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ORIGINAL REPORT

Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non–Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial

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ABSTRACT

Purpose

Although intensity-modulated radiation therapy (IMRT) is increasingly used to treat locally advanced non–small-cell lung cancer (NSCLC), IMRT and three-dimensional conformal external beam radiation therapy (3D-CRT) have not been compared prospectively. This study compares 3D-CRT and IMRT outcomes for locally advanced NSCLC in a large prospective clinical trial.

Patients and Methods

A secondary analysis was performed to compare IMRT with 3D-CRT in NRG Oncology clinical trial RTOG 0617, in which patients received concurrent chemotherapy of carboplatin and paclitaxel with or without cetuximab, and 60- versus 74-Gy radiation doses. Comparisons included 2-year overall survival (OS), progression-free survival, local failure, distant metastasis, and selected Common Terminology Criteria for Adverse Events (version 3) ≥ grade 3 toxicities.

Results

The median follow-up was 21.3 months. Of 482 patients, 53% were treated with 3D-CRT and 47% with IMRT. The IMRT group had larger planning treatment volumes (median, 427 *v* 486 mL; $P = .005$); a larger planning treatment volume/volume of lung ratio (median, 0.13 *v* 0.15; $P = .013$); and more stage IIIB disease (30.3% *v* 38.6%, $P = .056$). Two-year OS, progression-free survival, local failure, and distant metastasis–free survival were not different between IMRT and 3D-CRT. IMRT was associated with less ≥ grade 3 pneumonitis (7.9% *v* 3.5%, $P = .039$) and a reduced risk in adjusted analyses (odds ratio, 0.41; 95% CI, 0.171 to 0.986; $P = .046$). IMRT also produced lower heart doses ($P < .05$), and the volume of heart receiving 40 Gy (V40) was significantly associated with OS on adjusted analysis ($P < .05$). The lung V5 was not associated with any ≥ grade 3 toxicity, whereas the lung V20 was associated with increased ≥ grade 3 pneumonitis risk on multivariable analysis ($P = .026$).

Conclusion

IMRT was associated with lower rates of severe pneumonitis and cardiac doses in NRG Oncology clinical trial RTOG 0617, which supports routine use of IMRT for locally advanced NSCLC.

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INTRODUCTION

Non–small-cell lung cancer (NSCLC) is the leading cancer killer in the United States,[1] and the standard of care for locally advanced unresectable NSCLC is concurrent radiation therapy (RT) with cytotoxic chemotherapy.[2-5] Historically, locally advanced NSCLC has been treated with three-dimensional conformal external beam radiation therapy (3D-CRT) with concurrent chemotherapy,[6-8] but there has been increasing use of intensity-modulated radiation therapy (IMRT).[9-12] Although IMRT is more complex to plan and deliver than 3D-CRT, its potential clinical benefits have not previously been assessed in a multi-institutional prospective clinical trial.[13]

IMRT uses complex modulated radiation beams that sculpt the radiation dose to precisely conform to complex geometric targets, which creates sharper radiation dose gradients between

ASSOCIATED CONTENT

See accompanying Oncology Grand Rounds on page 6

Appendix
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Data Supplement
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tumor and normal tissue than 3D-CRT. For these reasons, IMRT can improve radiation coverage of tumors and enhance the therapeutic ratio by avoiding adjacent organs at risk. IMRT has a number of theoretical advantages over 3D-CRT for locally advanced NSCLC. Dosimetric studies have shown IMRT to reduce the doses delivered to adjacent normal tissue, such as the lungs, esophagus, and heart, by improving conformity of the RT dose distribution.[14-18] A retrospective MD Anderson Cancer Center study compared IMRT with 3D-CRT and found that IMRT provides equivalent survival to 3D-CRT despite IMRT patients having significantly worse performance status and larger tumors.[19] A SEER and a National Cancer Database study found IMRT to be associated with improved overall survival (OS) compared with 3D-CRT in patients treated in the United States for stage III NSCLC.[9,20] IMRT also resulted in favorable outcomes compared with historic controls in a Memorial Sloan Kettering Cancer Center study.[21] These findings have provided the impetus to evaluate IMRT in the context of a large, prospective, multi-institutional clinical trial for locally advanced NSCLC.[22]

NRG Oncology clinical trial RTOG 0617 was a randomized phase III trial that used a two-by-two factorial design to assess the role of RT dose escalation (60 *v* 74 Gy) and the addition of cetuximab to weekly carboplatin and paclitaxel (carboplatin and paclitaxel with or without cetuximab) for locally advanced NSCLC.[23] The use of IMRT or 3D-CRT was one of the stratification factors at random assignment, which resulted in a balanced use of these techniques within the 60- and 74-Gy arms. The current study is a secondary analysis comparing outcomes of IMRT versus 3D-CRT in NRG Oncology clinical trial RTOG 0617.

PATIENTS AND METHODS

Design, Setting, and Participants

All eligible patients enrolled in NRG Oncology clinical trial RTOG 0617 from November 2007 through November 2011were included in this secondary analysis. The study details of NRG Oncology clinical trial RTOG 0617 were reported in the primary outcome manuscript.[23] The CONSORT diagram for NRG Oncology clinical trial RTOG 0617 is shown in Figure 1. All patients had histologically proven NSCLC and had American Joint Committee on Cancer stage IIIA or IIIB disease with Zubrod performance status 0 to 1.

Statistical Considerations

All eligible patients were included in this secondary analysis. For patient and tumor characteristics, categorical data were compared with χ^2 or Fisher exact test as appropriate, and continuous data were compared with Wilcoxon rank sum test. Given the nature of the RT technique and the potentially confounding impact of RT dose levels, stratified analyses were used when applicable. The van Elteren test,[24] the stratified extension for Wilcoxon rank sum test, was used to compare dosimetric parameters after stratifying by RT dose levels. OS, progression-free survival (PFS), time to local failure (LF), and time to distant metastasis (DM) were calculated from the date of random assignment to the date of failure or last follow-up. The rates of OS and PFS were estimated using the Kaplan-Meier method, and the distributions of OS and PFS were compared using the log-rank test[25] stratified by RT dose levels.[26] The development of LF and DM was analyzed by using the cause-specific competing risks analysis method,[27] with deaths without LF or DM as competing events. The rates of LF and DM were estimated using cumulative incidence function,[27] and the distributions of LF and DM were compared using the log-rank test, stratified by RT dose levels. Cox proportional hazards regressions were used to evaluate the impact of RT technique and other factors on all outcomes after stratifying by RT dose levels.[27] All adverse events were graded with Common Terminology Criteria for Adverse Events (version 3) criteria. The association between adverse events or treatment interruptions and RT techniques was assessed with Cochran-Mantel-Haenszel statistics (stratified by RT dose levels and cetuximab usage) and logistic regression models. All statistical tests were two-sided and $P < .05$ was considered statistically significant. SAS 9.4 software (SAS Institute, Cary, NC) was used for all statistical analyses.

RESULTS

Treatment assignment and patient characteristics by RT technique were summarized and compared (Table 1). Due to stratification, the use of IMRT and 3D-CRT were similar in the 60- and 74-Gy dose arms. Marginally more patients had stage IIIB/N3 disease in the IMRT group than in the 3D-CRT group (30.3% *v* 38.6%, $P = .056$). Positron emission tomography (PET) staging was used more often in the IMRT group than in the 3D-CRT group (88.2% *v* 94.3%, $P = .019$). Patients treated with IMRT were less likely to have completed high school or to have education beyond high school ($P = .01$). Otherwise, the 3D-CRT and IMRT groups were not different with respect to other baseline prognostic factors and characteristics ($P > .05$).

There were substantial differences in dosimetry and target volumes between the 3D-CRT and IMRT plans after adjusting for RT dose levels (Table 2). The median planning treatment volume (PTV) size was greater in the IMRT group than in the 3D-CRT group (427 *v* 486 mL, $P = .005$), and the PTV/volume of lung ratio was significantly bigger in the IMRT group (0.13 *v* 0.15, $P = .013$). IMRT provided better PTV coverage by 100% of the prescription dose (median, 94.8% *v* 95.1%; $P = .058$), whereas it had a slightly lower minimum dose to the PTV (median, 55.2 *v* 53.4 Gy; $P < .001$). After stratifying by RT dose levels and PTV quartiles, 3D-CRT also had marginally higher mean lung doses (median, 18.1 *v* 17.7 Gy; $P = .088$) and marginally higher esophageal doses (median, 27.6 *v* 25.6 Gy; $P = .078$) than IMRT. The lung V20 was not different between groups (median, 30.5% *v* 29.9%; $P = .297$), although IMRT was associated with a larger lung V5 than 3D-CRT (median, 54.8% *v* 61.6%; $P < .001$). The maximum dose delivered to nontarget tissue outside the PTV was also significantly lower in patients treated with IMRT (median, 69.9 *v* 69.55 Gy; $P = .026$). Heart doses (V20, V40, and V60) were significantly lower in patients treated with IMRT ($P < .05$), despite the volume of heart inside the PTV was not different (median, 2.05 *v* 3.56 mL; $P = .183$).

With a median follow-up of 21.3 months, 3D-CRT and IMRT did not have different 2-year rates of OS, PFS, LF, and DM (Table 3). The heart V5, V20, V40, V60, and the size of the PTV were significantly ($P < .05$) associated with OS in univariable analysis (Appendix Table A1, online only). After adjusting for RT technique, age, and percent PTV covered by 100% of the prescription dose (Appendix Table A2, online only), site accrual volume, and PET staging, the heart V40 remained significantly associated with OS (hazard ratio, 1.012; 95% CI, 1.005 to 1.02; $P < .001$).

The severe adverse effect profile of 3D-CRT and IMRT were compared, defined as treatment-associated ≥ grade 3 events

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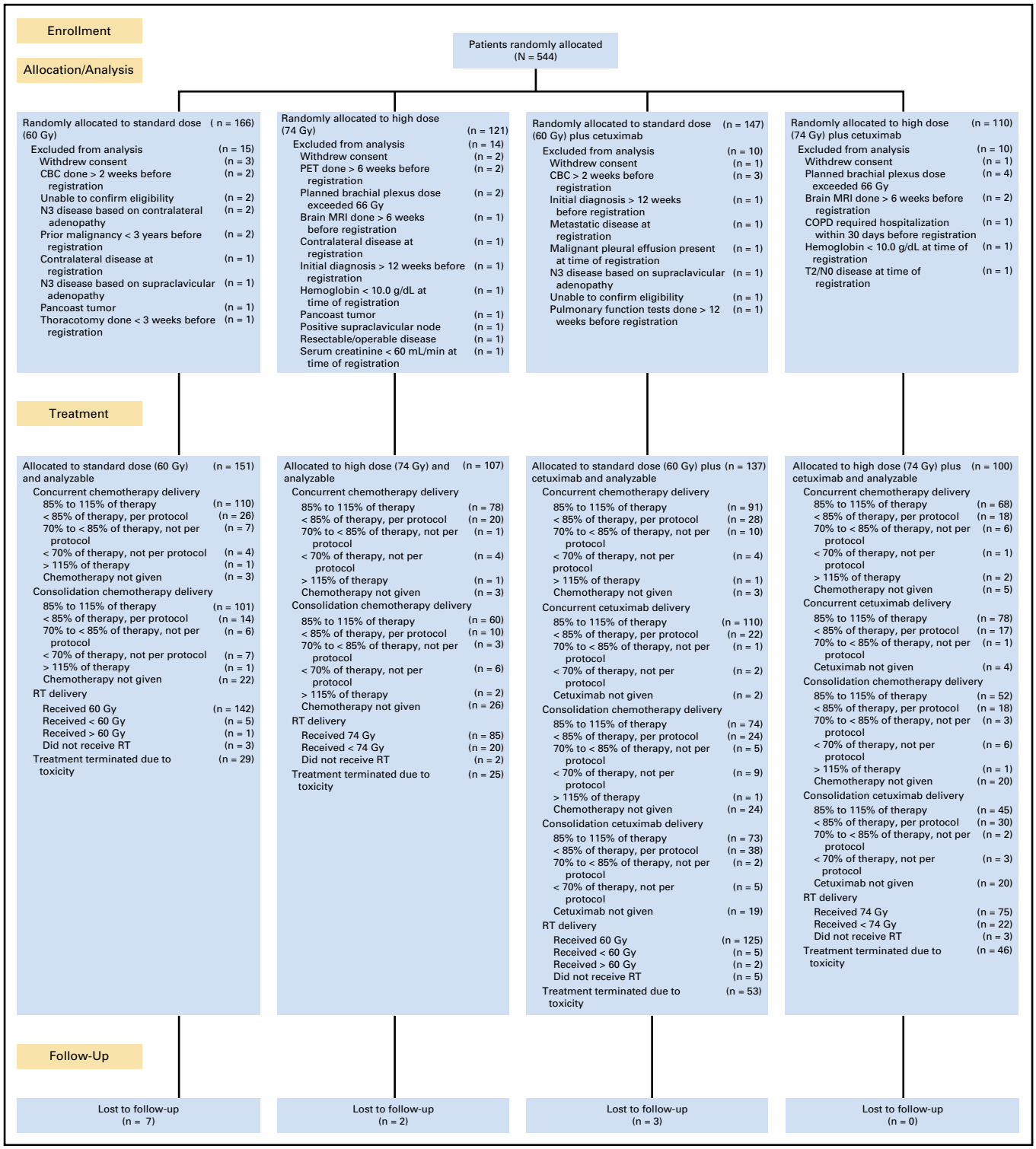

Fig 1. CONSORT diagram of NRG Oncology clinical trial RTOG 0617. COPD, chronic obstructive pulmonary disease; MRI, magnetic resonance imaging; PET, positron emissions tomography; RT, radiation therapy.

(Table 4). IMRT was associated with less ≥ grade 3 pneumonitis than 3D-CRT (7.9% *v* 3.5%, $P = .039$). The rates of ≥ grade 3 esophagitis and dysphagia, weight loss, and cardiovascular toxicity in both groups were not different ($P > .05$). Although the lung V5 was significantly larger in patients treated with IMRT, it was not associated with any kind of ≥ grade 3 toxicity (Appendix Table A3, online only).

To better understand the impact of radiation technique on ≥ grade 3 pneumonitis, further statistical analysis was performed. On multivariable analysis (Table 5), IMRT remained associated with

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Table 1. Demographic and Clinical Characteristics

Characteristic	3D-CRT, %	IMRT, %	*P*
No. of patients	254	228	
Radiation therapy dose level, Gy			.637
60	57.1	59.2	
74	42.9	40.8	
Cetuximab assigned			.953
Yes	47.6	47.4	
No	52.4	52.6	
Median age, years (range)	64 (37-82)	64 (38-83)	.903*
Sex			.966
Male	59.8	59.6	
Female	40.2	40.4	
Race			.19
Native American	0.8	0	
Asian	1.2	4.4	
Black or African American	10.2	9.6	
Pacific Islander or Native Hawaiian	0.4	0	
White	86.2	85.1	
Unknown	1.2	0.9	
Ethnicity			.357
Hispanic or Latino	3.9	1.8	
Non-Hispanic or Latino	92.9	94.7	
Unknown	3.1	3.5	
Education status			.01
Less than high school	16.1	12.3	
High school	34.7	44.3	
More than high school	41.7	30.7	
Other/unknown	7.5	12.7	
Zubrod performance status			.266
0	59.8	54.8	
1	40.2	45.2	
Positron emission tomography staging			.019
Yes	88.2	94.3	
No	11.8	5.7	
Histology			.241
Squamous carcinoma	46.5	39.9	
Adenocarcinoma	37	42.5	
Large cell undifferentiated	3.5	1.8	
Non–small cell not otherwise specified	13	15.8	
T stage			.331
Unknown	2.4	0.9	
T1	19.3	16.2	
T2	34.6	33.3	
T3	19.3	21.9	
T4	24.4	27.6	
N stage			.088
N0	4.7	7.5	
N1	5.1	3.9	
N2	83.1	75.9	
N3	7.1	12.7	
AJCC stage group			.056
IIIA	69.7	61.4	
IIIB	30.3	38.6	

Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; AJCC, American Joint Commission on Cancer; IMRT, intensity-modulated radiation therapy; N, clinical node stage; T, clinical tumor stage.
*P value from t test; otherwise, all other P values from χ^2 test.

a statistically significant reduction in pneumonitis risk (odds ratio, 0.41; 95% CI, 0.17 to 0.99; $P = .046$), whereas stage IIIB disease and lung V20 were associated with increased pneumonitis risk ($P < .05$). Neither the lung V5 nor the mean lung dose was significantly associated ($P > .05$) with ≥ grade 3 pneumonitis (Appendix Table A4, online only).

Treatment interruptions and the administration of full doses of concurrent chemotherapy were also compared between 3D-CRT and IMRT (Appendix Table A5, online only). There were similar rates of treatment interruptions due to adverse effects or illness (17.7% *v* 17.5%, $P = .969$), and administration of full doses of concurrent carboplatin (area under the curve, 2) and paclitaxel (45 mg/m^2) in the 3D-CRT and IMRT groups, respectively (70.1% *v* 66.7%, $P = .388$).

DISCUSSION

This secondary analysis of radiation technique in NRG Oncology clinical trial RTOG 0617 aimed to change clinical practice by clarifying the value of IMRT for locally advanced NSCLC based on findings from a large prospective multi-institutional trial. We found that patients treated with IMRT in NRG Oncology clinical trial RTOG 0617 did not have different 2-year survival outcomes from 3D-CRT despite IMRT having worse prognostic factors, such as larger tumors and more American Joint Committee on Cancer stage IIIB disease. Nevertheless, IMRT achieved equivalent lung V20s and better PTV coverage than 3D-CRT. In turn, IMRT was associated with a significant reduction in severe ≥ grade 3 pneumonitis. Moreover, IMRT was able to reduce radiation doses delivered to the heart, and heart doses were highly associated with OS on multivariable analysis. On the basis of these findings and in conjunction with a recent study that showed IMRT to be associated with improved quality of life in NRG Oncology clinical trial RTOG 0617,[28] we advocate for the routine use of IMRT in locally advanced NSCLC to reduce both severe lung toxicity and doses of radiation delivered to the heart.

Despite larger tumors, IMRT resulted in significantly lower rates of ≥ grade 3 pneumonitis. The lung V20 is a classic and the most frequently described dosimetric parameter believed to be a threshold dose that predicts probability of lung injury.[29] However, a number of retrospective analyses have correlated radiation pneumonitis with low-dose baths, such as the V5.[30-32] Low doses have not been found to predict pneumonitis in patients with medically inoperable early-stage NSCLC treated with stereotactic RT in a prospective Radiation Therapy Oncology Group trial.[33] Partly as a consequence of using more beam entry points, one of the hallmarks of IMRT is its ability to improve conformity of the intermediate- and high-dose region by spreading a low dose over a larger area, thereby increasing parameters such as the lung V5. Despite significantly greater lung V5 values, IMRT was associated with a better lung toxicity profile than 3D-CRT. The findings of this study provide no suggestion that the lung V5 is a predictor of toxicity in the RT of locally advanced NSCLC. Moreover, these results argue against using the lung V5 for IMRT plan optimization because an attempt to lower the V5 can potentially lead to less conformity of the high-dose region and an inability to reduce intermediate dose (V20), both of which were important objectives confirmed in this study.

In this study, patients treated with IMRT seem to have worse socioeconomic circumstances than those treated with 3D-CRT. Although socioeconomic variables such as income, health insurance status, and access to specialized care were not collected in NRG Oncology clinical trial RTOG 0617, we observed significant

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Table 2. Dosimetric Factors of 3D-CRT Versus IMRT

Dosimetric Factor	3D-CRT		IMRT		
	Median	Q1-Q3	Median	Q1-Q3	*P*
PTV volume, mL	426.7	298.1-586.5	486.2	347.6-677.3	.005*
Volume of lung excluding CTV, mL	3,331.4	2,676.7-4,045.0	3,215.7	2,754.6-4,020.0	.779*
PTV volume:lung volume ratio	0.13	0.09-0.19	0.15	0.10-0.21	.013*
Minimum dose to PTV, Gy	55.2	49.8-60.2	53.4	48.0-57.3	< .001†
Maximum dose to PTV, Gy	68.8	66.1-80.8	70.2	66.1-80.9	.256†
Dose to cover 95% of PTV, Gy	60.8	60.0-72.3	60.7	60.0-73.0	.088†
PTV covered by 100% Rx dose, %	94.8	87.0-96.4	95.1	92.1-97.0	.058*
Mean lung dose, Gy	18.1	15.4-20.6	17.7	14.4-20.1	.088†
Volume of lung, %					
V5	54.8	43.3-65.9	61.6	52.1-70.4	< .001†
V20	30.5	25.3-35.1	29.9	24.0-34.7	.297†
Mean esophagus dose, Gy	27.6	22.1-32.8	25.6	20.2-32.6	.078†
Volume of esophagus, %					
V20	47.6	39.4-56.9	46.8	36.7-56.7	.466†
V60	19.7	5.2-30.4	18.4	3.6-29.3	.927†
Volume of heart, %					
V20	23.5	7.8-46.0	19.3	5.2-36.5	.049†
V40	11.4	1.7-25.9	6.8	0.6-15.5	.003†
V60	2.4	0.0-8.3	1.4	0.0-5.0	.045†
Volume of heart inside PTV, mL	2.05	0.00-16.46	3.56	0.00-16.73	.183*
Maximum dose outside PTV, Gy	69.9	66.3-80.8	69.55	65.6-79.9	.026†

Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; CTV, clinical target volume; IMRT, intensity-modulated radiation therapy; PTV, planning treatment volume; Q1, quartile 1; Q3, quartile 3; Rx, prescription; V, volume receiving radiation dose.
**P* value from Wilcoxon test.
†*P* value from Wilcoxon test stratified by radiation therapy dose level (60 *v* 74 Gy).

differences in education status in patients treated with IMRT and 3D-CRT. Patients treated with IMRT were less likely to have completed high school or attain education beyond high school. We speculate that worse socioeconomic circumstances may account for the larger tumor volumes and more advanced-stage tumors seen in the IMRT group possibly due to barriers to health care access, which leads to later diagnoses. Despite indications that patients in the IMRT group had worse socioeconomic circumstances, these patients had a notably better severe toxicity profile, and OS was not different from that of the 3D-CRT group. IMRT could have mitigated a possible negative impact that socioeconomic status might have otherwise had on survival and coordination of care.

The dose of radiation to the heart was shown to be an important predictor of survival in NRG Oncology clinical trial RTOG 0617,[23] and this secondary analysis shows that IMRT is able to significantly reduce radiation doses delivered to the heart. Of note, IMRT did not have different survival rates from 3D-CRT despite treatment of larger and more advanced-stage tumors. Although this study was not designed to determine the survival impact of radiation doses to the heart, IMRT possibly mitigated the potential adverse survival effect conferred by larger and more advanced tumors by reducing radiation doses to the heart, such as the V40, which accounts for similar survival between the 3D-CRT and IMRT groups. However, longer follow-up may be needed to capture differences in cardiac toxicity associated with IMRT. Although institutional accrual status was previously shown to be associated with survival outcomes in NRG Oncology clinical trial RTOG 0617 patients,[34] the heart V40 remains significantly associated with OS on multivariable analysis, even with adjustment for institutional accrual status. Further pending analyses of heart doses in NRG Oncology clinical trial RTOG 0617 may provide critical insights into the effect of radiation doses on specific anatomic regions of the heart as well as pertinent heart radiation dose constraints.

Although survival outcomes appear to be equivalent between IMRT and 3D-CRT in this early analysis of outcomes in

Table 3. Outcomes at 2 Years by Radiation Therapy Technique

Outcome	3D-CRT, % (95% CI)	IMRT, % (95% CI)	*P*
Overall survival	49.4 (42.9 to 55.5)	53.2 (46.4 to 59.6)	.597
Progression-free survival	27.0 (21.5 to 32.7)	25.2 (19.7 to 31.1)	.595
Local failure	37.1 (31.0 to 43.1)	30.8 (24.8 to 36.9)	.498
Distant metastases	49.6 (43.2 to 55.8)	45.9 (39.2 to 52.3)	.661

NOTE. *P* values from a two-sided log-rank test stratified by radiation therapy dose level (60 *v* 74 Gy).
Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; IMRT, intensity-modulated radiation therapy.

Table 4. CTCAE ≥ Grade 3 Radiation-Related Adverse Events of 3D-CRT and IMRT

≥ Grade 3 Toxicity	3D-CRT, % (No.)	IMRT, % (No.)	*P*
No. of patients	254	228	
Pneumonitis	7.9 (20)	3.5 (8)	.039
Esophagitis/dysphagia	15.4 (39)	13.2 (30)	.534
Weight loss	2.8 (7)	3.9 (9)	.419
Cardiovascular	8.3 (21)	4.8 (11)	.131

NOTE. *P* values from a Cochran-Mantel-Haenszel test stratified by radiation therapy dose level (60 *v* 74 Gy) and cetuximab random assignment.
Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; CTCAE, Common Terminology Criteria for Adverse Events (version 3); IMRT, intensity-modulated radiation therapy.

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Table 5. Multivariable Logistic Regression Analysis of CTCAE ≥ Grade 3 Pneumonitis

Covariate	Comparison	OR (95% CI)	*P*
RT technique	3D-CRT (RL) *v* IMRT	0.410 (0.171 to 0.986)	.046
AJCC stage group	IIIA (RL) *v* IIIB	2.276 (1.009 to 5.137)	.048
Lung V20, %	Continuous	1.071 (1.008 to 1.137)	.026
PTV, mL	Continuous (log-transformed)	1.701 (0.708 to 4.085)	.235

NOTE. Results from multivariable logistic regression analysis stratified by radiation therapy (RT) dose levels.
Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; AJCC, American Joint Commission on Cancer; CTCAE, Common Terminology Criteria for Adverse Events (version 3); IMRT, intensity-modulated radiation therapy; lung V20, percentage of lung that receives ≥ 20 Gy; OR, odds ratio; PTV, planning treatment volume; RL, reference level.

NRG Oncology clinical trial RTOG 0617, the long-term effects of radiation technique remain to be answered. By reducing severe grade 3 or greater pneumonitis risks and lowering heart doses, IMRT may eventually be associated with improved OS on long-term follow-up. Continued follow-up of patients treated in NRG Oncology clinical trial RTOG 0617 is crucial to clarify whether long-term survival differences exist between 3D-CRT and IMRT.

In conclusion, the patients treated with IMRT for locally advanced NSCLC had lower rates of severe pneumonitis than patients treated with 3D-CRT in NRG Oncology clinical trial RTOG 0617 despite these patients having larger and more advanced tumors. IMRT should be used routinely for locally advanced NSCLC to allow greater tailoring of the conformity of the radiation dose distribution to patient anatomy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Univariate Cox Model for Overall Survival

Covariate	Comparison	HR (95% CI)	*P*
Radiation therapy technique	3D-CRT (RL) vs. IMRT	0.94 (0.74 to 1.18)	.598
Age	Continuous	1.014 (1.001 to 1.027)	.042
Percent PTV covered by 100% of Rx dose	Continuous	0.996 (0.992 to 1.000)	.080
Volume of heart			
V20	Continuous	1.008 (1.004 to 1.013)	< .001
V40	Continuous	1.013 (1.006 to 1.021)	< .001
V60	Continuous	1.023 (1.007 to 1.039)	.0051
Site accrual volume	Low (RL) *v* high volume	0.716 (0.566 to 0.905)	.0052
PET staging	No (RL) *v* yes	0.847 (0.583 to 1.231)	.3837

NOTE. Results are from respective univariate Cox models stratified by radiation therapy dose level (60 *v* 74 Gy). High volume, four or more patients accrued by institution; low volume, one to three patients accrued by institution.

Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; PET, positron emission tomography; PTV, planning treatment volume; RL, reference level; Rx, prescription; V, volume receiving radiation dose.

Table A2. Multivariable Cox Model for Overall Survival

Covariate	Comparison	HR (95% CI)	*P*
Radiation therapy technique	3D-CRT (RL) *v* IMRT	1.05 (0.83 to 1.34)	.682
Age	Continuous	1.012 (0.999 to 1.026)	.08
Percent PTV covered by 100% of Rx dose	Continuous	0.996 (0.992 to 1.001)	.107
Heart V40	Continuous	1.012 (1.005 to 1.02)	< .001
Site accrual volume	Low (RL) *v* high volume	0.75 (0.59 to 0.96)	.021
PET staging	No (RL) *v* yes	0.78 (0.54 to 1.15)	.207

NOTE. Results are from a multivariable Cox model stratified by radiation therapy dose level (60 *v* 74 Gy). High volume, four or more patients accrued by institution; low volume, one to three patients accrued by institution.

Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; PET, positron emission tomography; PTV, planning treatment volume; RL, reference level; Rx, prescription; V40, volume receiving ≥ 40 Gy.

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Table A3. Univariate Association of the Lung V5 With Treatment-Related CTCAE Grade 3 or Greater Toxicities

Grade 3 or Greater Toxicity	Lung V5 Comparison	OR (95% CI)	*P*
Pneumonitis	Continuous	1.020 (0.994 to 1.047)	.135
Esophagitis/dysphagia	Continuous	1.013 (0.996 to 1.030)	.148
Weight loss	Continuous	1.011 (0.978 to 1.04)	.519
Cardiovascular	Continuous	1.000 (0.977 to 1.023)	.993

NOTE. Results are from respective univariate logistic regression.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events (version 3); OR, odds ratio.

Table A4. Univariate Regression Model for CTCAE Grade 3 or Greater Pneumonitis

Covariate	Comparison	OR (95% CI)	*P*
Radiation therapy technique	3D-CRT (RL) *v* IMRT	0.43 (0.18 to 0.99)	.046
Radiation therapy dose level	60 (RL) *v* 74 Gy	0.64 (0.28 to 1.45)	.284
AJCC stage group	IIIA (RL) *v* IIIB	2.01 (0.93 to 4.32)	.075
PTV volume, mL	Continuous	1.001 (1.000 to 1.002)	.048
Mean lung dose	Continuous	1.097 (0.998 to 1.206)	.056
Lung V5, %	Continuous	1.020 (0.994 to 1.047)	.135
Lung V20, %	Continuous	1.069 (1.012 to 1.129)	.017

NOTE. Results are from respective univariable logistic regression.
Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; AJCC, American Joint Commission on Cancer; CTCAE, Common Terminology Criteria for Adverse Events (version 3); IMRT, intensity-modulated radiation therapy; OR, odds ratio; PTV, planning treatment volume; RL, reference level; V, volume receiving radiation dose.

Table A5. Treatment Interruptions and Chemotherapy Administration by RT Technique

Variable	3D-CRT, % (No.)	IMRT, % (No.)	*P*
No. of patients	254	228	
RT interrupted by adverse effect or illness	17.7 (45)	17.5 (40)	.969
Concurrent chemotherapy delivered in full	70.1 (178)	66.7 (152)	.388

NOTE. *P* value from a Cochran-Mantel-Haenszel test stratified by RT dose level (60 *v* 74 Gy) and cetuximab administration.
Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; IMRT, intensity-modulated radiation therapy; RT, radiation therapy.

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