CRT for LA-NSCLC treatment due to improvements in heart and lung doses.

Introduction

Treatment of locally advanced non-small cell lung cancer (LA-NSCLC) has progressed over the past several decades including concurrent chemotherapy, optimal dose-finding, and adjuvant immunotherapy, which have resulted in significant improvements in survival for these patients.[1] As treatments improve disease outcomes and patients live longer, there is a need to reduce early and late toxicity associated with definitive treatment, and thus, widen the therapeutic index for patients with LA-NSCLC.[2]

Technologic improvements in radiation therapy (RT) planning have evolved from three-dimensional conformal external beam radiation therapy (3D-CRT) to more conformal planning with intensity-modulated radiation therapy (IMRT) with multiple studies showing clear dosimetric advantages of IMRT over 3D-CRT. [3–5] While there are not randomized comparisons between treatment techniques, the most informative data comes from secondary analyses of RTOG 0617 in which treatment technique was a stratification factor.[6–8] While these analyses did not show a difference in acute esophageal toxicity, they did demonstrate long-term benefit in patient-reported outcome (PRO) measures, decreased rates of grade 3+ late pneumonitis (generally at >12 months), and decreased high dose to the heart (which is associated with improved overall survival) with IMRT vs 3D-CRT treatment.[6–8] Other non-randomized comparisons between IMRT and 3D-CRT have suggested improvements in late toxicity with IMRT.[9–14] Differences on clinical trials may not be broadly generalizable when evaluated in larger, more diverse patient populations who are treated with different techniques off a clinical trial protocol.[15] Therefore, we sought to clarify the impact of IMRT versus 3D-CRT treatment technique on toxicity, organ at risk dosimetry, and PROs among patients with LA-NSCLC in a large statewide collaborative for a broader evaluation of real-world outcomes.

Methods and Materials

Data collection and samples

The [quality consortium] is a multicenter, statewide collaborative quality initiative among academic and community practice treatment sites in partnership with [statewide health insurance provider]. [Quality consortium] represents approximately 60% of the radiation oncology volume in the state and is financially supported by [statewide health insurance provider partner program]. Although [statewide health insurance provider] and [quality consortium] work collaboratively, the opinions, beliefs, and viewpoints expressed by the authors do not necessarily reflect the opinions, beliefs, and viewpoints of [statewide health insurance provider] or any of its employees. [Quality consortium] maintains a prospectively collected database including patient-level demographic information, clinical and oncologic data, and treatment and dosimetric details including dose-volume histograms (DVHs), DICOM planning images, and RT structures and doses. The work of [quality consortium] is designated as quality improvement and has been reviewed by the [state university] Institutional Review Board (IRB), which has determined it to be exempt from further IRB oversight. Eligible patients included those with AJCC 7th ed. Stages II-III NSCLC who were treated with definitive-dose radiotherapy courses from 2012 to 2022. Patients were excluded if the overall treatment course included surgery, they received hypofractionated or palliative courses of treatment (24 fractions or fewer), and/or patients had missing covariates. The median dose for included patients was 60 Gy (interquartile range 60 Gy to 66 Gy) with median fractions 30 (interquartile range 30 to 33 fractions). A total of 1746 patients fit these inclusion criteria and **Figure 1** details the flow of patients into our analytical sample.

Outcome measures

Outcome measures included both physician recorded toxicity and PROs. Physician assessments of toxicity are recorded weekly during on treatment visits and in follow-up at 1-, 3-

and 6-month visits post-radiation therapy. Toxicity is scored using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Acute esophagitis was evaluated during treatment. For early pneumonitis, the maximum CTCAE grade observed at any evaluation during the last week of RT or later was recorded. Patient surveys for PROs are offered at baseline, at completion of RT, and at each follow-up (1-, 3- and 6-month visits post-RT). Participation in completing survey questions is voluntary and **Supplemental Table 1** highlights response rates at each timepoint. PROs were assessed using the Functional Assessment of Cancer Therapy Lung Trial Outcome Index (FACT-L TOI).[16] Changes of ≥5 points on the TOI are considered clinically meaningful.[17]

Statistical analysis

Generalized Linear Mixed Models were used to compare the rates of esophagitis and pneumonitis between the IMRT and 3D-CRT treated patients. To account for baseline differences between the two treatment groups and obtain unbiased estimates of the effect of treatment, we utilized Inverse Probability of Treatment Weights (IPTWs).[18] Weights were calculated as the inverse of the probability of actual treatment and estimated from a logistic regression propensity model. With this approach, the target estimand is the average treatment effect in the entire population represented in this study. The weights allow for balancing baseline covariates between the two treatment arms through upweighting patients that are underrepresented in one treatment group relative to the other. For example, patients with Stage IIIB disease in the 3D-CRT cohort are upweighted to account for the fact that there are fewer such patients treated with 3D-CRT compared to IMRT (**Table 1**). Covariates included in the propensity model are listed in **Supplemental Methods**. In addition to the IPTWs, the toxicity outcomes models included potentially prognostic covariates (**Supplemental Tables 2 and 3**) and a hospital level random intercept to account for differences between hospitals not captured by the patient covariates.

Separate models were fit for grade 2+ and grade 3+ acute esophagitis, grade 2+ and grade 3+ early pneumonitis, and for clinically meaningful declines in TOI at 1, 3, or 6 months. For the pneumonitis analyses, patients were weighted according to their follow-up (at end of treatment, 1, 3 and 6 months). Patients who had observed grade 2+ pneumonitis or who completed all 3 follow-up visits received a weight of 1 while other patients were downweighted in proportion to their follow-up. **Supplemental Table 4** lists follow-up at each timepoint and number of patients with toxicity. The follow-up and IPTWs were multiplied to obtain a single patient level weight in the pneumonitis analysis. Sensitivity analyses were performed comparing treatment groups separately at each follow-up time. SAS V14.3 was used for all analyses.

Results

Patient Characteristics

Patient characteristics for those treated with 3D-CRT (n=313) and IMRT (n=1433) are shown in **Table 1**. Of 1433 patients treated with IMRT, 985 (68.7%) were treated with volumetric modulated arc therapy, 376 (26.2%) with static field IMRT, and 72 (5.0%) with tomotherapy. Rates of the use of IMRT increased over time (**Supplemental Table 5**). The majority of patients received definitive treatment with concurrent chemoradiotherapy (276 patients, 88.2% 3D-CRT and 1296 patients, 90.4% IMRT, p=0.23). Initial groupings by treatment technique prior to IPTW were well balanced for patient demographics including age, BMI, comorbidity count, and receipt of concurrent chemotherapy. A greater proportion of IMRT-treated patients had Stage IIIB disease (34.3% vs 23.0%, p<0.0001) and, as such, had larger Planning Target Volumes (PTVs) (median 386cc vs 292cc, p<0.0001) that were more likely to be closer to critical structures: within 2 cm of the esophagus (94.3% vs 89.1%, p<0.001) or heart (92.3% vs 85.3%, p<0.0001) as compared to 3D-CRT-treated patients. A greater proportion of 3D-CRT-treated patients had performance status ECOG 2+ (32.6% vs 26.0%, p=0.017) and fewer received adjuvant

immunotherapy (14.1% vs 35.6%, p<0.0001) than IMRT-treated patients. After the use of IPTW, the patient characteristics were well-balanced between the 3D-CRT and IMRT comparison groups as shown in **Table 1**.

Dosimetric Analysis and Toxicity

Evaluation of radiation treatment plans using IPTW demonstrated no differences in esophageal mean dose or dose to the hottest 2 cc shown in **Figure 2A-B**. A total of 697 patients (39.9%) experienced grade 2+ esophagitis and 15 patients (0.9%) experienced grade 3+ esophagitis during treatment (**Supplemental Table 4**) with unweighted rates of acute esophagitis by treatment shown in **Figure 2C**. Using IPTW weights and generalized linear mixed effects models, there was no significant difference in the rate of grade 2+ or grade 3+ acute esophagitis between patients treated with IMRT or 3D-CRT (OR 1.02 (0.731-1.423 95% CI) p=0.9082, and OR 1.573 (0.360-6.868 95% CI) p=0.5466, respectively), **Figure 2D** and **Supplemental Table 2**.

For dosimetric parameters of the lung using IPTW, IMRT compared to 3D-CRT slightly increased the overall mean dose (mean 15.0 Gy vs 14.2 Gy, p=0.047) and lung V20Gy (mean 25.7% vs 23.8%, p=0.0036), had greater increase in lung V5Gy (mean 53.1% vs 46.4%, p<0.0001), while decreasing high dose to the lung (mean V30Gy 17.9% vs 19.2%, p=0.027) (**Figure 3A-B**). A total of 130 patients (7.4%) experienced grade 2+ pneumonitis and 14 patients (0.8%) experienced grade 3+ pneumonitis within 6 months following RT (**Supplemental Table 4**) with unweighted rates of early pneumonitis shown in **Figure 3C**. Using IPTW cohorts and generalized linear mixed effects models, there was no significant difference in the rate of grade 2+ or grade 3+ early pneumonitis between patients treated with IMRT or 3D-CRT (OR 1.623 (0.891-2.958 95% CI) p=0.1136, and OR 1.364 (0.308-6.052 95% CI) p=0.6824, respectively), **Figure 3D** and **Supplemental Table 3**.

IMRT similarly significantly reduced high dose to the heart compared to 3D-CRT using IPTW analysis (**Figure 4A-B**). Patients treated with IMRT had lower V30Gy (mean 12.4% vs 14.1%, p=0.045), V40Gy (mean 7.1% vs 9.9%, p<0.0001), and V60Gy (mean 1.7% vs 3.3%, p<0.0001). IMRT increased low dose to the heart (mean V5Gy 47.6% vs 37.0%, p=0.0011) but kept mean heart dose similar (mean 11.1 Gy vs 10.5 Gy, p=0.24). Specifically, compared to 3D-CRT IMRT significantly reduced the proportion of patients who did not meet a heart V40Gy≤20% metric (6.4% vs 15.3%, p<0.0001, **Figure 4C**). All dosimetric parameters using IPTW are expanded in **Supplemental Table 6**.

A total of 1044 patients in the cohort (59.8%) completed baseline patient reported outcomes surveys with sufficient responses for analysis (**Supplemental Table 1**). At baseline, there was no difference between IMRT and 3D-CRT-treated patients in mean TOI (56 vs 54, p=0.15). Through 6 months there was no significant difference in the proportion of patients reporting a clinically meaningful decline in TOI, although over time there was a trend of more 3D-CRT treated patients reporting a decline and fewer IMRT patients reporting a decline in TOI from baseline (**Figure 5**).

Discussion

In real-world data from a statewide consortium of academic and community radiation oncology practices, patients treated with IMRT (90.4% received concurrent chemotherapy) were more likely to have Stage IIIB disease, larger PTV sizes, and treatment targets close to the esophagus and heart than patients treated with 3D-CRT (88.2% received concurrent chemotherapy). This is similar to the secondary analyses of RTOG 0617 and other retrospective reports that patients with higher clinical stage and larger treatment targets are more likely to be treated with IMRT than with 3D-CRT.[7,9,12,13] Following balancing of baseline differences with

IPTW, in this statewide cohort patients treated with IMRT had significantly reduced high dose to the lung (V30Gy) and to the heart (V30Gy, V40Gy, V60Gy). This came at the expense of slightly higher lung mean doses and lung V20Gy (although both within acceptable clinical parameters for minimizing toxicity) and increased low dose (lung and heart V5Gy). Despite these dosimetric differences after IPTW propensity score adjustment, there was no significant difference between patients treated with IMRT or those with 3D-CRT in rates of grade 2 or 3+ acute esophagitis, grade 2 or 3+ early pneumonitis, or reporting clinically meaningful differences in PROs through 6 months after RT.

No study has reported acute esophagitis differences between 3D-CRT and IMRT and we did not find dosimetric differences in our cohort so this is not a surprising result.[7,8,11–13,19] Regarding pneumonitis, our follow-up robustly extends through 6 months and other studies with similar follow-up also did not find differences in rates of early pneumonitis, whereas those studies with median follow-up >6 months did report improvement in late pneumonitis with IMRT compared to 3D-CRT.[9–14] Long-term follow-up was also needed beyond 6 months to ascertain the decrease in late grade 3+ pneumonitis with IMRT compared to 3D-CRT for secondary analyses of RTOG 0617 (median follow-up 21.3 months, 3.5% vs 7.9%, p=0.039 and median follow-up 5.2 years, 3.5% vs 8.2%, p=0.03).[7,8] It is likely the clinical differences between treatment techniques were detected in the RTOG secondary analyses because patients were treated uniformly with similar volumes, expansions, and constraints on a prospective protocol with extended follow-up. In our real-world data cohort radiation treatment planning (volumes, expansions, and constraints) is not standardized as they are on a prospective clinical trial and our follow-up was shorter than for RTOG 0617, which may make it difficult to detect small differences attributable to the treatment technique itself, especially if subtle pneumonitis differences may be a late effect.[9,10,14,20–22] We also did not appreciate an improvement in PROs as was seen on RTOG 0617 with IMRT treatment, similarly attributable to our shorter follow-up out to 6 months as the clinically

meaningful differences in TOI on RTOG 0617 only became statistically significant at 12 months.[6] Our data hints at the possibility of PRO improvements with IMRT as the number of patients with a clinically meaningful decline in TOI decreased over time for patients treated with IMRT and increased over time for patients treated with 3D-CRT, while not rising to statistical significance.

It is encouraging that despite the heterogeneity of treatment centers with different treatment planning methods, a real-world cohort has consistently demonstrated improved heart doses with IMRT as compared to 3D-CRT in this study and prior.[23,24] Importantly, the proportion of patients not meeting the recently proposed metric of heart V40Gy≤20% from long-term RTOG 0617 analyses was significantly reduced by more than half with the use of IMRT over 3D-CRT in our statewide collaborative.[8] Data collection is ongoing to determine if this decreased cardiac dose will translate to improved overall survival as has been repeatedly shown from RTOG 0617.

The main strength of our study is the large number of patients representing a variety of institutional practices treating a heterogenous population of LA-NSCLC patients in a real-world setting with detailed collection of dosimetric data and collection of acute and early physician and patient-reported toxicity outcomes. Limitations include the non-randomized nature potentially allowing for confounding variables to have a greater impact. While IPTW propensity scoring can partially mitigate this by balancing measured confounders such as Stage, PTV size, and proximity to OARs, it does not account for unmeasured and unknown potential confounding variables and therefore cannot fully eliminate the risk of bias. As an example, interstitial lung disease was unfortunately not collected as a comorbidity and is known to impact pneumonitis risk. Further, because participation is voluntary for centers and patients, robust data only extends to 6 months with the present analysis. Our PRO analysis was also hampered by overall low response rates (albeit similar to other published series and RTOG 0617[6]) due to the

voluntary nature. Efforts are ongoing to extend this follow-up and collect cardiac toxicity, which was only recently added to the quality initiative and is still accruing.

Overall, patients are living longer after definitive treatment for LA-NSCLC and there is a need to better understand how we can reduce early and late treatment toxicity to widen the therapeutic window and improve quality of life for patients.[1,2] In our cohort of patients treated in a real-world setting with a variety of clinical practices, we found that IMRT did not significantly reduce acute esophagitis, early pneumonitis, or early QOL outcomes compared to 3D-CRT through 6 months. Nevertheless, in this heterogenous population IMRT significantly reduced high dose delivered to the lung and heart despite these patients being diagnosed more frequently with higher stage disease and having larger PTVs that were in greater proximity to critical structures than in patients treated with 3D-CRT. Furthermore, the reduction in high doses delivered to the heart and lung with IMRT has been shown on many studies with long follow-up to improve late pneumonitis and overall survival.[7–10,14] Therefore, our study's real-world dosimetric findings and the current literature on late toxicity support the continued preference of IMRT in RT planning for the definitive treatment of LA-NSCLC. Ongoing work will help to understand late toxicity improvement with IMRT and the potential clinical implications of reduced heart dose with IMRT in a real-world practice setting outside of a clinical trial.

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Figure Captions

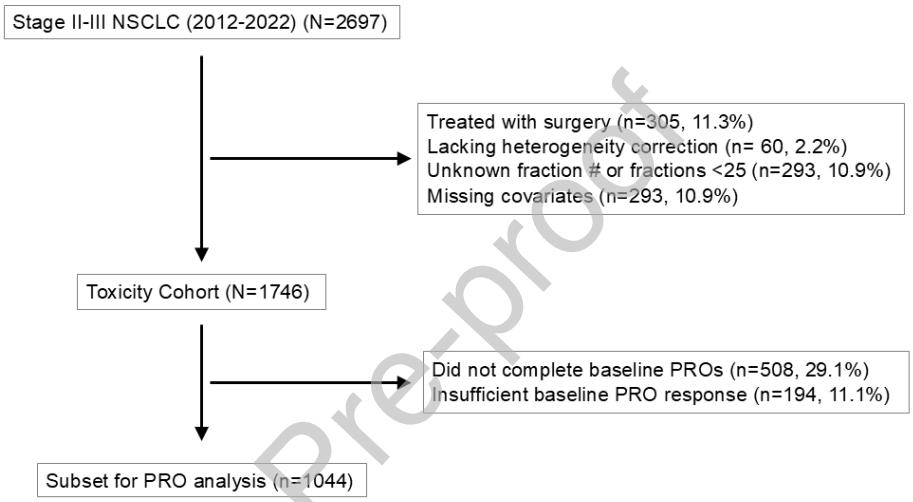
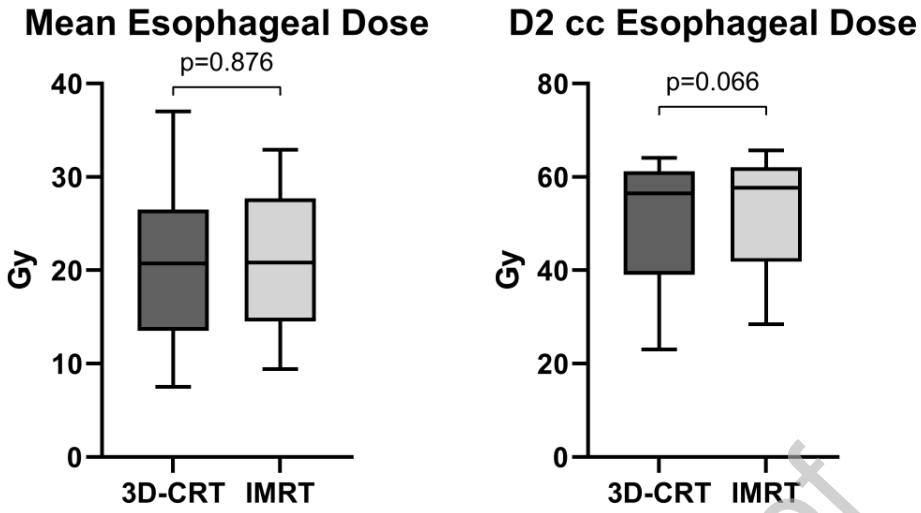
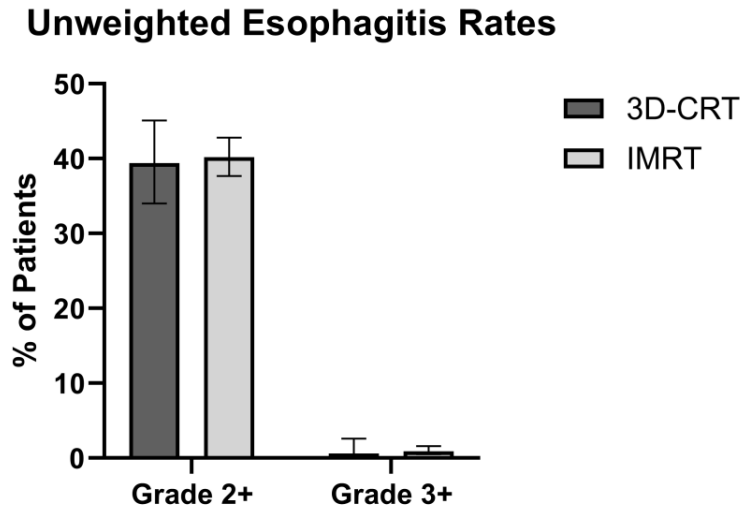


Figure 1: Flow diagram of patients in analyzed sample





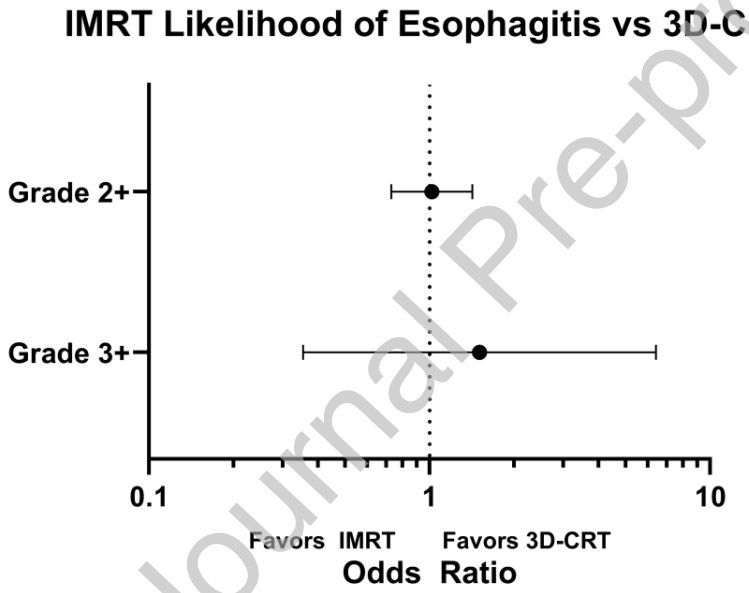
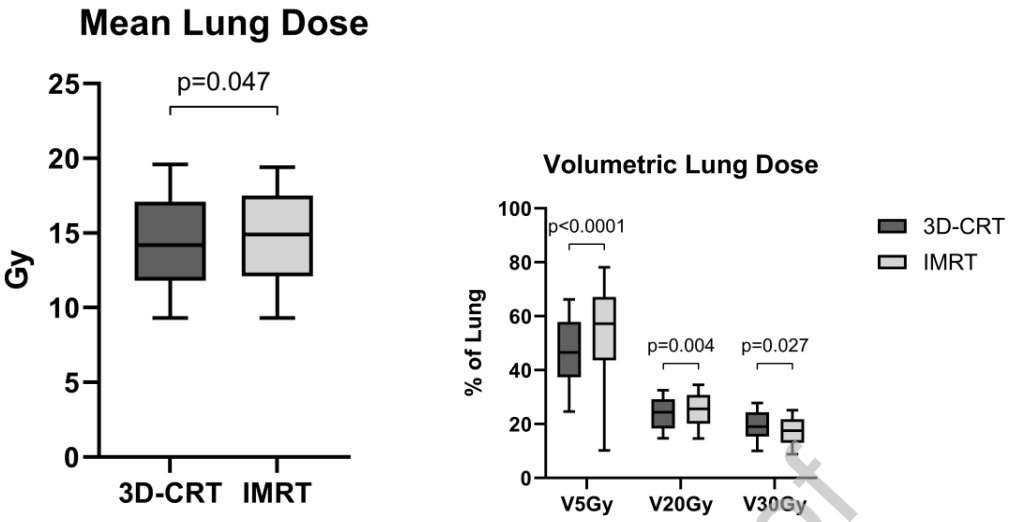


Figure 2: Esophageal dose and toxicity. Inverse probability of treatment weighted 3D-CRT vs IMRT cohort mean esophageal dose (A) and dose to hottest 2 cc (B). 3D-CRT vs IMRT cohort unweighted esophagitis rates (C) and inverse probability of treatment weighted generalized linear mixed effects model likelihood of esophagitis (D).



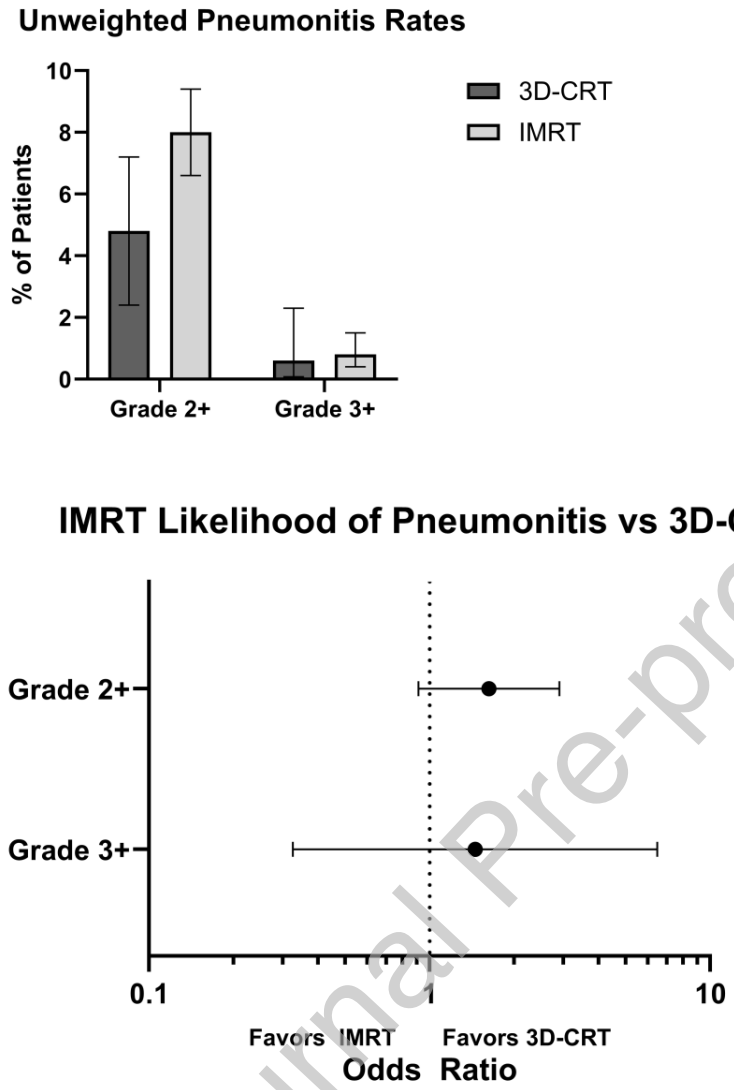
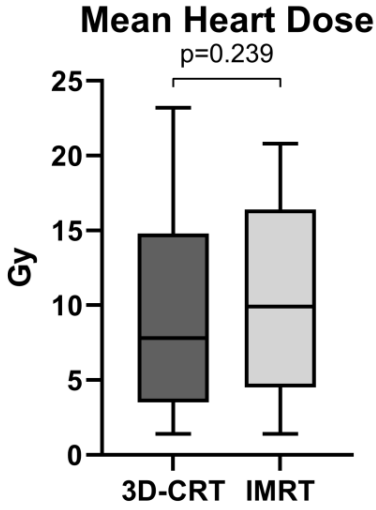
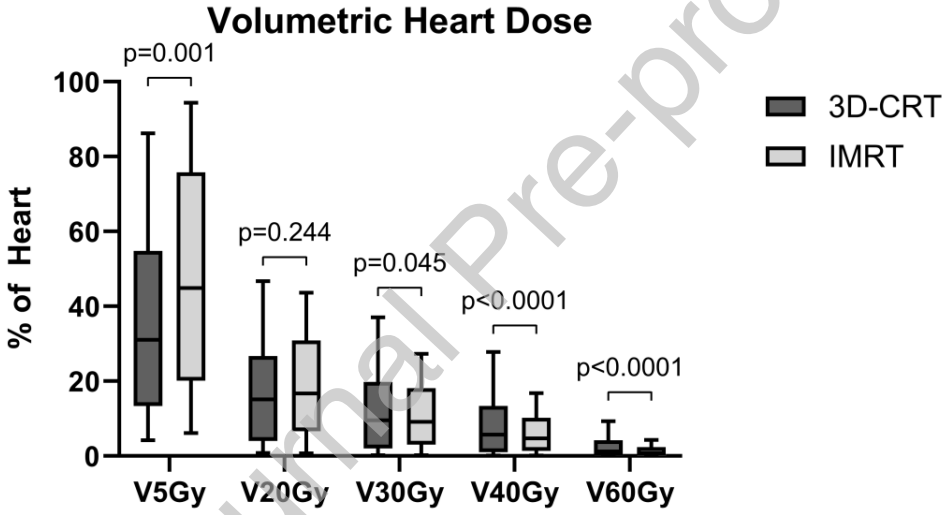


Figure 3: Lung dose and toxicity. Inverse probability of treatment weighted 3D-CRT vs IMRT cohort mean lung dose (A) and volumetric lung dose (B). 3D-CRT vs IMRT cohort unweighted pneumonitis rates (C) and inverse probability of treatment weighted generalized linear mixed effects model likelihood of pneumonitis (D).





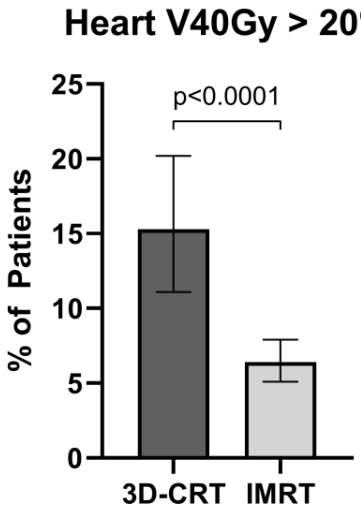


Figure 4: Heart dose. Inverse probability of treatment weighted 3D-CRT vs IMRT cohort mean heart dose (A) and volumetric heart dose (B). Inverse probability of treatment weighted 3D-CRT vs IMRT cohort percentage of patients failing to meet heart V40Gy ≤ 20% metric (C).

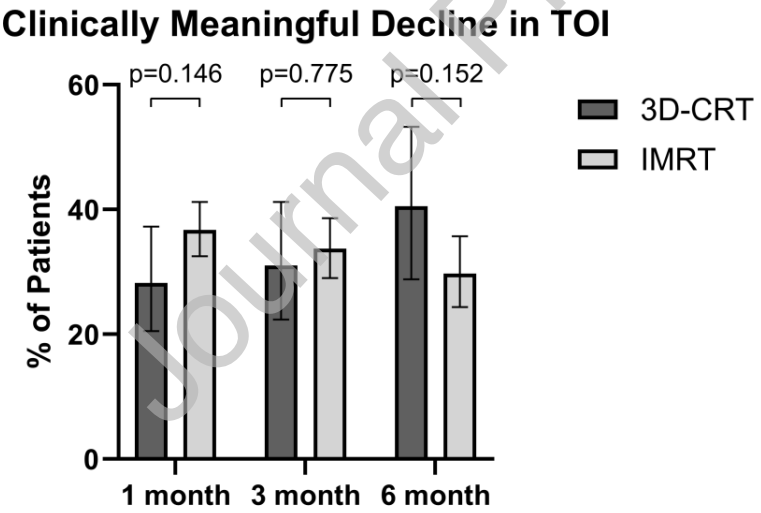


Figure 5: PRO toxicity. Timeline of patients with a clinically meaningful decline from baseline (≥5 points) in Functional Assessment of Cancer Therapy Lung Trial Outcome Index.

Table 1

Title: Unweighted and IPTW Weighted Patient Characteristics

	Unweighted			IPTW Weighted		
	3D-CRT (n=313)	IMRT (n=1433)	p-value	3D-CRT	IMRT	p-value
Age	68(9.4)	68(9.4)	0.7702	68(9.5)	68(9.4)	0.6212
Sex						
Female	145 (46.3%)	700 (48.8%)	0.4185	140 (45.3%)	698 (48.2%)	0.3479
Male	168 (53.7%)	733 (51.2%)		169 (54.7%)	750 (51.8%)	
Race						
Black	53 (16.9%)	211 (14.7%)	0.3784	53 (17.2%)	213 (14.7%)	0.3665
Other	6 (1.9%)	43 (3.0%)		5 (1.7%)	38 (2.6%)	
White	254 (81.2%)	1179 (82.3%)		251 (81.1%)	1198 (82.7%)	
ECOG performance status						
0-1	211 (67.4%)	1061 (74.0%)	0.0169	220 (71.1%)	1058 (73.1%)	0.4833
2+	102 (32.6%)	372 (26.0%)		89 (28.9%)	390 (26.9%)	
Body mass index						
Underweight <18.5	25 (8.0%)	83 (5.8%)	0.4578	24 (7.8%)	87 (6.0%)	0.6545
Normal 18.5-25	110 (35.1%)	488 (34.1%)		103 (33.1%)	503 (34.7%)	
Overweight 25-30	92 (29.4%)	453 (31.6%)		92 (29.7%)	441 (30.5%)	
Obese 30+	86 (27.5%)	409 (28.5%)		91 (29.3%)	417 (28.8%)	
Comorbidity count						
0	37 (11.8%)	192 (13.4%)	0.2605	41 (13.4%)	190 (13.1%)	0.4846
1	98 (31.3%)	371 (25.9%)		74 (23.9%)	380 (26.2%)	
2	83 (26.5%)	416 (29.0%)		83 (26.9%)	423 (29.2%)	
3+	95 (30.4%)	454 (31.7%)		111 (35.8%)	456 (31.5%)	
Smoker						
No	18 (5.8%)	80 (5.6%)	0.9068	17 (5.6%)	84 (5.8%)	0.8987
Yes	295 (94.2%)	1353 (94.4%)		292 (94.4%)	1365 (94.2%)	
Oxygen at start of treatment						
No	280 (89.5%)	1285 (89.7%)	0.9099	277 (89.6%)	1297 (89.6%)	0.9752
Yes	33 (10.5%)	148 (10.3%)		32 (10.4%)	151 (10.4%)	
Stage						
IIA	9 (2.9%)	34 (2.4%)	<.0001	10 (3.2%)	34 (2.4%)	0.7573
IIB	53 (16.9%)	145 (10.1%)		35 (11.4%)	164 (11.3%)	
IIIA	179 (57.2%)	763 (53.2%)		160 (51.6%)	781 (53.9%)	
IIIB	72 (23.0%)	491 (34.3%)		104 (33.7%)	469 (32.4%)	
Adjuvant chemotherapy						

No	278 (88.8%)	1370 (95.6%)	<.0001	291 (94.2%)	1365 (94.3%)	0.9425
Yes	35 (11.2%)	63 (4.4%)		18 (5.8%)	83 (5.7%)	
Concurrent chemotherapy						
No	37 (11.8%)	137 (9.6%)	0.2264	32 (10.3%)	157 (10.9%)	0.7734
Yes	276 (88.2%)	1296 (90.4%)		277 (89.7%)	1291 (89.1%)	
Adjuvant immunotherapy						
No	269 (85.9%)	923 (64.4%)	<.0001	212 (68.4%)	1002 (69.2%)	0.7929
Yes	44 (14.1%)	510 (35.6%)		98 (31.6%)	446 (30.8%)	
Practice setting						
Community	254 (81.2%)	1108 (77.3%)	0.1383	244 (79.0%)	1145 (79.1%)	0.9765
Academic	59 (18.8%)	325 (22.7%)		65 (21.0%)	303 (20.9%)	
Esophagus within 2 cm of PTV						
No	34 (10.9%)	82 (5.7%)	0.0009	24 (7.6%)	105 (7.3%)	0.8162
Yes	279 (89.1%)	1351 (94.3%)		286 (92.4%)	1343 (92.7%)	
Heart within 2 cm of PTV						
No	46 (14.7%)	110 (7.7%)	<.0001	30 (9.9%)	143 (9.8%)	0.995
Yes	267 (85.3%)	1323 (92.3%)		279 (90.1%)	1306 (90.2%)	
PTV Group (Deciles)						
1	53 (16.9%)	121 (8.4%)	<.0001	30 (9.6%)	149 (10.3%)	0.9843
2	41 (13.1%)	134 (9.4%)		30 (9.8%)	148 (10.2%)	
3	42 (13.4%)	133 (9.3%)		33 (10.6%)	141 (9.7%)	
4	35 (11.2%)	139 (9.7%)		29 (9.2%)	146 (10.1%)	
5	35 (11.2%)	140 (9.8%)		29 (9.4%)	151 (10.4%)	
6	22 (7.0%)	153 (10.7%)		32 (10.3%)	139 (9.6%)	
7	18 (5.8%)	156 (10.9%)		28 (9.1%)	143 (9.9%)	
8	22 (7.0%)	153 (10.7%)		29 (9.3%)	143 (9.9%)	
9	19 (6.1%)	156 (10.9%)		34 (10.8%)	149 (10.3%)	
10	26 (8.3%)	148 (10.3%)		37 (11.8%)	140 (9.6%)	
PTV Volume						
10th, median, 90th	91,292,763	144,386,849	<.0001	132,376,860	129,363,838	0.4528
PTV D95%[Gy]	58.5 (8.7)	59.6 (7.3)	0.002	58.8 (8.2)	58.7 (10.2)	0.9366

IPTW - Inverse Probability of Treatment Weights, 3D-CRT – three-dimensional conformal external beam radiation therapy, IMRT – intensity-modulated radiation therapy, ECOG – Eastern Cooperative Oncology Group, PTV – Planning Target Volume