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Treatment with Intensity-Modulated Radiation Therapy (IMRT) and Chemotherapy in Advanced Inoperable Non-Small Cell Lung Cancer (NSCLC): Toxicity, Survival and Patterns of Failure in Relation to Treatment with High and Low Radiation Dose

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Abstract

Purpose: To investigate the toxicity, survival and patterns of failure in patients with advanced lung cancer treated with intensity modulated radiation therapy (IMRT) and chemotherapy. Methods and Materials: Retrospective chart review of 68 total patients: 46 academic and 22 community center. Endpoints: Grade ≥ 3 pneumonitis, Grade ≥ 2 esophagitis, local, regional and distant failure, progression-free survival (PFS) and overall survival (OS). Results: For the academic center patients, median follow-up was 19.2 months. Esophagitis: 0% Grade 3, 35% Grade 2, no significant difference between dose bins: <70 Gy vs. 70 Gy, 25% vs. 45% (p = 0.22), <66 Gy vs. 66 - 70 Gy, 28% vs. 39% (p = 0.53). Lung dose metrics and PTV size were not associated with Grade ≥ 3 pneumoni-

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tis. Esophageal V35, V50, and mean dose but not PTV size was associated with Grade 2 esophagitis. 1 year local, regional and distant failure = 6.5%, 6.5%, and 30.4%. No endpoint differences were seen between dose bins, though patients with smaller PTVs treated with 70 Gy did demonstrate improved OS (ns) when compared to those treated with <70 Gy. Community Center: Median follow-up 6.2 months with 15% Grade 2 esophagitis, no Grade 3 esophagitis. Two patients (9%) experienced Grade ≥ 3 pneumonitis. Conclusions: IMRT chemoradiation was well tolerated in a population with advanced NSCLC both in the academic and community settings. Severe pneumonitis rates were low and comparable to other series using IMRT and chemotherapy. Esophagitis was mild and associated with V35, V50 and mean dose. No significant benefit was seen for higher doses regarding survival, local, regional or distant control despite that higher dose bins had smaller tumors. Though not statistically significant, we did find a trend toward worse OS for <70 Gy when the PTV was less than the median PTV.

Keywords

IMRT, NSCLC, Toxicity, Survival, Patterns of Failure, Chemotherapy

1. Introduction

Non-small cell lung cancer (NSCLC) remains the most common cause of cancer death in the United States [1]. Chemoradiation for locally advanced disease provides a 2-year overall survival (OS) of 20-30%, with local failure causing morbidity and mortality [2].

Recent studies have investigated dose escalation to improve local control. A MSKCC study demonstrated improved local control (LC) with dose escalation in stage III NSCLC with gross tumor volumes (GTV) exceeding 100 cc [3]. Intensity-modulated radiation therapy (IMRT) is a promising means of dose escalation due to its increased conformality [4] [5]. MDACC reported decreased pneumonitis with IMRT and chemoradiation in advanced lung cancer with 58% two-year LC and OS [6] [7].

However, published experience with lung IMRT is limited. We report the toxicity, survival, and recurrence patterns in locally advanced NSCLC using chemoradiation with IMRT.

2. Methods and Materials

2.1. Study Population Academic Center

The charts of 46 consecutive patients treated with IMRT and chemotherapy for newly diagnosed and pathologically confirmed advanced inoperable NSCLC between December 2007 and August 2011 at the Medical University of South Carolina were retrospectively reviewed. Exclusion criteria were prior major thoracic surgery or thoracic RT. The hospital's institutional review board (IRB) approved the collection and review of data.

2.2. Treatment and Surveillance

Patients were simulated supine using 3 mm slices, vac-lok and a wingboard. GTV included primary tumor and suspicious nodes incorporating PET. Elective nodal irradiation (ENI) was given to the hilum of a single patient. Expansions differed by physician, in general CTV = GTV + 5 mm and PTV = CTV + 8 - 10 mm. For some, PTV = GTV + 7 - 10 mm. Free-breathing four-dimensional CT (4D-CT) was used in 20%, generating an internal target volume (ITV) by contouring the GTV on all respiratory phases; the above expansions created the CTV and PTV. Lung dose-volume histograms (DVH) used total lung volume minus CTV or GTV in cases without a CTV.

Inverse-planned IMRT used Adaptive Convolve, 6 or 10 MV energy, heterogeneity corrections and step-and-shoot with a multi-leaf collimator. Minus 5% and +10% were PTV dose tolerances, with PTV V95% > 95% prescription dose. Attempted constraints included lung V20 < 35% and mean lung dose (MLD) < 16 Gy. The esophagus was spared without a specific constraint, attempting to avoid hotspots. The biologically effective dose (BED) was calculated using an α/β of 10 for tumor; the Linear Quadratic model was used with BED Gy_{10} = nd

$[(1 + d/(\alpha/\beta)]$.

Follow-up was 3 - 4 months for 2 years and 6 months thereafter. Imaging was PET/CT at 3 - 6 months and CT thereafter. Metastatic surveillance was performed when clinically indicated.

2.3. Toxicity Grading

Radiation toxicities were scored using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Toxicity endpoints were Grade ≥ 3 radiation pneumonitis and acute Grade ≥ 2 esophagitis.

2.4. Community Cohort

Twenty-two charts were reviewed at the Bismarck Cancer Center between 2007 and 2015. The center's IRB approved the collection and review of data. Eligibility, treatment planning, surveillance and toxicity grading were similar to the Medical University of South Carolina cohort.

2.5. Statistical Analysis

Characteristics were compared using either t-tests or Fisher's exact tests for continuous and categorical variables, respectively. Similar tests were used to compare average volume percentages for V5-V30 and dose bins between those who experienced esophagitis or pneumonitis and those who did not. Overall survival (OS) and progression free survival (PFS) were analyzed using Kaplan-Meier methods; dose bins were compared using the log-rank test. OS was defined as the time from the start of treatment to death, where living patients are censored at their last known follow-up date. PFS was defined as the time from the start of treatment to either recurrence (local, regional or distant) or death, where a patient is censored at the time of last known follow up if none of these events were experienced. Local failure (LF) was defined by evidence of persistent or recurrent disease after initial treatment within the treated volume (PTV). Regional failure (RF) was defined as evidence of disease in untreated nodal regions in the hilum, mediastinum or supraclavicular regions after initial treatment. Patients with simultaneous LRF were scored as local failure; patients with both regional and distant failure (DF) were scored as DF; patients with local, regional and distant failure were scored as distant failure.

3. Results

Median follow-up time after treatment was 19.2 months and 91% received concurrent chemotherapy most commonly with carboplatin plus paclitaxel (**Table 1**). The median GTV = 122.6 cc. Lower dose bins had larger tumor volumes with a median PTV of 386 cc for < 70 Gy vs. 281 cc for 70 Gy ($p = 0.04$) (**Table 2**). The median BED (Gy_{10}) using linear-quadratic modeling was compared between dose bins: 70 Gy vs. < 70 Gy = 84 Gy_{10} vs. 74.3 Gy_{10} ($p < 0.0001$); 66 - 70 Gy vs. < 66 Gy = 84 Gy_{10} vs. 74.3 Gy_{10} ($p < 0.0001$).

Five patients (10.8%) developed Grade ≥ 3 pneumonitis, with no significant differences between dose bins (**Table 3**). Grade ≥ 3 pneumonitis occurred at 45, 70, 100, 163, and 204 days after initiating radiation. Grade 5 pneumonitis occurred in 2 patients, both of whom had pre-treatment pulmonary hypertension. No patient developed Grade 3 esophagitis. Sixteen patients (35%) developed Grade 2 esophagitis, with no significant differences identified between dose bins (**Table 3**). Neither dose nor PTV size predicted Grade ≥ 3 pneumonitis. All esophageal parameters, but not PTV size, predicted Grade 2 esophagitis.

Twenty patients (43%) met a failure endpoint (**Table 4**). Three patients died of intercurrent disease. One-year local, regional and DF was 6.5, 6.5 and 30.4% respectively. There were no significant differences in OS or PFS between dose bins (**Figure 1**). Though not statistically significant, we did find a trend toward better OS in high dose bins when the PTV was less than the median PTV (**Figure 2**).

Community Cohort

Twenty-two patients were treated at the Bismarck Cancer Center (**Table 5**). Median follow-up was 6.2 months. The median dose was 66 Gy and 81% used volumetric modulate arc therapy. Concurrent chemotherapy was given to 95% of patients. Analysis of toxicity demonstrated that 15% experienced Grade 2 esophagitis with no Grade 3 esophagitis. Regarding pneumonitis, 2 patients (9%) experienced Grade ≥ 3 pneumonitis (**Figure 3**). One was a possible Grade 5 pneumonitis in an 87 year old patient with pre-treatment severe pulmonary fibrosis

Table 1. Patient demographics: Medical University of South Carolina.

	n/Volume (cc)
Age	
Median	62 (46 - 85)
Concurrent Chemo	
Yes	42
No	4
Consolidative Chemo	
Yes	20
No	26
Histology	
Adenocarcinoma	19
Squamous	20
NSCLC NOS[1]	7
Stage	
I/II	3
IIIA	26
IIIB	18
Gross Tumor Volume (GTV)	
Median	123 (21 - 771)
Planning Target Volume (PTV)	
Median	345 (108 - 1139)

[1]NOS = not otherwise specified.

Table 2. Patient characteristics stratified by high and low dose bins.

	<70 Gy (N = 24)	%	70 Gy (N = 22)	%	p	<66 Gy (N = 18)	%	66 - 70 Gy (N = 28)	%	p
Age (Mean)	61		67		0.033	61		66		0.08
Concurrent Chemo										
No	2	50	2	50	1	2	50	2	50	0.64
Yes	22	52	20	48		16	38	26	62	
Consolidation Chemo										
No	12	46	14	54	0.39	9	35	17	65	0.55
Yes	12	60	8	40		9	45	11	55	
Histology										
Adeno	13	68	6	32	0.15	9	47	10	53	0.36
Squamous	9	45	11	55		8	40	12	60	
NSC	2	29	5	71		1	14	6	86	
PTV (Median)	386		281		0.039	386		291		0.37
BED[1] (Median)	74.3		84.0			74.3		84.0		

[1]BED = biologically effective dose, $\alpha/\beta = 10$ for tumor.

Table 3. Association of dosimetric parameters and toxicity.

Dose Bin	Pneumonitis (p = 0.66)		Esophagitis (p = 0.22)	
	No	Yes	No	Yes
<70 Gy	22 (92)	2 (8)	18 (75)	6 (25)
70 Gy	19 (86)	3 (14)	12 (55)	10 (45)
	Pneumonitis (p = 0.64)		Esophagitis (p = 0.53)	
	No	Yes	No	Yes
<66 Gy	17 (94)	1 (6)	13 (72)	5 (28)
66 - 70 Gy	24 (86)	4 (14)	17 (61)	11 (39)

Vx[1]	Pneumonitis		p
	No	Yes	
V5	50.8	58.3	0.31
V13	33.2	30.7	0.42
V20	25.0	22.8	0.59
V25	20.6	19.2	0.75
V30	17.0	16.1	0.83
Mean	13.8	13.8	1
PTV (Mean)	313	326	0.80
	Esophagitis		p
	No	Yes	
V35	31.5	42.2	0.010
V50	20.6	30.8	0.008
Mean	22.3	29.2	0.002
PTV (Mean)	286	376	0.10

[1]Vx = volume of organ that receives "x" dose (Gy).

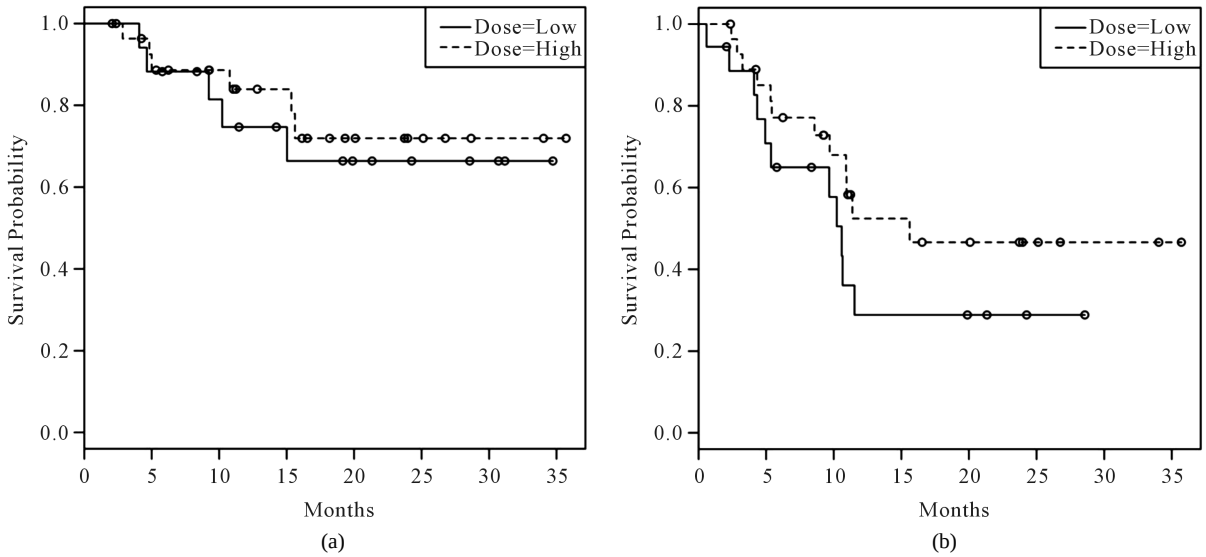

Figure 1. Overall (p = 0.77) and progression-free (p = 0.19) survival between 70 Gy (high) and <70 Gy (low) dose bins.

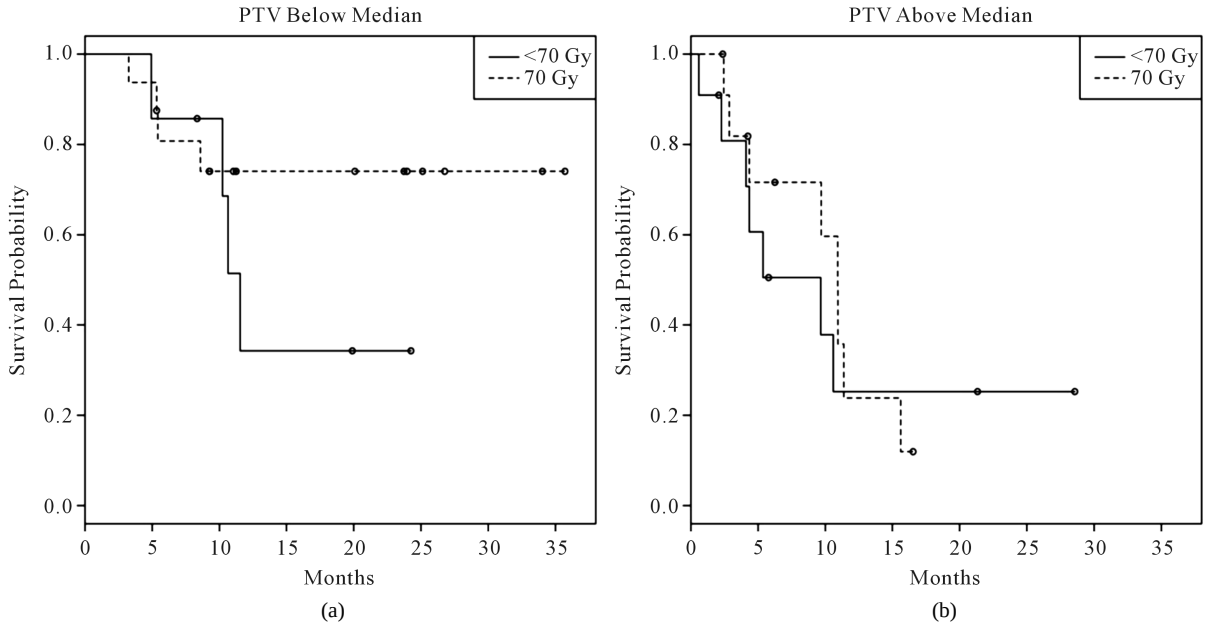

Figure 2. Overall survival between 70 Gy (high) and <70 Gy (low) dose bins stratified by size. (a) PTV below median, p = 0.25; (b) PTV above median, (p = 0.70).

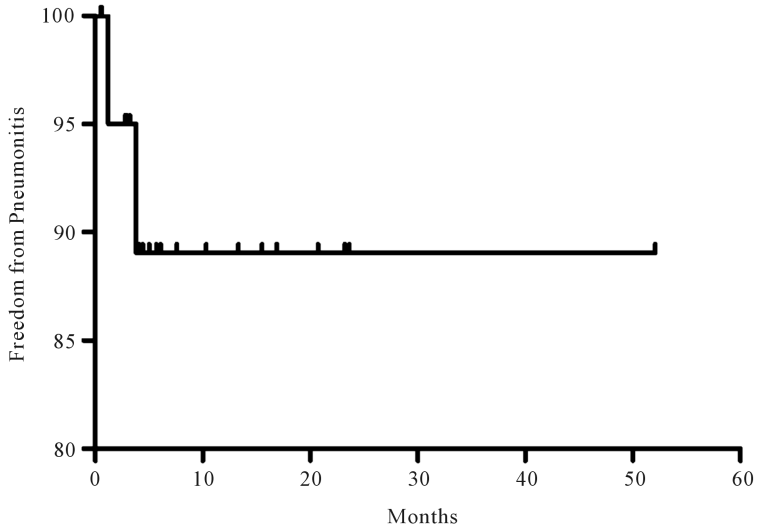

Figure 3. Pneumonitis rates for the Bismarck Cancer Center.

Table 4. Failure outcomes stratified by dose bins.

	Low Dose	High Dose	Total
No Recurrence Or Death	7	16	23
Local	0	3	3
Regional	3	0	3
Distant	7	7	14
Death (No Recurrence)	1	2	3
Total	18	28	46

Table 5. Patient demographics: Bismarck Cancer Center.

Age	
Median	73 (55 - 87)
Stage	
II	4
IIIA	11
IIIB	7
TNM	
T1/2/3/4/x	3/5/8/5/1
N0/1/2/3	6/3/10/3
Staging PET	
Yes	21
No	1
Mediastinal Staging	
Imaging	13
Surgical	7
Other	2
Histology	
Adenocarcinoma	12
Squamous	6
NOS	4
KPS	
90	11
80	6
70	4
60	1
RT Dose/BED Gy10	
70 Gy/84	9
66 Gy/79.2	9
60 Gy/72	4
RT technique	
VMAT[1]	18
Static	4
Neoadjuvant Chemo	
Yes	5
No	17
Concurrent Chemo	
Yes	21
No	1
Consolidation Chemo	
Yes	7
No	14
Unknown	1

[1]VMAT = volumetric modulated arc therapy.

who received 66 Gy in 33 fractions and died of developing respiratory failure 4.5 months after chemoradiation completion. The second patient was an 82 year old with who received 70 Gy in 35 fractions and developed grade 3 pneumonitis one month after chemoradiation completion, which was successfully treated with steroids. Overall, eight deaths occurred but overall survival was not reported due to short median follow-up.

4. Discussion

Work by Fletcher and the RTOG established initial lower and upper lung radiation dose limits. RTOG 9410 and Phase I/II dose escalation trials suggested 74 Gy as the maximum tolerated dose with chemotherapy [8] [9]. Recently RTOG 0617 compared 60 to 74 Gy chemoradiation using 3D-CRT or IMRT. The 74 Gy arm was closed prematurely due to crossing of protocol-specified futility boundaries. OS was significantly better in the low-dose arm; 28.7 months versus 20.3 months [10].

Machtay *et al.*, using RTOG data, showed improved OS and local-regional failure with increasing BED [11]. Similarly, Kong *et al.* found that improved OS with dose escalation (63 Gy - 103 Gy) [12].

Motion management is essential for thoracic IMRT success as shown in a study comparing 3D-CRT to 4DCT/IMRT with improved OS and lower toxicity with IMRT [13]-[15]. In contrast, a recent population-based analysis of 4000 stage III patients found no difference in esophageal or pulmonary toxicity rates when comparing IMRT to 3D-CRT [16]. Adaptive IMRT, decreasing monitor units and beam number may decrease lung doses using IMRT [17]-[21].

In our study, Grade ≥ 3 pneumonitis using IMRT was 10.8%; similar to MSKCC (11%), MDACC (11% - 14%) and Shi *et al.* (11%), but differed from others with 0% [7] [22]-[24]. A recent review found a variety of pneumonitis predictive doses [25]. We found no significant relationship between Grade ≥ 3 pneumonitis and V5, V13, V20, V25, V50, MLD, PTV size or dose bin. Differences in toxicity grading (we used CTCAE v4.0), patient populations and treatment planning may account for toxicity variations. Grade 3 esophagitis in CTCAE v3.0 distinguishes between IV fluid duration, whereas v4.0 does not use the term "IV fluids", but states "oral supplements or hospitalization indicated". Regarding pneumonitis, in RTOG steroid use is Grade 3, whereas steroids are Grade 2 in CTCAE v4.0. Also, this allows subjectivity in that toxicity grading may be altered based on physician proclivity to intervene medically, *i.e.* steroids.

Various dose/volume parameters to various anatomic descriptors of the esophagus have been reported [26]-[28]. RTOG 0617 constrained to mean <34 Gy based on the findings of Singh *et al.* [29]. The mean esophageal dose for our cohort was 24.7 Gy (range, 8 - 41 Gy) and the mean max dose was 69 Gy (range, 54 - 76 Gy). We observed no Grade ≥ 3 esophagitis despite that we had no formal constraint. Sura *et al.* found 4% Grade 3 esophagitis and NEAR Trial had 3.3% [7] [30]. In contrast, MDACC reported 22.4% Grade 3 for stage III chemoradiation [22]. They had a larger median PTV (739 vs 325 cc) and more IIIB disease, requiring mediastinal nodal radiation. Recent IMRT chemoradiation studies reported Grade 2 toxicity of ≈38% and identified V50 as the best predictor of esophagitis, though these studies used hyperfractionation [31] [32].

Our 80% 1-year OS was equivalent to MSKCC, MDACC, Govaert *et al.* and the DART study [7] [22] [24] [33], yet superior to Kong *et al.* NSCLC 3D-CRT experience [12]. We observed no differences in OS between dose bins, in contrast to earlier studies showing improved survival benefit with dose escalation [11] [12] [24]. Though not reaching statistical significance, we did identify a suggestion of improved OS using dose escalation in smaller tumors (below median PTV). It is possible that the doses used in this study are adequate to eradicate a proportion of smaller tumors but not larger tumors.

Local control (LC) was achieved in 93.5% of patients at 1 year, while MSKCC and MDACC stage III patients had 1-year LC rates of approximately 80% [7] [22]. Our distant failure rate of 30% is consistent with published findings. This leaves a small fraction of patients for which improved OS can be demonstrated through increased local control. Local control will become more important as systemic therapies improve.

Some limitations to our study are as follows: 1) Subject to biases and limitations of retrospective analysis; 2) Only 20% of our patients had 4DCT planning, which may have altered our treatment approach compared to other previously mentioned studies; 3) Our separation of dose bins may not have been powered sufficiently to detect any significant differences due to our low cohort numbers; 4) We do not report late toxicity, such as pulmonary fibrosis or esophageal stricture rates; 5) Low pneumonitis rates may have prevented significant dosimetric predictors.

Future areas include a PET-boost technique and RTOG 1106 is investigating PET-guided adaptive RT [34].

5. Conclusion

IMRT with concurrent chemotherapy was well tolerated in a population with advanced inoperable NSCLC, both in the academic and community settings. Severe pneumonitis rates were low and comparable to other series using IMRT and chemotherapy. Esophagitis was mild and was associated with dosimetric parameters of V35, V50 and mean dose. We saw a suggestion of improved OS using dose escalation in smaller tumors. We did not find any statistically significant benefit of higher doses for survival, local, regional or distant failure despite that the higher dose bins had smaller tumors.

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