Optimal Radiation Dose for Stage III Lung Cancer—Should "Definitive" Radiation Doses Be Used in the Preoperative Setting?

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ABSTRACT

Introduction: There are currently two recommended radiation strategies for clinical stage III NSCLC: a lower "preoperative" (45–54 Gy) and a higher "definitive/nonsurgical" (60–70 Gy) dose. We sought to determine if definitive radiation doses should be used in the preoperative setting given that many clinical stage III patients planned for surgery are ultimately managed with chemoradiation alone.

Methods: Using the National Cancer Database data from 2006 to 2016, we performed a comparative effectiveness analysis of stage III N2 patients who received chemoradiotherapy. Patients were stratified into subgroups across 2 parameters: (1) radiation dose: lower (45–54 Gy) and higher (60–70 Gy); and (2) the use of surgery (i.e., surgical and nonsurgical treatment approaches). Long-term survival and perioperative outcomes were evaluated using multivariable Cox proportional hazards and logistic regression models.

Results: A cohort of 961 patients received radiation before surgery including 321 who received a higher dose and 640 who received a lower dose. A higher preoperative dose revealed similar long-term mortality risk (hazard ratio = 0.99, 95% confidence interval: 0.82–1.21, p = 0.951) compared with a lower dose. There was no significant association between radiation dose and 90-day mortality (p = 0.982), 30-day readmission (p = 0.931), or prolonged length of stay (p = 0.052) in the surgical cohort. A total of 17,904 clinical-stage IIIA-N2 patients were treated nonsurgically, including 15,945 receiving higher and 1959 treated with a lower dose. A higher dose was associated with a reduction in long-term mortality risk (hazard ratio = 0.64, 95% confidence interval: 0.60–0.67, p < 0.001) compared with a lower dose.

Conclusions: For clinical stage III NSCLC, the administration of 60 to 70 Gy of radiation seems to be more effective than the lower dose for nonsurgical patients without compromising surgical safety for those that undergo resection. This evidence supports the implementation of 60 to 70 Gy as a single-dose strategy for both preoperative and definitive chemoradiotherapy.

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Introduction

Over the past 70 years, the role of radiation in NSCLC has greatly evolved in terms of indications and dose.[1] For patients with clinical stage III NSCLC, several key clinical trials have established a variety of practice standards.[2–8] At present, radiation is largely used in two contexts: (1) "preoperative" radiation in combination with chemotherapy before surgical management or (2) as a part of nonsurgical or "definitive" chemoradiation. Currently, the recommended radiation dose differs between these contexts. For example, the National Comprehensive Cancer Network (NCCN) currently recommends a lower dose of 45 to 54 Gy for preoperative radiation and a higher dose of 60 to 70 Gy for patients managed nonsurgically.[9] The rationale for varying radiation across indications is unclear, but may represent concerns of higher-dose radiation affecting surgical safety.[6,10,11]

The current separation of radiation dose across treatment strategies for surgical and nonsurgical patients with stage III NSCLC is potentially problematic because treatment plans frequently change. More specifically, it has been suggested that roughly half of patients with N2 disease designated for surgery as part of a multimodality approach never actually go on to have the surgery.[12,13] Several explanations have been offered for this attrition, including disease progression, patient health, or change in patient priorities. However, changing from a surgical plan to a nonsurgical strategy after radiation has been completed could be problematic for patients assuming reduced effectiveness of lower radiation doses (45–54 Gy) in the nonsurgical setting. At least one study found a decrease in survival when a lower radiation dose was used with definitive chemoradiation.[5]

We sought to determine whether 60 to 70 Gy as a single-dose strategy for both surgical and nonsurgical patients with stage IIIA NSCLC is warranted. The short- and long-term outcomes of clinical patients with stage III NSCLC managed surgically and nonsurgically were evaluated across a strata of higher (60–70 Gy) and lower (45–54 Gy) radiation dose in the National Cancer Database (NCDB).

Materials and Methods

Data Source

The NCDB is jointly sponsored by the American College of Surgeons and the American Cancer Society and collects data from over 1500 Commission on Cancer accredited facilities. The NCDB represents a nationwide sample that captures over 70% of patients with newly diagnosed cancer.[14] This study was part of a protocol approved by the Yale School of Medicine institutional review board with consent waived.

Patient Population

The NCDB was queried for adult patients at least 20 years of age, with clinical stage IIIA NSCLC involving at least one ipsilateral mediastinal lymph node (N2) who underwent multiagent chemotherapy and radiotherapy between 2006 and 2016. Data were available for patients in the sixth and seventh editions of TNM stage classification. However, for data analysis, patients were backstaged to the sixth edition. Concurrent chemoradiation was defined as chemotherapy and radiation therapy that was initiated within 30 days of one another. Surgical procedures included segmentectomy, lobectomy, and pneumonectomy (wedge resections were not included). Patients were excluded who had an incomplete follow-up, who received surgery before chemoradiation, if surgery occurred more than 180 days after the start of radiation (as this may represent salvage surgery for persistent disease), or if they had a previous history of cancer (Supplementary Fig. 1).

Patient Subsets

Patients were stratified into subgroups across radiation dose (i.e., higher and lower) and the use of surgery (i.e., surgical and nonsurgical treatment approaches). Specifically, two groups were created on the basis of the recommended radiation dose including lower (45–54 Gy) and higher dosimetry (60–70 Gy). These two strata were selected as they represent the recommended dose for "preoperative" chemoradiation (45–54 Gy) and "definitive" chemoradiation (60–70 Gy) approaches to clinical stage IIIA N2 in national guidelines (e.g., NCCN).[14] To be clear, the preoperative and definitive nomenclature refers only to corresponding guideline recommendations, not what ultimately happened with a patient (or was planned to happen). For example, some of the patients with a preoperative dose (45–54 Gy) never had surgery (and may never have been planned to undergo surgery), whereas some of the patients treated with a definitive dose received surgery. For this reason, we refer to dose throughout the text as higher (60–70 Gy) and lower (45–54 Gy) to prevent confusion. Patients were further stratified on the basis of whether they were managed with a surgery-based approach (chemotherapy radiation then surgery) or a nonsurgical approach (chemotherapy and radiation without surgery).

Patient Cohorts for Secondary Analyses

Planned Nonsurgical Patients. There may be differences across patient cohorts depending on whether surgery was ever a part of their treatment planning. The NCDB captures a "reason no surgery" field. In an attempt to evaluate the cohort of planned definitive chemoradiation patients, a subset analysis was performed in

only those patients coded as "Surgery not performed because it was not part of the planned first course of treatment" (Supplementary Table 1).

Planned Surgical Patients Who Never Had Surgery. An attempt was made to evaluate the patients who changed from a surgical plan to a nonsurgical treatment strategy during their first course of treatment. A subset analysis was performed in only those patients "whose reason no surgery" coding indicated that surgery was contraindicated owing to patient risk factors, which include "progression of the tumor before planned surgery" (Supplementary Table 1).

Low-Risk Patients. To mitigate bias from particularly poor health or locally aggressive tumors, a subset of low-risk patients was created. Patients were excluded if: (1) "surgery of the primary site was not recommended/performed because it was contraindicated owing to patient risk factors (comorbid conditions, advanced age, etc.)"; (2) had any comorbidities that were documented (Charlson-Deyo comorbidity index >0); (3) had T4 tumors; and (4) lived less than 90 days after radiation was initiated.

Variables

Independent variables studied included patient age, sex, ethnicity, Charlson-Deyo comorbidity index (stratified as 0, 1, and $\geq$2), and facility type (academic, community, and comprehensive community cancer program). Tumor-level variables included tumor diameter (clinical T stage), year of diagnosis, location, tumor histology, and grade. Definitions of variables by the NCDB are publicly available online.[14]

Outcome variables were evaluated including treatment effect, such as pathologic downstaging to a complete pathologic response (ypT0N0N0). Surgical outcomes were evaluated including 90-day mortality, prolonged length-of-stay (>14 d) as a surrogate for complications (this association was derived for lobectomy; therefore, only lobectomy patients were considered in this outcome),[15] and unplanned readmissions to the reporting hospital within 30 days after surgery. The overall survival in days was calculated from the day of diagnosis.

Statistical Analysis

Missing Data Strategy. At least one piece of data was missing for 4472 of the 18,865 patients; however, for most variables, the rate of missing data was less than 5%. A multiple imputation approach for missing data was used for modeling all variables except the clinical stage, laterality, and tumor grade. For the clinical stage,

tumor grade, and laterality, a complete-case analysis was used, because of the particular importance of these variables to short or long-term outcomes.

We identified the distribution of covariates by radiation dose for the surgical and nonsurgical samples and computed descriptive statistics using the raw data. After applying the missing data strategy, models were generated to assess the mortality and treatment effect after surgery. Adjusted long-term mortality hazard was compared using Cox proportional hazards models, adjusting for radiation dose, age, sex, ethnicity, Charlson-Deyo score, year of diagnosis, clinical T stage, tumor location, laterality, facility type, histology, radiation type, tumor grade, and type of surgical resection (segmentectomy, lobectomy, pneumonectomy). Satisfaction of the proportional hazards assumption was tested using the martingale residuals in the adjusted Cox models. No violations of the proportional hazards assumption were identified.

To characterize survival differences differently in the nonsurgical cohort, propensity matching was performed in a one-to-two fashion between lower and higher radiation doses, respectively (using the variables above). The standardized differences of matched pairs were less than 0.1 for all variables. Kaplan-Meier survival estimates and log-rank tests were performed on the subsets of propensity-matched patients.

Two-sided *p* values less than 0.05 were considered statistically significant. All data analysis was conducted with Statistical Analysis System version 9.4 (SAS Institute, Cary, NC).

Results
Patients

Overall, 18,865 clinical patients with stage III N2-positive NSCLC were identified, including 961 treated with a surgical approach (chemoradiation then surgery) and 17,904 treated with a nonsurgical approach (chemoradiation without surgery). In general, the patients managed with a surgical approach tended to be younger, with a median age of 61 (interquartile range: 54–68) versus age of 66, (interquartile range: 58–73, *p* < 0.001), more likely female sex (49% versus 42%, *p* < 0.001), treated at an academic facility (41% versus 28%, *p* < 0.001), and were more likely to have adenocarcinoma (59% versus 46%, *p* < 0.001) in comparison with patients undergoing nonsurgical treatment (Supplementary Table 2).

Patients who underwent nonsurgical treatment were stratified according to radiation dose, with 15,945 receiving a higher dose (60–70 Gy) and 1959 receiving the lower dose (45–54 Gy). In general, among these nonsurgical patients, those that received the higher

Table 1. Distribution of Covariates by Radiation Dose Among Nonsurgical and Surgical Patients

	Nonsurgical Patients					Surgical Patients				
	45-54 Gy		60-70 Gy			45-54 Gy		60-70 Gy		
Variable	Median	IQR	Median	IQR	p Value	Median	IQR	Median	IQR	p Value
Age	65	57-72	66	58-73	0.003	61	55-68	61	53-68	0.99
	N	Column, %	N	Column, %	p value	N	Column, %	N	Column, %	p value
Age group					0.151					0.588
<55	369	18.84	2,727	17.1		185	28.91	103	32.09	
55-75	1,278	65.24	10,718	67.22		422	65.94	203	63.24	
>75	312	15.93	2,500	15.68		33	5.16	15	4.67	
Sex					0.981					0.012
Male	1,140	58.19	9,247	57.99		306	47.81	181	56.39	
Female	819	41.81	6,698	42.01		334	52.19	140	43.61	
Race/ethnicity					0.325					
White non-Hispanic	1,615	82.44	13,196	82.76						
Black	248	12.66	2,052	12.87						
Hispanic	33	1.68	289	1.81						
Other/unknown	63	3.22	408	2.56						
Charlson-Deyo comorbidity index					0.290					0.282
0	1,190	60.75	9,472	59.40		416	65	200	62.31	
1	530	27.05	4,531	28.42		163	25.47	96	29.91	
≥2	239	12.20	1,942	12.18		61	9.53	25	7.79	
Year of diagnosis					<0.001					<0.001
2006-2009	720	36.75	4,207	26.38		130	20.31	39	12.15	
2010-2012	632	32.26	4,832	30.30		253	39.53	100	31.15	
2013-2016	607	30.99	6,906	43.31		257	40.16	182	56.70	
Tumor laterality					0.474					0.748
Right	1,223	62.43	10,103	63.36		418	65.31	213	66.36	
Left	736	37.57	5,842	36.64		222	34.69	108	33.64	
Tumor location					<0.001					
Upper lobe	1,231	62.84	10,664	66.88						
Middle lobe	72	3.68	614	3.85						
Lower lobe	525	26.8	3,760	23.58						
Overlapping Lung	19	0.97	189	1.19						
Lung NOS	112	5.72	718	4.50						
Facility type					0.028					0.003
Missing/unknown[a]	338	17.25	2,297	14.41		111	17.34	42	13.08	
Community	250	12.76	1,891	11.86		44	6.88	18	5.61	
Comprehensive	891	45.48	7,295	45.75		249	38.91	101	31.46	
Academic	480	24.50	4,462	27.98		236	36.88	160	49.84	
Histology					<0.001					0.153

(continued)

Table 1. Continued

	N	Column, %	N	Column, %	p value	N	Column, %	N	Column, %	p value
Adenocarcinoma	997	50.89	7,251	45.48		370	57.81	201	62.62	0.525
Squamous	962	49.11	8,694	54.52		270	42.19	120	37.38	
Tumor grade					<0.001					
1	46	2.35	352	2.21		26	4.06	13	4.05	
2	313	15.98	2,920	18.31		157	24.53	83	25.86	
≥3	699	35.68	4,922	30.87		284	44.38	127	39.56	
Missing/unknown	901	45.99	7,751	48.61		173	27.03	98	30.53	
Clinical T stage					0.002					
Missing/unknown	242	12.35	1,555	9.75						
1	151	7.71	1,496	9.38						
2	483	24.66	4,414	27.68						
3	483	24.66	4,111	25.78						
4	600	30.63	4,369	27.40						

[a] Raw data numbers including missing data were presented in descriptive tables; however, the missing data strategy described in the Methods was used for all regression models.

Note: Per the NCDB, cells with values less than 10 are suppressed; thus, the following variables are not included in the table: race/ethnicity, tumor location, margins, surgical resection type, and tumor size. IQR, interquartile range; NCDB, National Cancer Database; NOS, not otherwise specified.

radiation dose were more likely to have been treated in the more recent era (43% versus 31%, $p < 0.001$) and have a lower T stage (Table 1).

When surgically managed patients were stratified according to radiation dose, 321 received a higher dose (60–70 Gy) and 640 received the lower dose (45–54 Gy). In the surgical cohort, those that received the higher dose were more likely to be men (56% versus 48%, $p = 0.012$), treated at an academic facility (50% versus 37%, $p = 0.003$), and treated more recently (2013–2016) (57% versus 40%, $p < 0.001$) compared with patients who received the lower radiation dose (Table 1).

Survival in Nonsurgical Subset

Among the patients who were treated with chemoradiation, a Cox proportional hazards model was used to identify predictors of overall survival. The use of higher dose was also associated with a decreased mortality hazard (hazard ratio [HR] = 0.64, 95% confidence interval [CI]: 0.60–0.67, $p < 0.001$) compared with lower radiation dose (Fig. 1). Having identified a survival difference in an adjusted Cox model, attempts were made to further characterize this survival difference using propensity matching. Kaplan-Meier survival analysis was performed of propensity-matched patients who had received lower and higher radiation doses. The higher radiation dose was associated with a superior 5-year overall survival (17.9% versus 12%) and median survival (19 mo versus 10.7 mo) compared with the lower dose, with a p value of less than 0.001 (Fig. 2).

Several secondary analyses were performed in the nonsurgical cohort to mitigate bias from competing for mortality risk (see Methods section: Patient Cohorts for Secondary Analyses). Among patients treated with "planned" definitive chemoradiation (i.e., surgery not a part of initial treatment planning, n = 15,760) the use of higher radiation was associated with lower mortality risk compared with lower radiation dose (HR = 0.64, 95% CI: 0.60–0.67, $p < 0.001$) (Supplementary Table 3). For nonsurgical patients in the low-risk subgroup (N = 6111) (which excluded patients with documented comorbidities), T4 tumors, and those who lived less than 90 days from the start of radiation, the use of higher radiation dose was also associated with a decreased mortality hazard (HR = 0.68, 95% CI: 0.63–0.75, $p < 0.001$) compared with lower radiation dose (Supplementary Fig. 2).

Treatment Response and Survival in the Surgical Cohort

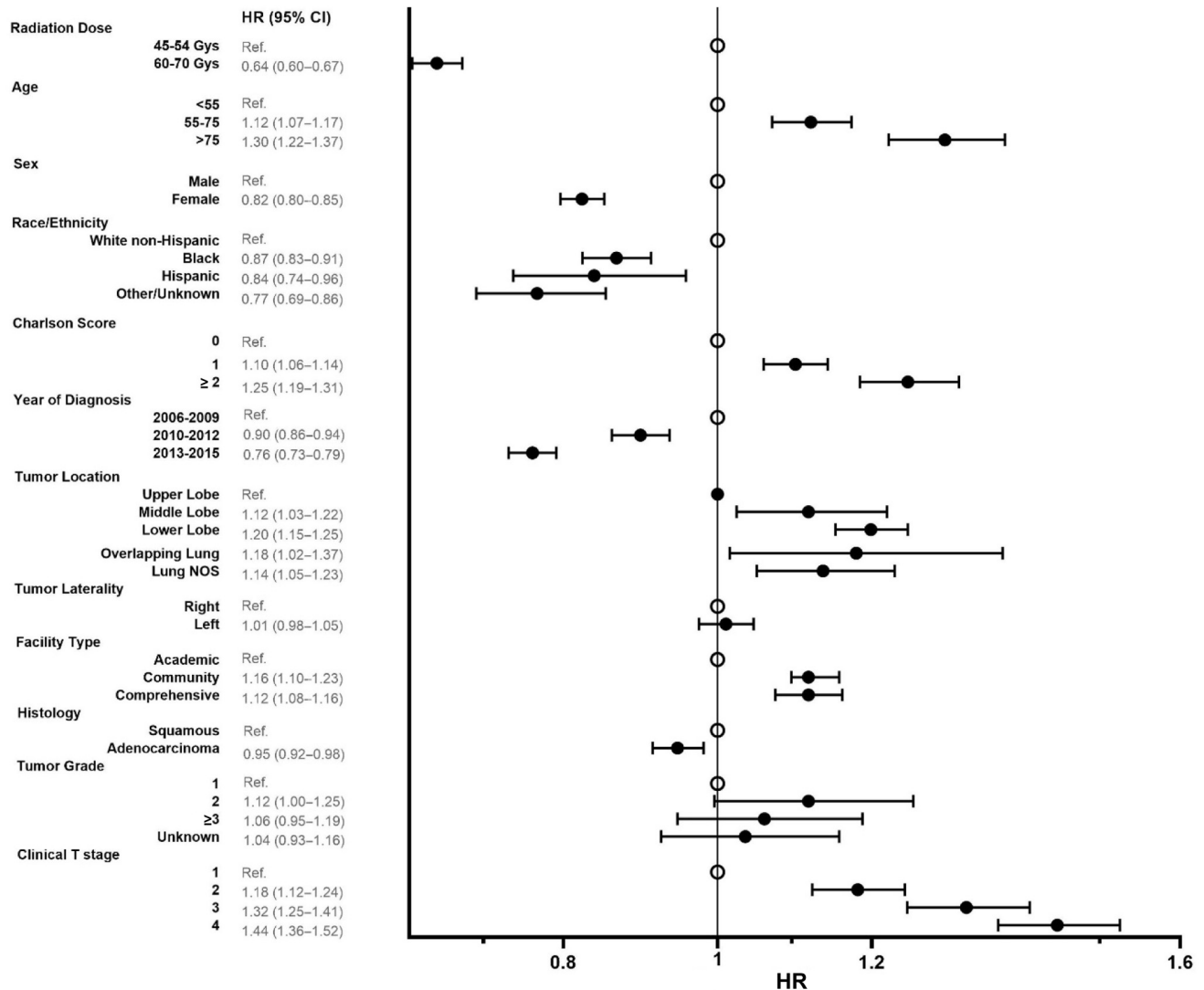Surgical resection allows for the response to chemoradiation to be assessed, with the maximal

Figure 1. Forest plots for overall survival for patients treated with chemoradiation only. HRs less than one for overall survival suggest that the variable level is associated with improved overall survival compared with the Ref. category. CI, confidence interval; HR, hazard ratio; Ref., reference.

effect being noted as a "complete pathologic response" (ypT0N0M0). The prevalence of ypT0N0N0 after surgery was assessed according to radiation dose in logistic regression. There was a trend toward higher radiation being associated with a higher prevalence of complete pathologic response (OR = 1.2, 95% CI: 0.99–1.45, p = 0.062) compared with a lower dose, but failed to reach significance (Table 2).

To assess the relationship between long-term survival and radiation dose in the surgery cohort, a Cox proportional hazards model was built. The use of a higher dose was not associated with a decreased mortality hazard (HR = 0.99, 95% CI: 0.82–1.21, p = 0.95) compared with a lower radiation dose (Fig. 3).

Safety in the Surgical Cohort

To assess the relationship between safety and radiation dose in the preoperative setting, several perioperative outcomes were assessed in adjusted logistic regression models. Among lobectomy patients, the use of a higher dose was not associated with an increased risk for prolonged length-of-stay compared with a lower dose (OR = 0.69, 95% CI: 0.48–1.01, p = 0.052) (Supplementary Table 4). Similarly, within the full surgical cohort (all resection types) there was no significant association between radiation dose and the risk for hospital readmission (OR = 1.03, 95% CI: 0.52–2.05, p = 0.93) (Supplementary Table 5) or the risk of 90-day mortality after surgery (OR = 1.00, 95% CI: 0.76–1.30, p = 0.98) (Supplementary Table 6).

Product-Limit Survival Estimates
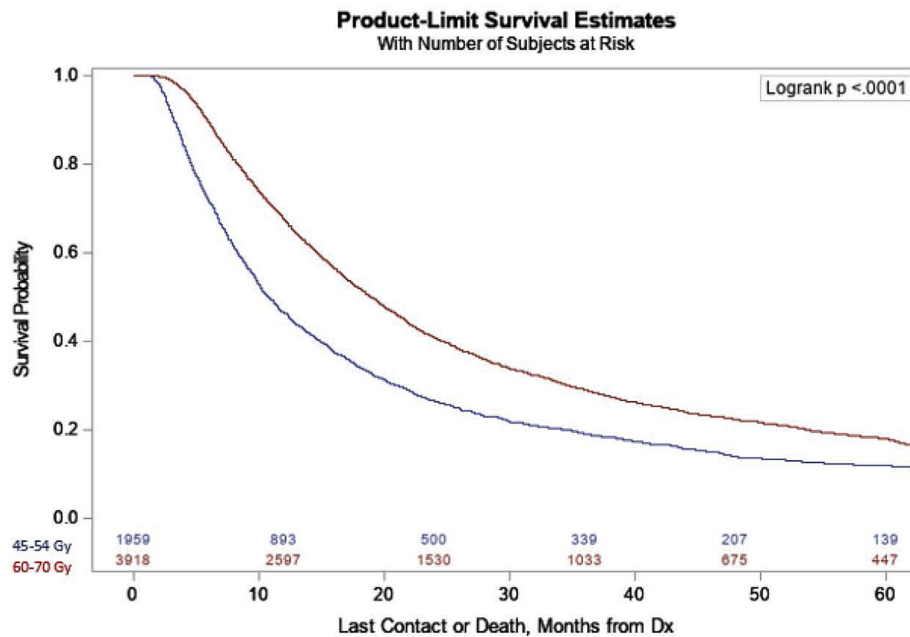With Number of Subjects at Risk

Figure 2. Kaplan-Meier survival estimates of propensity-matched subsets of nonsurgical patients according to Dx. Lower Dx patients (45-54 Gy) were matched 1:2 with higher dose (60-70 Gy) patients using the following characteristics: age group, sex, race/ethnicity, Charlson-Deyo comorbidity score, year of diagnosis, facility location, tumor laterality, site, histology, grade, and clinical stage. The survival estimates of patients treated with higher Dx (shown in red) are superior to patients treated with lower Dx (highlighted in blue). The log-rank *p* value less than 0.0001. Dx, radiation dose.

Discussion

The current findings indicate that a higher radiation dose (60–70 Gy) is more effective than 45 to 54 Gy in patients undergoing nonsurgical treatment. These findings were not entirely surprising, and they support the current NCCN recommendation for 60 to 70 Gy for definitive chemoradiation. More specifically, radiation dose has been extensively studied in lung cancer; and the landmark Radiation Therapy Oncology Group (RTOG) 7301 revealed improved recurrence-free survival (but not overall survival) with 60 Gy compared with lower doses.[5] The current study extends these findings in several important ways. First, this is the largest contemporary study to report a survival advantage across these doses (and not just local control). Second, the survival advantage is characterized in a more granular fashion that may be more understandable to clinicians and oncologists (e.g., the difference in median survival of around 9 mo). Finally, we attempted to adjust for different scenarios that could lead to a nonsurgical patient having received lower radiation dosimetry (as opposed to a more standard higher nonsurgical dose). We performed a series of sensitivity analyses including evaluation of only the following: (1) subsets of patients who seemed to have been planned for definitive chemoradiation, and (2) low-risk nonsurgical patients least likely to have been considered inoperable (patients free of documented comorbidities without tumor invasion

often considered inoperable structures). All of the sensitivity analyses revealed similar results to the full data set, suggesting the difference between higher and lower radiation doses persists irrespective of the evolution of the treatment approach.

For surgically managed clinical stage IIIA-N2, we did not identify a survival advantage to using higher radiation doses in the preoperative setting. Our results are similar to a multitude of observational studies.[6,8,13,16,17] In many of these observational studies, higher radiation led to more frequent sterilization of mediastinal lymph node metastases in the surgical specimens (i.e., cN2àypN0), which was also a trend in the current study. However, the higher response in the mediastinum failed to translate into a survival advantage.

The current study suggests that higher radiation (i.e., 60–70 Gy) is as safe as lower dose radiation (45–54 Gy) in the preoperative setting. Our results are similar to several retrospective studies, which did not identify an association between radiation dose and major perioperative complications,[16] 30-day mortality,[6] or readmission rates.[6] In contrast, other studies did identify higher surgical complication rates with higher radiation doses.[10,11] However, it should be noted that in these earlier studies, the excess mortality predominantly occurred in patients undergoing pneumonectomy after chemoradiotherapy—a practice that has become less common over time.

Table 2. Logistic Regression for Complete Pathologic Response Among Surgical Patients

Variable	OR	95% Lower	95% Upper	p Value
Radiation dose				
45-54 Gy	Reference			
60-70 Gy	1.200	0.991	1.454	0.062
Age group, y				
<55	Reference			
55-75	1.206	0.847	1.716	0.299
>75	0.732	0.394	1.359	0.324
Sex				
Male	Reference			
Female	0.854	0.707	1.032	0.102
Race/ethnicity				
White non-Hispanic	Reference			
Black	1.239	0.661	2.324	0.504
Hispanic	0.705	0.201	2.468	0.584
Other/unknown	1.354	0.528	3.475	0.528
Charlson-Deyo comorbidity index				
0	Reference			
1	1.354	1.016	1.806	0.039
≥2	1.137	0.773	1.671	0.515
Year of diagnosis				
2006-2009	Reference			
2010-2012	1.422	1.066	1.897	0.017
2013-2016	1.417	1.069	1.879	0.016
Clinical T stage				
1	Reference			
2	0.989	0.750	1.305	0.937
3	0.938	0.649	1.357	0.736
4	1.397	0.927	2.105	0.111
Tumor location				
Main bronchus	—			
Upper lobe	Reference			
Middle lobe	1.369	0.558	3.356	0.493
Lower lobe	1.034	0.582	1.839	0.909
Overlapping lung	0.746	0.201	2.767	0.661
Lung NOS	0.697	0.185	2.624	0.594
Tumor laterality				
Right	Reference			
Left	1.153	0.951	1.399	0.148
Facility type				
Community	1.088	0.643	1.840	0.752
Comprehensive	0.954	0.676	1.346	0.785
Academic	Reference			
Histology				
Adenocarcinoma	0.571	0.471	0.692	<0.001
Squamous	Reference			
Tumor grade				
1	Reference			
2	0.700	0.446	1.100	0.122
≥3	1.117	0.750	1.663	0.586
Unknown	2.840	1.910	4.224	<0.001
Surgical resection type				
Segmentectomy	1.029	0.221	4.789	0.971
Lobectomy	Reference			
Pneumonectomy	0.861	0.374	1.984	0.726

NOS, not otherwise specified.

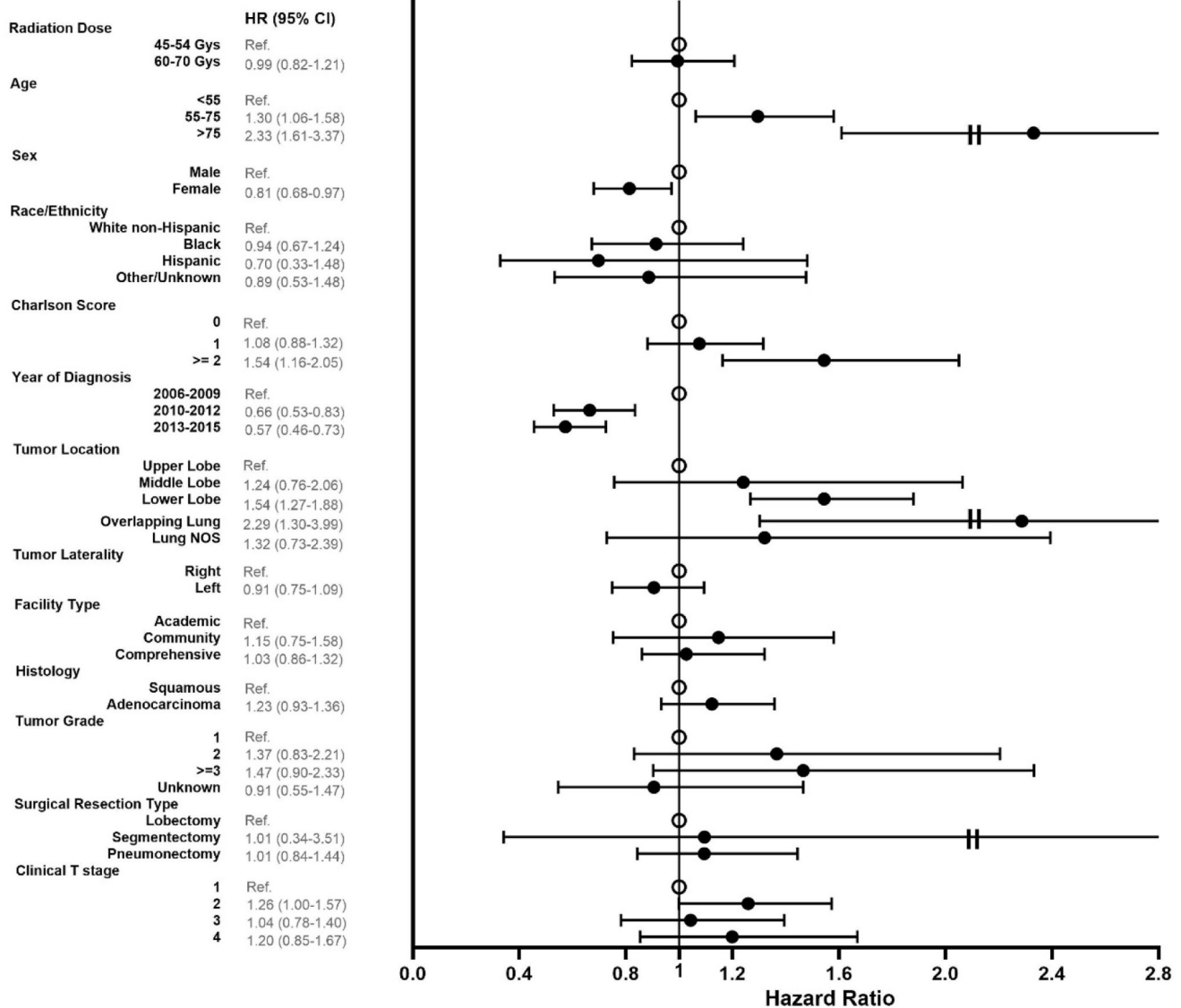|	HR (95% CI)
Radiation Dose	
45-54 Gys	Ref.
60-70 Gys	0.99 (0.82-1.21)
Age	
<55	Ref.
55-75	1.30 (1.06-1.58)
>75	2.33 (1.61-3.37)
Sex	
Male	Ref.
Female	0.81 (0.68-0.97)
Race/Ethnicity	
White non-Hispanic	Ref.
Black	0.94 (0.67-1.24)
Hispanic	0.70 (0.33-1.48)
Other/Unknown	0.89 (0.53-1.48)
Charlson Score	
0	Ref.
1	1.08 (0.88-1.32)
>= 2	1.54 (1.16-2.05)
Year of Diagnosis	
2006-2009	Ref.
2010-2012	0.66 (0.53-0.83)
2013-2015	0.57 (0.46-0.73)
Tumor Location	
Upper Lobe	Ref.
Middle Lobe	1.24 (0.76-2.06)
Lower Lobe	1.54 (1.27-1.88)
Overlapping Lung	2.29 (1.30-3.99)
Lung NOS	1.32 (0.73-2.39)
Tumor Laterality	
Right	Ref.
Left	0.91 (0.75-1.09)
Facility Type	
Academic	Ref.
Community	1.15 (0.75-1.58)
Comprehensive	1.03 (0.86-1.32)
Histology	
Squamous	Ref.
Adenocarcinoma	1.23 (0.93-1.36)
Tumor Grade	
1	Ref.
2	1.37 (0.83-2.21)
>=3	1.47 (0.90-2.33)
Unknown	0.91 (0.55-1.47)
Surgical Resection Type	
Lobectomy	Ref.
Segmentectomy	1.01 (0.34-3.51)
Pneumonectomy	1.01 (0.84-1.44)
Clinical T stage	
1	Ref.
2	1.26 (1.00-1.57)
3	1.04 (0.78-1.40)
4	1.20 (0.85-1.67)

Figure 3. Forest plots for overall survival for patients treated with pneumonectomy, lobectomy, or segmentectomy surgery within 180 days of chemoradiation. HRs less than one for overall survival suggest that the variable level is associated with improved overall survival compared with the Ref. category. CI, confidence interval; HR, hazard ratio; Ref., reference.

We believe this study informs a challenging but common scenario in stage IIIA-N2 NSCLC – a pivot from a surgical to nonsurgical treatment strategy. Historically, around 50% to 60% of stage III patients who were planned to undergo chemoradiation followed by surgery never went on to have surgery.[12,13] Current guidelines recommend a preoperative radiation dose of 45 to 54 Gy,[9] a dosimetry that our findings suggest would be less effective in the nonsurgical setting. Therefore, patients who switched treatment strategies may end up with inferior nonsurgical treatment, simply because they opted to begin down the surgical pathway. By illustrating that higher radiation is more effective in the nonsurgical setting but safe in the surgical setting, our findings may facilitate decision-making by supporting the use of a singular radiation dose of 60 to 70 Gy for both preoperative and definitive chemoradiotherapy.

This study has several limitations beyond those that are intrinsic to observational studies. First, there is no way of knowing why patients were treated the way they were in terms of radiation dose or surgical versus nonsurgical treatment. It is possible that attributes relating to the patient's health or tumor aggressiveness may have influenced the type of treatment (either radiation dose or surgical versus nonsurgical approach) that was selected, and these same attributes could have influenced prognosis (creating bias). In addition to using adjusted models, we attempted to further mitigate this potential source of bias by performing a series of

secondary analyses, which revealed similar results as the primary study cohort.

Second, some complications related to radiation are often delayed in presentation and are inherently difficult to quantify using the NCDB. We used prolonged length-of-stay and 90-day mortality (instead of 30-d mortality) as surrogates for significant perioperative complications.

Third, immunotherapy has become an important component of the nonsurgical management of stage IIIA NSCLC[18] and it is unclear if the safety and effectiveness of the studied radiation regimens would differ in the context of immune checkpoint inhibitors (ICIs). One possible concern was recently raised by a meta-analysis that suggested greater rates of symptomatic pneumonitis with ICIs concurrently with chemoradiotherapy compared with a sequential approach.[19] Further investigation with the use of ICIs and chemoradiotherapy is warranted.

In addition, we compared radiation dose recommendations by the NCCN, which used a 60 to 70 Gy dose range for definitive chemoradiotherapy. Although we did not compare doses within the 60 to 70 Gy range, recent evidence suggests the optimal dose (balancing risks and benefits associated with escalating dose) is likely closer to 60 Gy compared with 70 Gy.[20–22]

Finally, without knowing if or when treatment planning changed for patients, it is possible that the higher radiation dose led to toxicity, which "converted" more surgical patients to nonsurgical patients. Although that detail is not captured in the NCDB, clinical trials have revealed similar rates of surgical resection after higher and lower preoperative radiation doses.[3,8,23]

In conclusion, for patients with clinical stage IIIA NSCLC, the use of higher doses of radiation (60–70 Gy) seems to represent a safe dose in the preoperative setting and a more effective dose for those patients treated without surgery. Our findings support the practice of administering a singular radiation dose (60–70 Gy) for both preoperative and definitive chemoradiotherapy.

CRediT Authorship Contribution Statement

Areo G. Saffarzadeh: Conceptualization, Methodology, Writing-original draft, Writing-review, and Editing.

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Samantha L. Walters: Visualization, Analysis, Writing-review, and Editing.

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Roy H. Decker: Conceptualization, Supervision, Writing-original draft, Writing-review, and Editing.

Daniel J. Boffa: Conceptualization, Methodology, Writing-original draft, Writing-review, Editing, and Supervision.

Supplementary Data

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