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Mark C. Kenamond
West Virginia University

R. Alfredo Siochi
West Virginia University

Malcolm D. Mattes
West Virginia University

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The dosimetric effects of limited elective nodal irradiation in volumetric modulated arc therapy treatment planning for locally advanced non-small cell lung cancer

Mark C. Kenamond[1], **R. Alfredo Siochi**[2], and **Malcolm D. Mattes**[2]

[1]West Virginia University School of Medicine, Morgantown, WV, USA

[2]Department of Radiation Oncology, West Virginia University, One Medical Center Drive, PO Box 9234, Morgantown, WV, USA

Abstract

Objective—Contemporary radiotherapy guidelines for locally advanced non-small cell lung carcinoma (LA-NSCLC) recommend omitting elective nodal irradiation, despite the fact that evidence supporting this came primarily from older reports assessing comprehensive nodal coverage using 3D conformal techniques. Herein, we evaluated the dosimetric implications of the addition of limited elective nodal irradiation (LENI) to standard involved field irradiation (IFI) using volumetric modulated arc therapy (VMAT) planning.

Method—Target volumes and organs-at-risk (OARs) were delineated on CT simulation images of 20 patients with LA-NSCLC. Two VMAT plans (IFI and LENI) were generated for each patient. Involved sites were treated to 60 Gy in 30 fractions for both IFI and LENI plans. Adjacent uninvolved nodal regions, considered high risk based on the primary tumor site and extent of nodal involvement, were treated to 51 Gy in 30 fractions in LENI plans using a simultaneous integrated boost approach.

Results—All planning objectives for PTVs and OARs were achieved for both IFI and LENI plans. LENI resulted in significantly higher esophagus D_{mean} (15.3 vs. 22.5 Gy, $p < 0.01$), spinal cord D_{max} (34.9 vs. 42.4 Gy, $p = 0.02$) and lung D_{mean} (13.5 vs. 15.9 Gy, $p = 0.02$), V_{20} (23.0 vs. 27.9%, $p = 0.03$), and V_5 (52.6 vs. 59.4%, $p = 0.02$). No differences were observed in heart parameters. On average, only 32.2% of the high-risk nodal volume received an incidental dose of 51 Gy when untargeted in IFI plans.

Conclusion—The addition of LENI to VMAT plans for LA-NSCLC is feasible, with only modestly increased doses to OARs and marginal expected increase in associated toxicity.

Correspondence to: Malcolm D. Mattes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Statement of informed consent was not applicable since the manuscript does not contain any patient data.

Keywords

Lung cancer; Lymph node; Radiation therapy; Non-small cell lung cancer; Intensity modulated radiotherapy

Introduction

Current guidelines recommend omission of elective nodal irradiation (ENI) in favor of involved field irradiation (IFI) in the definitive management of locally advanced non-small cell lung cancer (LA-NSCLC), with the rationale for this being that smaller target volumes enable lower rates of toxicity due to greater sparing of organs-at-risk (OARs), as well as improved local control by enabling dose escalation to gross disease [1, 2]. Omission of ENI is supported by several retrospective series showing only modest increases in nodal recurrence (5–10%) [3–7], as well as two randomized trials showing improvements in overall survival with IFI [8, 9].

However, there are several important caveats when interpreting this data. First, although highly conformal intensity modulated radiation therapy (IMRT) is most commonly used in contemporary practice, the vast majority of studies assessing ENI were carried out using three-dimensional conformal radiation therapy (3DCRT), which delivers a significant "incidental" dose to non-targeted nodal regions that may contribute towards the reportedly low elective nodal recurrence rate [5, 10, 11]. Delivering a similar dose to uninvolved nodal regions with IMRT would require explicit targeting. Furthermore, the reported rates of isolated regional failure may also be artificially low because of ascertainment bias, and even if one does assume a 5–10% regional recurrence rate, this is relatively substantial considering that only 15–25% of locally advanced NSCLC will be cured. Finally, the elective nodal volume that was historically treated (including in the above randomized trials) encompassed the ipsilateral hilum, entire mediastinum, and supraclavicular nodal regions, an immense area that would certainly cause undue cardiopulmonary toxicity. In summary, while data exists on all or nothing approaches to ENI using 3DCRT, there is little data on treating more limited elective nodal target volumes using IMRT, and it is not surprising that a recent survey showed great discrepancy in practice patterns for the use of various extents of prophylactic nodal irradiation [12].

The primary goal of this study is to determine the dosimetric impact of limited elective nodal irradiation (LENI) targeting prophylactic regions of the mediastinum at highest risk for harboring microscopic disease using modern treatment planning techniques. We hypothesize that the addition of these limited volumes treated to a lower dose will increase the dose to OARs but to a small enough degree such that all dosimetric objectives can still successfully be met and the expected increase in clinical toxicity is marginal.

Methods

This is a treatment planning system (TPS)-only study using CT simulation images from a population of 20 patients who were previously treated with definitive radiation therapy for locally advanced NSCLC at our institution from 2015 to 2016. Specific patients were

selected for inclusion such that the entire cohort would represent a variety of types of target volumes. For instance, we included 10 patients with hilar lymph node involvement only (N1) and 10 patients with mediastinal lymph node involvement (N2), and an equal number of patients with primary tumors located in each of the five lobes of the lung. All patients underwent positron emission tomography/computed tomography (PET/CT) prior to treatment for the purpose of staging and radiotherapy treatment planning, and lymph nodes were considered involved with malignancy if their short axis diameter was greater than 1 cm on CT or standardized uptake value (SUV) was greater than 3.0 on PET.

All treatment planning was carried out for the Varian TrueBeam linear accelerator (Varian Medical Systems, Palo Alto, CA) using the Eclipse treatment planning system (version 11). All involved field target volumes were contoured according to standard methods described in recent Radiation Therapy Oncology Group (RTOG) clinical trials [13]. Briefly, the gross tumor volume (GTV) consisted of all known gross disease based on the planning CT scan and pretreatment PET/CT scan. An iGTV included the union of the GTVs on all respiratory correlated images on a 4DCT scan acquired at the time of simulation. The clinical target volume (CTV) included the iGTV plus an 8-mm margin to account for miscroscopic extension without extending into uninvolved organs. No uninvolved (elective) nodal regions were added to the CTV for the IFI plans. The CTV was expanded isotropically by 5 mm to generate a planning target volume that was prescribed a dose of 60 Gy in 30 fractions (PTV60).

LENI plans utilized the same PTV60 taken to the same prescription dose as the IFI plans; however, an additional planning target volume encompassing adjacent nodal regions at high risk for harboring microscopic disease was also prescribed a dose of 51 Gy in 30 fractions (PTV51). The LENI plans delivered a dose to the two target volumes in a single plan via a simultaneous integrated boost. The high-risk nodal regions encompassed in the PTV51 were individualized for each patient, based on the patient's primary tumor site and involved nodal stations. Table 1 shows the nodal stations considered to be at high risk in various scenarios, based on known patterns of nodal spread as described in previous surgical series, and guidelines from the LungART clinical trial for postoperative NSCLC patients in which elective nodal coverage is recommended [14–19]. In order to ensure accuracy of the elective nodal contouring, all lymph node stations were contoured as separate structures for every patient using the 2015 International Association for the Study of Lung Cancer (IASLC) lymph node map as a guideline [20]. The elective nodal CTV was generated by combining the contours of the nodal regions considered high risk for a given patient. A 5-mm isotropic expansion was added to generate the PTV51. Finally, OARs were contoured according to the current RTOG consensus atlas [21]. All contouring was carried out under the supervision of a board-certified radiation oncologist.

IFI and LENI plans were generated using volumetric modulated arc therapy (VMAT) using Varian Eclipse RapidArc and the Acuros 10 algorithm for dose calculations. Each plan used 6MV photos, and either a single or double arc. Equivalent dose-volume constraints for PTV's and OAR's were used for each patient and each plan; however optimization conditions varied on an individual basis depending on the level of difficulty in meeting these constraints for each plan. Each plan was normalized such that 95% of the PTV60 received

100% of the prescription dose, with an acceptable maximum dose to PTV60 less than 110% of the prescription dose and an acceptable minimum dose to the PTV60 greater than 90% of the prescription dose. The OAR objectives can be found in Table 2. Figure 1 shows representative IFI and LENI plans.

Dose-volumetric parameters evaluated for the purpose of comparing the plans included the total lung V_{20}, V_5, and D_{mean}; heart V_{60}, V_{45}, V_{30}, and D_{mean}; esophagus D_{max} and D_{mean}; and spinal cord D_{max}. V_x is defined as the volume of the OAR receiving at least dose x (Gy). The maximum and minimum doses were defined as the highest and lowest dose, respectively, within 0.03 cm^3 of a given structure. IFI and LENI plans were compared using two-tailed Student's t tests, for both the entire cohort and subsets of patients stratified according to their nodal stage (N1 vs. N2). Finally, for IFI plans, the percentage of each high-risk elective nodal station receiving 51 Gy was determined for each patient in order to determine the extent of incidental coverage. This study was approved by the local institutional review board.

Results

The mean (and standard deviation (STD)) dose-volumetric results for all OARs are shown in Table 2. Compared to IFI plans, LENI plans had higher doses to all OARs. However, the average LENI plans still achieved all OAR constraints. LENI resulted in significantly higher esophagus D_{mean} (15.3 vs. 22.5 Gy, $p < 0.01$), spinal cord D_{max} (34.9 vs. 42.4 Gy, $p = 0.02$) and lung D_{mean} (13.5 vs. 15.9 Gy, $p = 0.02$), V_{20} (23.0 vs. 27.9%, $p = 0.03$), and V_5 (52.6 vs. 59.4%, $p = 0.02$). No statistically significant differences were observed in heart parameters between IFI and LENI plans. A subgroup analysis of the impact of LENI for stage N1 and N2 patients is shown in Supplementary Table 1. Several statistically significant differences were observed, though the absolute differences between IFI and LENI plans were comparable for N1 and N2 subgroups for each parameter.

Table 3 indicates the percentage of nodal volume outside of the PTV60 receiving at least 51 Gy for IFI plans. On average, only 32.2% of the high-risk nodal volume targeted in LENI plans received an incidental dose of 51 Gy when untargeted in IFI plans. Furthermore, on average, only 44.9% of the uninvolved portions of involved nodal stations received an incidental dose of 51 Gy when untargeted in IFI plans.

Discussion

Comprehensive ENI using a 3DCRT technique has been previously shown to result in unfavorable outcomes compared to IFI in terms of both toxicity and tumor control. However, to extrapolate this data to contemporary treatment, planning techniques incorporating a more restricted and better selected elective nodal volume is likely to falsely exaggerate the disadvantages of ENI. In this treatment planning system study, we have shown that with the use of VMAT, the addition of LENI treated to a prophylactic dose does not impair the achievement of dosimetric objectives compared to standard IFI for NSCLC. Furthermore, contrary to prior studies assessing 3DCRT plans, we have shown that incidental dose deposition in these high-risk areas is minimal when not explicitly targeted using a VMAT

plan, and likely inadequate to sterilize microscopic disease. The implications of these findings are not limited to definitive treatment of LA-NSCLC, but are also relevant to small cell lung cancer and post-operative radiation for NSCLC, where some degree of elective nodal coverage is currently more accepted.

Not unexpectedly, the larger target volume in LENI plans was associated with higher dose to OARs despite all dosimetric objectives being achieved. An important question is how these observed dosimetric changes may correlate with actual risks of toxicity in patients. According to Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) and Normal Tissue Complications Probability (NTCP) models, the increase in the average mean lung dose from 13.5 to 15.9 Gy with LENI in this study predicts an increased risk of symptomatic pneumonitis of 3.1% [22]. Similarly, based on the observed increase in the average lung V_{20} from 23.0 to 27.9%, the risk of grade 2 or higher pneumonitis would be increased only 2–3% [23]. There is limited data available to quantify the risk of pneumonitis at different levels of the lung V_5, though two studies suggest that an increase from 52.6 to 59.4% should minimally increase the risk [24, 25]. The 7.2-Gy average increase in esophageal D_{mean} could increase acute esophagitis during treatment to some extent, but because the observed doses were all substantially lower than QUANTEC constraints, and the D_{max} was below 60 Gy, severe esophageal toxicity would not be expected [22, 26, 27]. The spinal cord D_{max} did not exceed 50 Gy in any plan, so no toxicity would be expected during or after this course of treatment [22]. Most nodes were distant from the heart, so heart parameters were minimally affected. For all of these reasons, we expect that the clinical significance of these increased doses to OARs in LENI plans is likely to be marginal.

This is not to say, though, that LENI should be used indiscriminately. For instance, in cases of larger, more central primary tumors with multiple involved mediastinal nodes, the addition of LENI may compromise esophageal constraints. Likewise, if the primary tumor and involved nodal areas encompass a larger longitudinal distance within the lung, implementing LENI may jeopardize the lungs. In our assessment, a risk-adapted approach to treatment planning is appropriate in which the elective target volumes are tailored to a patient's individual situation, in terms of cardio-pulmonary function, age, performance status, and extent of disease.

The expected benefit of LENI based on this study is harder to quantify. Although regional recurrence is not nearly as common as distant recurrence in NSCLC, given the low cure rate of LA-NSCLC, LENI may better optimize the chances of cure for those patients without micrometastatic disease at diagnosis who have a reasonable chance at cure in the first place. What is clear from our data is that the concept of incidental dose going to these other elective nodal areas by only targeting involved areas is simply not true when advanced treatment planning techniques like VMAT with its much greater conformity and more rapid dose falloff (compared to 3DCRT) are used. Specifically, our data demonstrates that the percentage of nodal volume receiving 51 Gy increases from 32.2 to 99.1% with the incorporation of LENI. Due to the coplanar nature of most radiotherapy fields, most of this incidental coverage was also in the same axial plane as the gross disease, whereas minimal dose was deposited only a few millimeters superior to it. During surgical excision of NSCLC, a complete resection requires removal of at least one nodal station above the

highest involved station [28], yet current IFI protocols would fail to deliver dose to this same area unless it were explicitly targeted.

The most important limitation of this study is that it was conducted solely with a treatment planning software and not in actual patients. As such, we could only estimate the effects of the observed dosimetric changes, and assessing the clinical benefit of LENI was beyond our scope. While the number of patients we included would be small for a clinical trial, it is an adequate sample size for a treatment planning system study such as this, and a variety of primary tumor locations and involved nodal stations were chosen intentionally in an attempt to ensure that our findings were generalizable. Another potential limitation is the applicability of our findings to clinicians using different dose levels or other types of IMRT besides VMAT. The 60-Gy dose we used for involved sites is relatively standard since the publication of RTOG 0617 [13], and the 51-Gy dose to elective nodal stations is within the realm of what would be considered adequate to eradicate microscopic disease for most malignancies. Our integrated boost approach to delivering the dose was chosen for simplicity and for a fairer comparison of one IFI plan to one LENI plan (instead of two plans for LENI had we not used an integrated boost). Employing the same radiation technique, dose/fractionation, and normalization were also necessary for a fair comparison between planning techniques. Although the absolute differences may change slightly were we to treat to a higher total dose or use other forms of IMRT planning, we believe that the basic findings highlighted in this study would remain largely intact.

Conclusion

Herein, we have demonstrated the feasibility of the addition of LENI to standard IFI when using VMAT to treat patients with locally advanced NSCLC, observing only modestly increased doses to OARs and marginal expected increase in associated toxicity. As such, we believe that it should be considered for selected patients likely to benefit in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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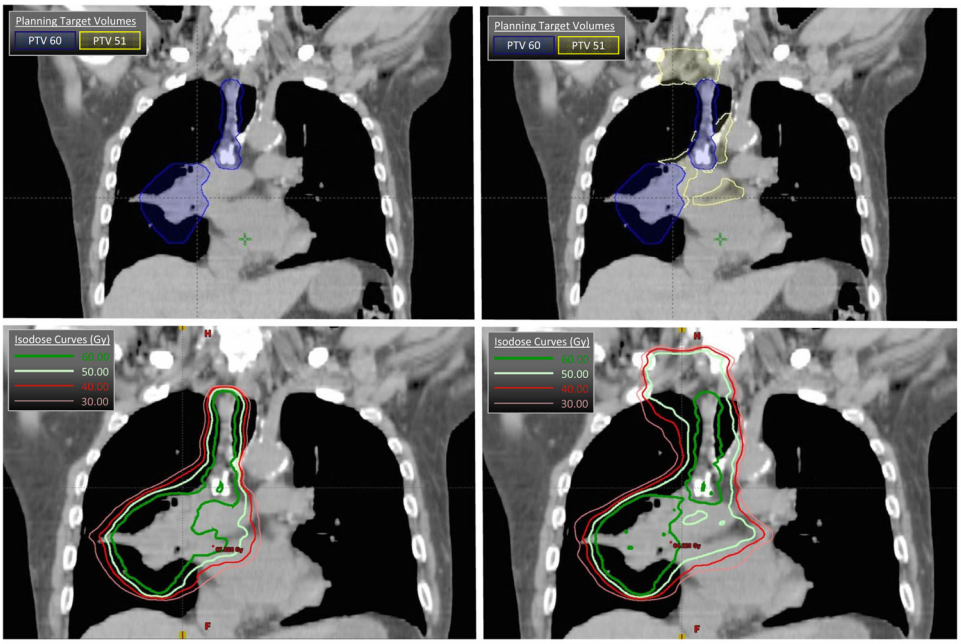

Fig. 1.

Representative planning target volumes and isodose curves for IFI (left panel) and LENI (right panel) plans for a patient with an RML primary tumor and involved nodal stations 10R, 7, 4R, and 2R

Table 1

Thoracic nodal stations targeted for ENI based on primary tumor site and other stations involved with malignancy

Primary tumor site	Elective nodal regions targeted
Right upper lobe	All patients: 10–11R, 4R, 2R
	If 2R involved, add 1R
	If 4R involved, add 7
Right middle lobe	All patients: 10–11R, 4R, 7
	If 4R involved, add 2R
	If 2R involved, add 1R
Right lower lobe	All patients: 10–11R, 4R, 7
	If 4R involved, add 2R
	If 2R involved, add 1R
Left upper lobe	All patients: 10–11L, 4L, 5, 6
	If 4L or 5 involved, add 2L, 4R, and 7
	If 6 involved, add 2L
	If 2L involved, add 2R and 1L
Left lower lobe	All patients: 10–11L, 4L, 7
	If 4L involved, add 4R, 5, 6, and 2L
	If 7 involved, add 4R

Table 2

Dose-volume parameters and objectives for organs-at-risk (OARs), as well as a comparison of the mean value of each parameter for involved field irradiation (IFI) and limited elective nodal irradiation (LENI) plans

Parameter	Objective	IFI plans Mean (STD)	LENI plans Mean (STD)	Absolute difference	Percentage difference	*p* value
Esophagus D_{max} (Gy)	< 65 Gy	54.2 (12.8)	59.8 (3.6)	+ 5.6	10.3%	0.07
Esophagus D_{mean} (Gy)	< 34 Gy	15.3 (6.4)	22.5 (5.2)	+ 7.2	47.1%	< 0.01
Spinal cord D_{max} (Gy)	< 50 Gy	34.9 (11.8)	42.4 (7.4)	+ 6.5	21.5%	0.02
Heart D_{mean} (Gy)	< 35 Gy	11.3 (8.3)	13.3 (9.5)	+ 2.0	17.7%	0.48
Heart V_{60} (%)	< 30%	1.4 (1.8)	1.9 (3.3)	+ 0.5	35.7%	0.54
Heart V_{45} (%)	< 35%	4.9 (5.5)	8.1 (9.0)	+ 3.2	65.3%	0.18
Heart V_{30} (%)	< 50%	12.6 (12.5)	16.7 (16.5)	+ 4.1	32.5%	0.38
Lungs D_{mean} (Gy)	< 20 Gy	13.5 (3.1)	15.9 (3.0)	+ 2.4	17.8%	0.02
Lungs V_{20} (%)	< 35%	23.0 (7.0)	27.9 (6.5)	+ 4.9	21.3%	0.03
Lungs V_5 (%)	< 60%	52.6 (8.8)	59.4 (8.3)	+ 6.8	12.9%	0.02

Table 3

Incidental dose deposition in non-targeted high-risk elective nodal stations from IFI plans

Patient/tumor site	Involved nodal stations	Incidental dose to high-risk mediastinal nodal stations (excluding volumes covered by PTV60) from IFI plans (percentage receiving 51 Gy)								
		1R	1L	2R	2L	4R	4L	5	6	7
1/LUL	11L						0.0	2.8	65.4	
2/LUL	10L						26.1	41.6	3.6	
3/LUL	6/5				19.2	0.4	26.1	100.0	28.7	1.0
4/LUL	4L				0.0	3.1	55.6	20.4	5.6	12.6
5/LLL	10L						0.0			1.8
6/LLL	10L						0.0			0.8
7/LLL	7/4L				0.0	0.0	4.6	87.8	11.4	27.9
8/LLL	7/6/5/4R/4L			0.0	0.0	31.2	36.9	94.6	6.4	66.6
9/RUL	10R			45.5		49.6				
10/RUL	11R/10R			8.4		26.5				
11/RUL	10R/7			20.4		89.3				36.6
12/RUL	10R/4R/2R/1R	33.8		55.6		100.0				6.2
13/RML	11R					0.0				0.0
14/RML	11R					0.0				0.0
15/RML	10R/7/4R			11.1		97.8				15.6
16/RML	10R/7/4R/2R	0.9		18.9		65.0				50.4
17/RLL	10R					29.8				27.0
18/RLL	11R/10R					10.3				3.0
19/RLL	11R/10R/7					0.0				26.7
20/RLL	10R/7/4R			0.0		2.8				24.4