Title

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Journal

Journal of Thoracic Oncology, 14(2)

ISSN

1556-0864

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Publication Date

2019-02-01

DOI

10.1016/j.jtho.2018.09.021

Peer reviewed

BRIEF REPORT

Toxicity Related to Radiotherapy Dose and Targeting Strategy: A Pooled Analysis of Cooperative Group Trials of Combined Modality Therapy for Locally Advanced Non–Small Cell Lung Cancer

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Received 15 August 2018; revised 10 September 2018; accepted 24 September 2018
Available online - 4 October 2018

ABSTRACT

Objective: Concurrent chemoradiotherapy (CRT) was the standard treatment for locally advanced NSCLC (LA-NSCLC). This study was performed to examine thoracic radiotherapy (TRT) parameters and their impact on adverse events (AEs).

Methods: We collected individual patient data from 3600 patients with LA-NSCLC who participated in 16 cooperative group trials of concurrent CRT. The TRT parameters examined included field design strategy (elective nodal irradiation [ENI] versus involved-field [IF] TRT [IF-TRT]) and TRT dose (60 Gy versus ≥60 Gy). The primary end point of this analysis was the occurrence of AEs. ORs for AEs were calculated with univariable and multivariable logistic models.

Results: TRT doses ranged from 60 to 74 Gy. ENI was not associated with more grade 3 or higher AEs than IF-TRT was (multivariable OR = 0.77, 95% confidence interval [CI]: 0.543–1.102, $p = 0.1545$). Doses higher than 60 Gy (high-dose TRT) were associated with significantly more grade 3 or higher AEs (multivariable OR = 1.82, 95% CI: 1.501–2.203, $p < 0.0001$). In contrast, ENI was associated with significantly more grade 4 or higher AEs (multivariable OR = 1.33, 95% CI: 1.035–1.709, $p = 0.0258$). Doses higher than 60 Gy were also associated with more grade 4 or higher AEs (multivariate OR = 1.42, 95% CI: 1.191–1.700, $p = 0.0001$). Grade 5 AEs plus treatment-related deaths were more frequent with higher-dose TRT ($p = 0.0012$) but not ENI ($p = 0.099$).

Conclusions: For patients with LA-NSCLC treated with concurrent CRT, IF-TRT was not associated with the overall risk of grade 3 or higher AEs but was associated with

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Disclosure: Dr. Schild writes and edits for UpToDate on various subjects related to radiation therapy, receiving personal fees. Dr. Vokes reports personal fees from AbbVie, Amgen, Ariad, AstraZeneca, Bayer, Biolumina, BMS, Boehringer-Ingelheim, Celgene, Eli Lilly, Serono EMD, Genentech, Leidos, Merck, Regeneron, Synta, Takeda, VentiRx, and Novartis outside the submitted work. Dr. Ramalingam reports personal fees from Astra Zeneca, Amgen, Bristol-Myers Squibb, Merck, Takeda, Genentech, Roche, and Lilly outside the submitted work. Dr. Bradley reports grants and personal fees from Mevion Medical Systems, Inc.; grants, personal fees, and reimbursement for travel from and service as an advisory board member of ViewRay, Inc.; and personal fees and reimbursement for travel from and service as an advisory board member of Varian Medical Systems outside the submitted work. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2018.09.021

significantly fewer grade 4 or higher AEs than ENI TRT. This is likely the result of irradiation of a lesser amount of adjacent critical normal tissue. Higher TRT doses were associated significantly with grade 3 or higher and grade 4 or higher AEs. On the basis of these findings and our prior report on survival, CRT using IF-TRT and 60 Gy (conventionally fractionated) were associated with more favorable patient survival and less toxicity than was the use of ENI or higher radiotherapy doses.

Keywords: Non-small cell lung cancer; Combined modality therapy; Toxicity; Adverse events; Doses; Field design

Introduction

Important controversies remain in the treating locally advanced (LA) NSCLC (LA-NSCLC). Basic questions related to radiotherapy (RT) have not been answered: what dose-fractionation pattern is best? and should thoracic RT (TRT) target only radiographically visible disease with involved-field (IF) TRT (IF-TRT), or should it also target the adjacent lymph nodes that are radiographically normal with elective nodal irradiation (ENI)? To address these questions, we performed a pooled analysis. The first goal of the analysis was to establish which RT strategies were associated with survival.[1] IF-TRT was associated with significantly better survival than ENI was, and doses higher than 60 Gy were not associated with better survival than 60 Gy was.[1] We hypothesized that ENI and higher doses of TRT were associated with toxicity and performed this analysis.

Methods and Materials

This pooled analysis included 3600 patients with LA-NSCLC who had participated in 16 chemoradiotherapy (CRT) trials. These trials and patient characteristics were summarized in our previous survival analysis.[1]

The cooperative groups provided individual patient data for patients with unresectable LA-NSCLC who participated in concurrent CRT trials (1990–2012).[1] The goal was to identify associations between adverse events (AEs) and both TRT dose and targeting strategies. The primary end point of this analysis was the occurrence of AEs, as determined by use of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). The RT variables evaluated included nodal coverage strategy (IF-TRT versus ENI TRT) and total TRT dose (60 Gy versus >60 Gy). IF-TRT generally included targeting of the primary lesion and regional lymph nodes measuring more than 1 cm in the short diameter and those that were hypermetabolic on positron emission tomography (PET). ENI generally included IF-TRT plus regional lymph nodes that were radiographically normal.

Statistical Analysis

The associations between TRT and other patient characteristics were evaluated with the chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables. The associations between radiation parameters as categorical variables and the occurrence of AEs were examined by using the chi-square test. The analyses evaluating the associations between AEs and radiation parameters were performed with univariable and multivariable logistic regression models; the ORs and corresponding confidence intervals (CIs) were reported. p Values were two sided and were not adjusted for multiple comparisons.

Results

Patient characteristics and treatment details were previously reported; 64% of the patients were men with an average age of 62 years.[1] The cohort was divided evenly between patients with stage IIIa and stage IIIb disease. Patients were followed for 0.01 to 14 years (median 6.1 years).

The TRT field strategy (ENI versus IF) was evaluated with respect to AEs; 756 patients (21%) had IF-TRT and 2844(79%) had ENI. Patients were divided into two dose groups: 60 Gy (a low-dose group of 1322 patients [37%]) and 60.1 to 74 Gy (a high-dose group of 2278 patients [67%]). Candidate covariates used for backward selection were TRT dose, TRT strategy (ENI versus IF), treatment pattern, age, performance status, stage, sex, race, weight loss, and number of chemotherapy drugs. Covariates in the multivariate models were backward-selected by the logistic model (Table 1).

Toxicity was first examined by overall grade 3 or higher and grade 4 or higher AEs (see Table 1). ENI was not associated with more grade 3 or higher AEs than IF-TRT was (univariable OR = 1.10, 95% CI: 0.88–1.36, p = 0.3997; multivariable OR = 0.77, 95% CI: 0.543–1.102, p = 0.1545). Doses higher than 60 Gy (the high-dose group) were associated with an increased risk of grade 3 or higher AEs (univariable OR = 1.73, 95% CI: 1.44–2.07, $p < 0.0001$; multivariable OR = 1.87, 95% CI: 1.481–2.371, $p < 0.0001$). In contrast, ENI was associated with more grade 4 or higher AEs (univariable OR = 1.36, 95% CI: 1.16–1.60, $p = 0.0002$; multivariable OR = 1.33, 95% CI: 1.035–1.709, p = 0.0258). Doses higher than 60 Gy were associated with more grade 4 or higher AEs (univariable OR = 1.54, 95% CI:1.34–1.76, $p < 0.0001$; multivariable OR = 1.42, 95% CI: 1.19–1.70, $p = 0.0001$). Grade 5 AEs plus treatment-related deaths were summed to represent mortality that was at least

Table 1. AEs with Univariable and Multivariable Analyses

Model	n	Events	%	*p* Value[a]	Logistic Unadjusted Model OR	95% Wald CI	*p* Value[b]	Logistic Multivariable Adjusted Model OR	95% Wald CI	*p* Value[b]
Model 1: grade ≥3 AEs										
TRT field				0.3996			0.3997			0.1545
IF	756	629	83.20		1.00			1.00		
ENI	2844	2402	84.46		1.10	(0.88-1.36)		0.77	(0.543-1.102)	
TRT total dose				<0.0001			<0.0001			<0.0001
Low	1322	1050	79.43		1.00			1.00		
High	2278	1981	86.96		1.73	(1.44-2.07)		1.87	(1.481-2.371)	
Model 2: nonhematologic grade ≥3 AEs										
TRT field				<0.0001			<0.0001			0.5133
IF	756	525	69.44		1.00			1.00		
ENI	2844	1751	61.57		0.71	(0.59-0.84)		1.10	(0.821-1.483)	
TRT total dose				<0.0001			<0.0001			<0.0001
Low	1322	775	58.62		1.00			1.00		
High	2278	1501	65.89		1.36	(1.19-1.57)		1.82	(1.501-2.203)	
Model 3: hematologic grade ≥3 AEs										
TRT RA field				0.0002			0.0002			0.9130
IF	756	422	55.82		1.00			1.00		
ENI	2844	1797	63.19		1.36	(1.15-1.60)		1.02	(0.777-1.326)	
TRT RA total dose				<0.0001			<0.0001			<0.0001
Low	1322	658	49.77		1.00			1.00		
High	2278	1561	68.53		2.20	(1.91-2.53)		2.45	(2.043-2.940)	
Model 4: grade ≥4 AEs										
TRT field				0.0002			0.0002			0.0258
IF	756	293	38.76		1.00			1.00		
ENI	2844	1316	46.27		1.36	(1.16-1.60)		1.33	(1.035-1.709)	
TRT total dose				<0.0001			<0.0001			0.0001
Low	1322	503	38.05		1.00			1.00		
High	2278	1106	48.55		1.54	(1.34-1.76)		1.42	(1.191-1.700)	
Model 5: nonhematologic grade ≥4 AEs										
TRT field				0.3093			0.3094			<0.0001
IF	756	155	20.50		1.00			1.00		
ENI	2844	632	22.22		1.11	(0.91-1.35)		2.38	(1.795-3.145)	
TRT total dose				<0.0001			<0.0001			0.0008
Low	1322	218	16.49		1.00			1.00		
High	2278	569	24.98		1.69	(1.42-2.01)		1.46	(1.170-1.822)	
Model 6: hematologic grade ≥4 AEs										
TRT field				<0.0001			<0.0001			0.0026
IF	756	179	23.68		1.00			1.00		
ENI	2844	950	33.40		1.62	(1.34-1.94)		1.51	(1.156-1.982)	
TRT total dose				<0.0001			<0.0001			<0.0001
Low	1322	328	24.81		1.00			1.00		
High	2278	801	35.16		1.64	(1.41-1.91)		1.55	(1.272-1.890)	

Note: Candidate covariates for multivariate analysis are radiation field, radiation total dose, treatment pattern, age, performance status, sex, race, stage, weight loss, and number of agent. Selected variables for the multivariate model are as follows: model 1: TRT field, total dose, treatment pattern, age, performance status, sex, and number of chemotherapy agents; model 2, TRT field, total dose, treatment pattern, age, performance status, sex, race, weight loss, and number of chemotherapy agents; model 3, TRT field, total dose, treatment pattern, age, and number of chemotherapy agents; model 4, TRT field, total dose, treatment pattern, age, race, and number of chemotherapy agents; model 5, TRT field, total dose, treatment pattern, age, race, and weight loss; and model 6, TRT field, total dose, treatment pattern, age, race, and number of chemotherapy agents.

[a]Chi-square *p* value.

[b]Type 3 analysis chi-square *p* value.

AE, adverse event; CI, confidence interval; TRT, thoracic radiotherapy; IF, involved field; and ENI, elective nodal irradiation.

possibly related to therapy. These were more frequent with high doses (7.24% versus 4.54% [$p = 0.0012$]) but not with a specific targeting strategy (5.91% with ENI versus 7.54% with IF-TRT [p = 0.099]). Also examined were specific AEs by organ system affected (Table 2).

Discussion and Conclusions

This study examined RT parameters used in LA-NSCLC cooperative group trials with the goal of determining which were associated with AEs. These data supplement our previous analysis of survival associated with similar TRT parameters.[1] Taken together, the results are helpful when choosing specific targeting strategies (IF-TRT versus ENI) and radiation doses for concurrent CRT. Our previous study examined survival and found that IF-TRT was associated with better survival than ENI was. Doses within the range used in these trials (60–74 Gy) were not associated with survival.[1] We hypothesized that the decrease in survival with ENI was due to the irradiation of more surrounding normal structures such as the heart, lungs, esophagus, bone marrow, and other immunologic tissues than IF-TRT was, thus resulting in more AEs. ENI resulted in significantly more grade 4 or higher AEs than IF-TRT did. Doses of RT higher than 60 Gy were associated with more grade 3 or higher and grade 4 or higher AEs. Importantly, grade 5 AEs plus deaths associated with therapy were more common with doses higher than 60 Gy but not with RT targeting strategy (ENI versus IF-TRT).

Three randomized CRT trials compared ENI with IF-TRT. The study by Yuan et al. included 200 patients.[2] The 2-year survival rates were significantly different ($p = 0.048$), favoring IF-TRT. Toxicity was not different between the arms except for pneumonitis, which occurred in 29% of patients after ENI and in 17% after IF-TRT(p = 0.044). Our analysis did not confirm this particular finding (see Table 2).

Yang et al. performed another trial; it included 55 patients who received CRT and either ENI or IF-TRT.[3] The median survival times were 15 months with IF-TRT and 13 months with ENI ($p = 0.084$). In contrast to the present study, Yang et al. detected no differences in AEs between the treatment arms.[3]

Chen et al. performed another randomized CRT trial, in which 85 patients were assigned to IF-TRT or ENI.[4] The 2-year survival rates were 53% with IF-TRT versus 35% with ENI ($p = 0.08$). There were no differences in toxicity between the two arms. This contrasts with the present study that found more grade 4 or higher AEs with ENI.

Fernandes et al. performed a retrospective analysis of 108 patients.[5] Grade 3 or higher esophagitis developed in more patients treated with ENI than in patients treated with IF-TRT (38% versus 17% [p = 0.01]). This

Table 2. Adverse Events by Organ System

	Grade ≥3 AEs						Grade ≥4 AEs					
	TRT Field			TRT Dose			TRT Field			TRT Dose		
System	ENI, n (%) (n = 2884)	IF-TRT, n (%) (n = 756)	Chi-square p Value	Low, n (%) (n = 1322)	High, n (%) (n = 2278)	Chi-square p Value	ENI, n (%) (n = 2884)	IF-TRT, n (%) (n = 756)	Chi-square p Value	Low, n (%) (n = 1322)	High, n (%) (n = 2278)	Chi-square p Value
Leukopenia/heme	1749 (61.50%)	394 (52.12%)	<0.0001	628 (47.50%)	1515 (66.51%)	<0.0001	921 (32.38%)	164 (21.69%)	<0.0001	314 (23.75%)	771 (33.85%)	<0.0001
Pulmonary/lung	710 (24.96%)	227 (30.03%)	0.0048	322 (24.36%)	615 (27.00%)	0.0818	195 (6.86%)	45 (5.95%)	0.3757	68 (5.14%)	172(7.55%)	0.0053
General/constitutional	779 (27.39%)	216 (28.57%)	0.5189	306 (23.15%)	689 (30.25%)	<0.0001	183 (6.43%)	20 (2.65%)	<0.0001	41 (3.10%)	162 (7.11%)	<0.0001
GI	10.66 (37.48%)	210 (27.78%)	<0.0001	297 (22.47%)	979 (42.98%)	<0.0001	241 (8.47%)	14 (1.85%)	<0.0001	52 (3.93%)	203 (8.91%)	<0.0001
Clotting/heme	401 (14.10%)	161 (21.30%)	<0.0001	144 (10.89%)	418 (18.35%)	<0.0001	152 (5.34%)	67 (8.86%)	0.0003	63 (4.77%)	156 (6.85%)	0.0117
Anemia/heme	308 (10.83%)	79 (10.45%)	0.7643	90 (6.81%)	297 (13.04%)	<0.0001	29 (1.02%)	8 (1.06%)	0.9257	12 (0.91%)	25 (1.10%)	0.5864
Metabolic	354 (12.45%)	167 (22.09%)	<0.0001	170 (12.86%)	351 (15.41%)	0.0361	70 (2.46%)	24 (3.17%)	0.2743	25 (1.89%)	69 (3.03%)	0.039
Dehydration	270 (9.49%)	111 (14.68%)	<0.0001	112 (8.47%)	269 (11.81%)	0.0017	32 (1.13%)	6 (0.79%)	0.4279	8 (0.61%)	30 (1.32%)	0.044
Heart/vascular	289 (10.16%)	79 (10.45%)	0.8163	117 (8.85%)	251 (11.02%)	0.0384	118 (4.15%)	26 (3.44%)	0.376	40 (3.03%)	104 (4.57%)	0.0231
Infection	371 (13.05%)	76 (10.05%)	0.0266	94 (7.11%)	353 (15.50%)	<0.0001	70 (2.46%)	10 (1.32%)	0.0591	22 (1.66%)	58 (2.55%)	0.0835
Neuro	356 (12.52%)	63 (8.33%)	0.0014	166 (12.56%)	253 (11.11%)	0.1908	37 (1.30%)	4 (0.53%)	0.0754	9 (0.68%)	32 (1.40%)	0.0485
GU	45 (1.58%)	11 (1.46%)	0.8016	19 (1.44%)	37 (1.62%)	0.662	12 (0.42%)	1 (0.13%)	0.2379	5 (0.38%)	8 (0.35%)	0.8963

AE, adverse event; TRT, thoracic radiotherapy; ENI, elective nodal irradiation; IF-TRT, involved-field thoracic radiotherapy; GI, gastrointestinal; Neuro, neurologic; GU, genitourinary; HEME, hematologic.

finding was consistent with the present study (see Table 2).

Cooperative group trials used both IF RT and ENI, as which strategy is best was unknown. These trials were analyzed in the present pooled analysis to provide objective evidence regarding AEs. Our previous analysis, which included the same cohort, found significantly better survival with IF-TRT than with ENI, but survival was not associated with dose.[1] These data provide strong evidence that IF-TRT is preferred because of its associations with better survival and less toxicity. IF-TRT avoids irradiation of large regions, thus decreasing the dose delivered to the heart, lungs, esophagus, and the immune/hematologic system. Exposure of the heart to therapeutic irradiation has been associated with severe toxicity and poorer survival.[6–8]

Additionally, Jin et al. reported that more RT received by the immune system was independently associated with inferior survival of patients with LA-NSCLC.[9] Over time, more trials have been designed to include IF-TRT, owing to concerns regarding toxicity and recognizing that the survival rates in early studies using IF-TRT were favorable.

In addition to IF-TRT, the use of newer TRT technologies can reduce toxicity. Chun et al. reported significantly less severe pneumonitis with IMRT than with three-dimensional (3D) TRT.[10] Additionally, Speirs et al. reported significantly less pneumonitis and cardiac toxicity associated with IMRT than with 3D TRT.[7] Proton beam therapy (PBT) may also decrease toxicity, as was reported by Sejpal et al.[11] Rates of grade 3 or higher pneumonitis and esophagitis in the PBT group (2% and 5%, respectively) were lower than in 3D-RT group (30% and 18%, respectively) or IMRT group (9% and 44%, respectively) ($p < 0.001$ for all). The same institution performed a randomized phase II trial that compared 3D PBT with IMRT; however, that study did not confirm the earlier results.[12] A phase III CRT trial comparing IMRT with PBT is currently in the accrual stage.

It was hoped that higher doses of conventionally fractionated TRT would improve the survival of patients with LA-NSCLC. However, with the RT technology used in these trials (primarily 3D TRT), escalation of total dose alone increased AEs without improving survival.[6] It is possible that altered fractionation programs using either multiple daily fractions or fewer larger fractions will improve survival without undue toxicity.[13] Regimens including multiple daily doses of TRT were found to positively affect survival at the cost of increased AEs.[14]

Strengths of the present study are the large size of the cohort (N = 3600) and the prospective nature of the trials. Limitations include the retrospective nature of this analysis. The use of IF RT was most common in the modern series, and improvements in supportive care over time may have also influenced outcomes. We did not compare intensity-modulated RT (IMRT) with 3D TRT, as IMRT was used in some of the patients in a single trial. Although 550 patients did have PET scans, there were no other PET data within our database and we were therefore unable to examine its potential influence on outcome. PET was required in one trial, CALGB-30407, and although not required, PET was performed in 449 patients (91%) participating in RTOG-0617. There were no tumor size or dose-volume histogram data to correlate with AEs. Although these trials included dose constraints, it would have been helpful to have had dose-volume histogram data to correlate with AEs. Advances in imaging have contributed to increasingly accurate staging and treatment planning allowing for smaller, more precise IF-TRT. Additionally, we lacked specific data regarding lymphopenia, which may be important in the immunologic effects of therapy.

This pooled analysis of AEs after CRT supplements the findings of our previous study that focused on survival.[1] In conclusion, taken together, these pooled analyses of 3600 patients with LA-NSCLC treated with concurrent CRT found that IF-TRT was associated with significantly fewer grade 4 or higher AEs and better survival than ENI was.[1] This was possible with innovations in imaging and treatment planning that generate smaller fields covering only radiographically apparent disease while sparing the adjacent normal tissues to a greater extent than was previously possible. In contrast, the use of higher total doses (>60 Gy) was associated with more severe AEs but not with improved survival. Therefore, the use of IF-TRT and 60 Gy in 2-Gy daily fractions should remain the standard of care for CRT of LA-NSCLC. Future progress in the treatment of LA-NSCLC is dependent on research improving systemic therapy, imaging, and TRT.

Acknowledgments

Supported by National Institutes of Health grant No. R21-AG042894 (to Dr. Stinchcombe, Dr. Vokes , Dr. Pang, and Dr. Wang), Health and Medical Research Fund grant No.12133251 (to Dr. Pang), National Cancer Institute grant No.P01-CA142538 (to Dr. Wang) and National Institutes of Health grant 5P30CA014236-44 (to Ms. Fan and Dr. Wang).

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