



## Original Article

# Clinical outcomes after intensity-modulated proton therapy with concurrent chemotherapy for inoperable non-small cell lung cancer

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## ABSTRACT

**Background & purpose:** We report disease control, survival, and toxicity in patients with advanced inoperable non-small cell lung cancer (NSCLC) receiving concurrent chemotherapy and intensity-modulated proton therapy (IMPT) at a single institution.

**Material and methods:** All patients were treated with IMPT with concurrent chemotherapy. Endpoints assessed were local, regional, and distant control, disease-free survival (DFS), and overall survival (OS). **Results:** Fifty-one patients were enrolled with a median follow-up time of 23.0 months; 39 (76%) were treated with a simultaneous integrated boost to the gross tumor volume (GTV). The median GTV dose was 67.3 CGE and the median CTV dose was 60.0 CGE. Median OS and DFS times were 33.9 months and 12.6 months. The 3-year local control rate was 78.3%. Treatment was well tolerated, with a grade 3 toxicity rate of 18% (9 events: 4 esophagitis, 3 dermatitis, 1 esophageal stricture, and 1 fatigue) and no grade 4 or 5 toxicity. The most common grade 2 toxic effects were esophagitis (22 [43%]), dermatitis (16 [31%]), pain (15 [29%]), and fatigue (14 [27%]).

**Conclusions:** Treatment of inoperable NSCLC with IMPT and concurrent chemotherapy achieves excellent disease control with tolerable toxicity.

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Radiation therapy with concurrent chemotherapy is the recommended treatment for patients with locally advanced inoperable non-small cell lung cancer (NSCLC). Unfortunately, local and distant relapses are common, and the median survival time is only about 20–30 months [1]. Moreover, cardiopulmonary disease is common in such patients, which can make concurrent chemoradiotherapy difficult to tolerate [2]. More effective modalities that allow systemic and local therapies to be combined can improve outcomes.

Proton beam radiation therapy can offer substantial dosimetric advantages over photon radiation therapy owing to the unique dose-depth distribution of the Bragg peak, which allows the dose to the tumor to be escalated while sparing nearby critical organs such as the heart and lungs. Intensity-modulated proton therapy (IMPT), also known as pencil beam scanning proton therapy, is currently the most advanced form of proton radiation therapy. With IMPT, conformal dose distributions are achieved by magnetic scanning of proton particles of different energies to cover the treatment

volume layer by layer [3,4]. IMPT allows tight control and conformality of dose distributions and has dosimetric advantages over both passively scattered proton therapy (PSPT) and intensity-modulated photon radiation therapy (IMRT) [5,6].

Despite the dosimetric advantages of IMPT, skepticism has been expressed regarding the accuracy of dose modeling in the thorax arising from uncertainties in the relative biological effectiveness (RBE) of protons at the distal edge of the beam, the heterogeneity of tissues in the beam trajectory, and interplay between motion of the scanning beam and lung aeration and diaphragmatic movement [7]. Despite these uncertainties, treatment of locally advanced NSCLC with IMPT is becoming more widely adopted as the numbers of proton therapy centers continue to grow worldwide [8]. Given the limited number of proton centers with commissioned IMPT for the treatment of lung malignancies, however, there exists a shortage of clinical outcomes on patients with NSCLC treated with IMPT.

Herein we report disease control, survival, and treatment-related toxicity after IMPT with concurrent chemotherapy for locally advanced inoperable NSCLC at a single institution.

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## Materials and methods

### Patient characteristics

Patients with newly diagnosed or recurrent stage II or III NSCLC who received definitive chemotherapy with IMPT at a single institution from 2012 through 2016 were followed. Patients with recurrent disease were included only if the primary treatment was surgery. Patients with prior thoracic radiation were excluded. A total of 51 patients were included, of whom 3 had recurrent disease after surgical resection. All patients were enrolled on a registry protocol designed to assess normal tissue effects of proton therapy (clinicaltrials.gov NCT00991094).

Disease was staged according to the 7th (2010) edition of the American Joint Commission on Cancer staging system and confirmed histopathologically in all cases. All patients were evaluated with thoracic computed tomography (CT) and positron emission tomography (PET)/CT, bronchoscopy with endobronchial ultrasonography, or mediastinoscopy for mediastinal node staging. Inoperability for medical reasons or for unresectability was evaluated and confirmed by thoracic surgeons. All patients received concurrent chemotherapy, most often with carboplatin and paclitaxel, as weekly intravenous infusions during proton therapy. The type of chemotherapy, timing, and dose was at the discretion of the treating physician. In the event of toxicity, chemotherapy was withheld, also at the discretion of the treating physician. Toxicity related to treatment was assessed according to the Common Terminology Criteria for Adverse Effects version 4.0.

### Proton therapy treatment planning and delivery

All patients underwent 4D CT-based treatment simulation to account for respiratory motion. Patients were immobilized while supine in an upper body cradle with arms overhead. All patients were treated with image-guided IMPT. Tumors were contoured over all phases of the respiratory cycle to form the internal gross tumor volume (iGTV). A 7- to 8-mm expansion of the iGTV was used to create the clinical target volume (CTV), and an additional 5-mm expansion of the CTV was used to create the planning target volume (PTV). For patients treated with a simultaneous integrated boost (SIB), an SIB volume (SIBV) was defined as the iGTV + 5 mm and was treated to a higher dose. Orthogonal kilovoltage image guidance was used for daily set-up.

Multifield-optimized IMPT plans were designed using three or four beams. Because IMPT plans are more sensitive to setup and range uncertainties than are PSPT or IMRT plans, an in-house-developed IMPT workflow with robustness optimization was used to create treatment plans. Briefly, data from CT on tumor and normal tissue structures were exported from the treatment planning system to the in-house IMPT system for optimization and dose calculations that incorporated machine delivery constraints and robustness criteria [9,10]. The optimized spot weights as determined by the in-house system were saved as a DICOM file and imported into the commercial treatment planning system, which then recalculated the dose. We recently incorporated a robust optimization strategy into the Eclipse treatment planning system (Varian Medical Systems) [11]; these robustness evaluation tools are used to analyze the IMPT plans against 3-mm setup and 3.5% range uncertainties. To ensure that each IMPT plan was optimally designed, the IMPT plan was compared against a VMAT plan that was also optimized by an in-house-developed automated planning system [12].

Interplay effects are managed based on published consensus guidelines [4]. Briefly, during the treatment planning phase, we evaluate tumor motion with 4D CT-based water equivalent analysis to facilitate choice of the best beam arrangement for that

patient. We also use dynamic dose calculation to determine the magnitude of the motion (and hence that of the interplay effects). If the motion is large, we use 4D robust optimization to enhance the robustness of the plan to the effects of intrafractional motion [13,14]. During the planning approval process, we use the dose distributions calculated from the T0 and T50 phases to quantify the extremes of systematic dose degradation caused by respiratory motion. For beam delivery, we use layered rescanning to reduce interplay effects and optimize the delivery sequence, including scanning direction, to minimize interplay effects [15].

### Treatment evaluation

Patients were evaluated every 3–6 months after treatment completion with interim history, physical examination, lab work, and axial CT. PET/CT scans were obtained at the discretion of the treating physician. At each follow-up visit, toxicity was assessed and scored in accordance with Common Terminology Criteria for Adverse Effects version 4.0. Local failure was defined as disease recurrence anywhere within the high-dose radiation field. Regional failure was defined as development of intrathoracic disease outside the high dose radiation field. Distant recurrence was defined as recurrence outside the thorax.

### Statistical analysis

Data were analyzed with Stata/MP 15.0 statistical software [16]. Fisher's exact tests were used to assess measures of association in frequency tables. The equality of group medians was assessed with the Wilcoxon rank-sum test.

The survival function was assessed using the Kaplan–Meier estimates, with log-rank tests used to assess the equality of the survivor function across groups. Survival time was calculated from the radiation therapy start date to the first occurrence of the considered event. Endpoints assessed include local failure, regional failure, distant metastasis, any recurrence (local, regional, or distant), and overall survival.

A Cox proportional hazards model was used for univariate and multivariate analyses to assess the effect of patient, tumor, and other factors potentially associated with the endpoints assessed, with estimated hazard ratios (HRs) reported and the Wald test used to assess the role of covariates in the model. All factors found to have a *P* value of 0.25 or less on univariate analysis were included in the multivariable assessment, with each factor eliminated in a step-wise manner by backward elimination until the most significant variables were identified. *P* values of 0.05 or less were considered to be statistically significant. Statistical tests were based on a two-sided significance level.

## Results

Patient, treatment, and disease characteristics are outlined in Table 1. Of the 51 enrolled patients, most (24 [47%]) had stage IIIB disease; 21 (41%) had stage IIIA disease, and 6 (12%) had stage II disease. The median age at time of diagnosis was 70 years (range 43–83 years). Thirty-nine patients (76.4%) received an SIB, and the other 12 did not. The median GTV was 95.3 cm<sup>3</sup>. The median dose prescribed to the GTV for all patients was 67.3 CGE, and the median dose prescribed to the CTV was 60.0 CGE. The median follow-up time was 23.0 months (range 0.9–60.1 months). All patients received concurrent chemotherapy with proton therapy.

The median overall survival time was 33.9 months and the median disease-free survival time was 12.6 months (Fig. 1, Table 2). The overall survival rate for all patients was 42.8% at 3 years. In all, 27 patients experienced recurrence, at a median interval of 6.2 months. Local failures occurred in 7 patients at a median

**Table 1**  
Patient characteristics.

	No. of patients (%)
All patients	51
Sex	
Female	22 (42)
Male	29 (58)
Age at diagnosis, years	
Median	70.0
Mean	68.8
Range	43–83
Smoking status	
Current	7 (14)
Never	7 (14)
Former	38 (72)
Smoking pack-years	
No. of cases	43
Median	47.0
Mean	51.5
Range	3–150
Tumor status	
Primary	48 (94)
Recurrence	3 (6)
Disease stage	
II	6 (12)
IIIA	21 (41)
IIIB	24 (47)
GTV, cm <sup>3</sup>	
Median	95.3
Mean	144.1
Range	2.33–686.04
GTV Target Dose, CGE	
Median	67.3
Mean	68.47
Range	59.40–78.00
CTV Target Dose, CGE	
Median	60.0
Mean	62.98
Range	54.00–78.00

Abbreviations: GTV, gross tumor volume; PTV, planning target volume; CTV, clinical target volume.

interval of 9.5 months, for a local control rate of 78.3% at 3 years. Regional failures appeared at a median interval of 5.5 months, and regional control was 79.8% at 3 years. Distant failure occurred in 21 patients at a median interval of 6.4 months, for a distant failure-free survival rate of 51.0% at 3 years.

Potential associations between the variables age, sex, smoking status, disease stage, use of SIB, GTV, GTV prescribed dose, mean lung dose, and heart V40 and overall and disease-free survival were assessed with Cox regression analysis (Table 3). The only significant association found was between overall survival and heart V40. No variables were associated with disease-free survival in univariate (Table 3) or multivariate analysis (not shown).

Toxicity rates were low overall (Table 4). No patients experienced grade 4 or grade 5 toxicity. Nine patients experienced acute and late grade 3 toxicity (4 esophagitis, 3 dermatitis, 1 esophageal stricture, and 1 fatigue).

## Discussion

Here we report clinical outcomes after IMPT (median dose 67.3 CGE [range 59.4–78 CGE]) with concurrent chemotherapy for locally advanced inoperable NSCLC. We found IMPT to be well tolerated, with no grade 4–5 toxicity and a grade 3 toxicity rate of 18%, and effective, with 3-year rates of local control of 78.3% and median overall survival time of 33.9 months. Disease stage was

not associated with overall survival, but cardiac dose (heart V40) was associated with poorer prognosis.

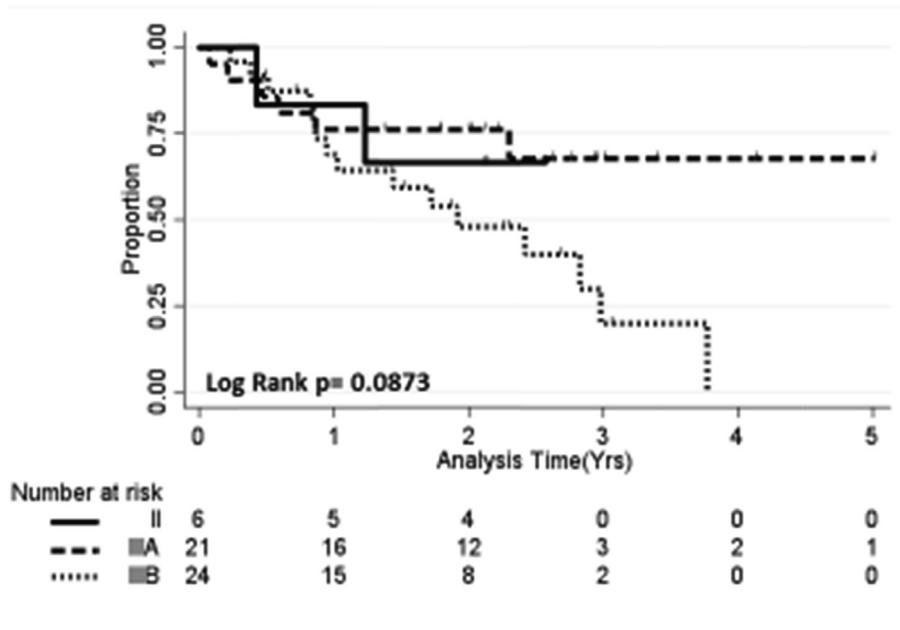
We previously reported outcomes of PSPT for inoperable NSCLC at the same institution [17]. In that study, the local–regional control rate for all patients was 55.8% at 3 years. In the current study, the local–regional recurrence-free survival rate was 64.5% at 3 years. One notable difference between studies is that the median GTV was 70 cm<sup>3</sup> in the PSPT study versus 95.3 cm<sup>3</sup> in the current study. This difference of 36% is reassuring in that the use of IMPT for large and anatomically complex tumors seems to produce comparable if not better disease control over PSPT. Similarly, Chang et al. reported long-term outcomes from a phase II protocol to evaluate concurrent chemotherapy with PSPT to 74 CGE for locally advanced NSCLC. The median survival time in this study was 26.5 months; the local control rate at 5 years was 84%; and toxicity rates were acceptably low (23% grade 2 and 3 pneumonitis, no grade 4–5 toxicity) [18].

The first randomized clinical comparison of PSPT versus IMRT for locally advanced NSCLC was recently reported by Liao and colleagues [19]. The primary endpoints were rates of radiation pneumonitis and local control at 1 year for patients with stage II–IIIB NSCLC, stage IV NSCLC with a single brain metastasis, or recurrent disease after surgical resection. A Bayesian adaptive trial design was used to detect differences in treatment outcomes and to adaptively weight randomization to the favorable arm as those outcomes became available. The goal of this design was to reduce the number of patients allocated to potentially less effective treatment. Pairs of IMRT and PSPT plans were generated for all patients, and if both plans met lung constraints, patients were eligible for randomization. In that study, PSPT led to lower lung V5–V10, higher lung V20–V80, and significantly lower mean heart dose relative to IMRT. No differences were found between groups in 1-year rates of grade  $\geq 3$  pneumonitis (6.5% IMRT and 10.5% PSPT,  $P = 0.40$ ) and local failure (10.9% IMRT and 10.5% PSPT,  $P = 1.0$ ) or in median survival times (29.5 months IMRT and 26.1 months PSPT,  $P = 0.30$ ). In the current study, treatment with IMPT led to no grade  $\geq 3$  pneumonitis and comparable local failure rates of 8.8% at 1 year, suggesting that IMPT is comparable to PSPT and IMRT for disease control, with potentially less toxicity.

Although the Liao et al. trial showed no difference in primary endpoints, we caution against concluding that proton therapy has no benefit in NSCLC. Among patients who were not eligible for randomization, PSPT was the only modality that could meet dose constraints in 13 patients, illustrating that for subsets of patients with NSCLC, protons had a clear dosimetric advantage and treatment with IMRT may necessitate underdosing the tumor to meet normal tissue constraints. Moreover, patients in the current study were all treated with IMPT. A detailed dosimetric comparison of IMPT, PSPT, and IMRT showed that IMPT could deliver the highest mean tumor dose (with improved conformality) while simultaneously achieving the lowest dose to heart, lungs, and esophagus for patients with anatomically complex thoracic tumors [20]. In our practice, patients with large bilateral tumors are usually treated with IMPT because dose constraints are difficult to meet with PSPT or IMRT and because IMPT does not seem to compromise local control.

Efforts to escalate radiation dose with photon-based techniques to improve outcomes for patients with locally advanced NSCLC proved ineffective in the phase III randomized controlled trial RTOG 0617. That trial allowed treatment with IMRT or 3D conformal radiotherapy, and image guidance was encouraged but not mandated. Despite similar local control and cancer-specific survival rates from standard-dose (60 Gy) and high-dose (74 Gy) therapy, overall survival was worse in the high-dose group. Several potential explanations have been advanced to explain the lack of benefit from dose escalation, among them that the high-dose

## Overall Survival



## Local Failure Free Survival

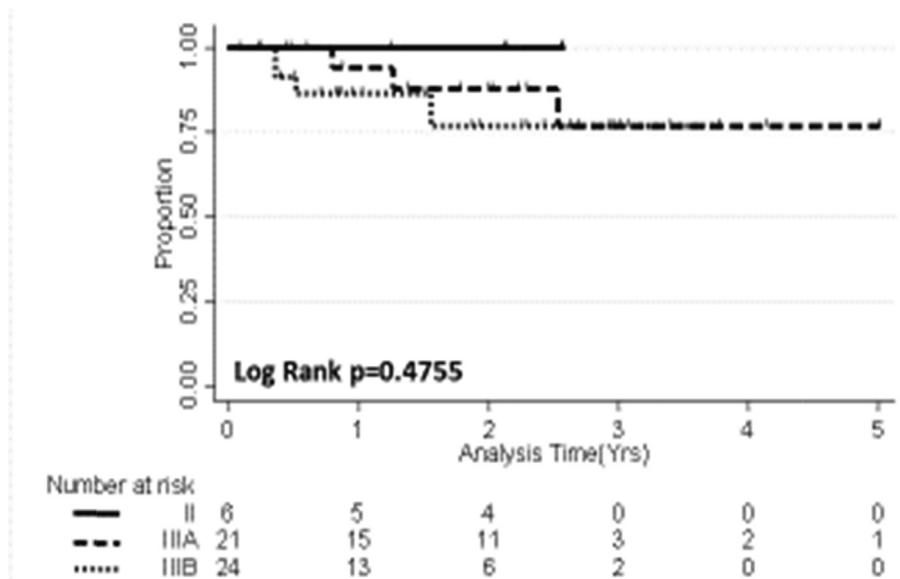


Fig. 1. Overall and local failure-free survival estimates by disease stage.

therapy may have caused more cardiopulmonary toxicity from higher doses to heart and lungs. This association suggests that sub-clinical cardiopulmonary toxicity was present but was not captured by adverse event reporting. We also found a significant association between cardiac V40 and overall survival. Notably, we examined several other cardiac variables including mean and max heart dose as well as V10, V20, and V30; however, cardiac V40 showed the strongest association with overall survival. Because all of the cardiac dosimetric variables were codependent, only cardiac V40 was included in the multivariate model.

The detrimental effects of radiation dose to the heart and lungs have been established in numerous studies [21–23]. Speirs et al.

analyzed heart and lung doses in 416 patients with locally advanced NSCLC and found that heart V50 and lung V5 were both independently associated with overall survival [24]. Similarly, Xu et al. measured cardiac troponin after concurrent chemoradiation and showed that mean heart doses >20 Gy led to significant increases in troponin and that a doubling or more in troponin levels relative to baseline was associated with worse overall survival [25]. Although dose escalation was thought to be beneficial in several prospective trials before RTOG 0617, that benefit is likely negated if the dose escalation results in fatal cardiopulmonary toxicity. Thus, even though RTOG 0617 did not show a benefit from dose escalation, its results are confounded by increased cardiopul-

**Table 2**  
Survival and disease control outcomes by disease stage.

Rates, %, at					
	1 Year	2 Years	3 Years	4 Years	5 Years
<b>Overall survival</b>					
All Patients	73.9	62.9	42.8	28.5	28.5
II	83.3	66.7	—	—	—
IIIA	76.2	76.2	67.7	67.7	67.7
IIIB	68.9	48.0	20.0	—	—
<b>Disease-free survival (any failure)</b>					
All Patients	56.0	42.9	37.5	37.5	37.5
II	66.7	44.4	—	—	—
IIIA	58.9	47.6	38.1	38.1	38.1
IIIB	50.0	37.5	37.5	—	—
<b>Local–regional failure-free survival</b>					
All patients	78.6	70.3	64.5	64.5	64.5
II	100	100	—	—	—
IIIA	79.4	68.1	58.3	58.3	58.3
IIIB	72.9	64.8	64.8	—	—
<b>Local failure-free survival</b>					
All Patients	91.2	84.8	78.3	78.3	78.3
II	100	100	—	—	—
IIIA	94.1	87.8	76.9	76.9	76.9
IIIB	86.5	76.9	76.8	—	—
<b>Regional failure-free survival</b>					
All patients	85.1	79.8	79.8	79.8	79.8
II	100	100	—	—	—
IIIA	84.7	73.4	73.4	73.4	73.4
IIIB	81.8	81.8	81.8	—	—
<b>Distant metastasis-free survival</b>					
All patients	68.2	51.0	51.0	51.0	51.0
II	66.7	44.4	—	—	—
IIIA	64.3	53.0	53.0	53.0	53.0
IIIB	71.0	48.7	48.7	—	—

**Table 3**  
Univariate and multivariate Cox regression analyses of factors associated with overall survival and disease-free survival.

Variable	Overall Survival				Disease-Free Survival	
	Univariate		Multivariate		Univariate	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
<b>Sex</b>						
Male (vs. female)	0.42 (0.18–1.00)	0.05	1.01 (0.095–1.07)	0.73	1.15 (0.53–2.49)	0.72
<b>SIB</b>						
Yes (vs. no)	0.97 (0.36–2.63)	0.954			0.73 (0.31–1.73)	0.47
<b>Age at diagnosis</b>						
Continuous	0.98 (0.94–1.03)	0.459			1.00 (0.95–1.05)	0.93
<b>Smoking pack-years</b>						
Continuous	1.00 (0.99–1.02)	0.65			1.00 (0.97–1.04)	0.82
<b>Disease stage</b>						
IIIA (vs. II)	0.70 (0.14–3.54)	0.67			1.17 (0.33–4.22)	0.81
IIIB (vs. II)	1.92 (0.43–8.47)	0.39			1.40 (0.44–4.93)	0.60
<b>GTV target dose</b>						
Continuous	1.00 (0.9989–1.000)	0.33			1.00 (0.999–1.0002)	0.14
<b>CTV target dose</b>						
Continuous	1.00 (0.000–1.0007)	0.58			1.00 (0.000–1.001)	0.997
<b>PTV</b>						
Continuous	1.0001 (0.999–1.001)	0.96			1.00 (0.9995–1.001)	0.44
<b>Heart V40</b>						
Continuous	1.00 (0.999–1.10)	0.001	1.07 (1.02–1.12)	0.006	0.95 (0.87–1.04)	0.44
<b>Mean lung dose</b>						
Continuous	1.001 (0.9999–1.002)	0.07	1.001 (1.00–1.002)	0.16	1.00 (0.999–1.001)	0.96

Abbreviations: SIB, simultaneous integrated boost; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume.

monary exposure from the large numbers of patients being treated with 3D conformal radiation without modern image guidance and respiratory tracking.

Effective use of IMPT to improve patient outcomes in the future depends on accurate modeling of particle–matter interactions and set-up uncertainties. Relative to photon therapy, interactions

**Table 4**  
Treatment-related toxicity.

Toxicity type & grade	No. of cases (%)
	51 (100)
Pneumonitis	
Grade 1	8 (16)
Grade 2	7 (14)
Cardiac Toxicity*	
Grade 1	3 (6)
Grade 2	4 (8)
Esophagitis	
Grade 1	19 (37)
Grade 2	22 (43)
Grade 3	4 (6)
Radiation dermatitis	
Grade 1	17 (33)
Grade 2	16 (31)
Grade 3	3 (6)
Pain	
Grade 1	19 (37)
Grade 2	15 (29)
Esophageal stricture	
Grade 3	1 (2)
Fatigue	
Grade 1	32 (63)
Grade 2	14 (27)
Grade 3	1 (2)

\* Cardiac ischemia, pericardial effusion, tachycardia, atrial fibrillation, and atrial flutter.

between proton particles and matter are more challenging to model and depend more strongly on heterogeneities in tissue density and motion. Uncertainties in treatment planning are more pronounced for IMPT than for PSPT, as the individual fields can generate significant dose gradients within the treatment volume. Many proton therapy treatment systems available today use simple analytical algorithms to calculate dose rather than Monte Carlo algorithms. Analytic algorithms can miscalculate dose to the target by as much as 31% compared with 12% with Monte Carlo [26]. Also, current treatment planning systems do not account for variations in RBE, although preclinical and clinical studies suggest that RBE depends on a variety of factors, include tumor molecular characteristics, tissue density, and proton particle trajectory.

To our knowledge, this is one of the largest series to date of IMPT and concurrent chemotherapy for locally advanced NSCLC. Despite the concerns and uncertainties surrounding the use of IMPT to treat thoracic tumors, our findings indicate promising outcomes and low toxicity in a subset of patients with large bulky inoperable tumors. However, our study is limited by relatively short follow-up time as well as the inherent limitations of a single-institution, non-randomized analysis including selection bias. Additional prospective randomized trials are needed to validate the efficacy of IMPT, particularly in the context of dose escalation. RTOG 1308 is an ongoing phase III randomized trial in which IMRT is compared with proton therapy and overall survival is the primary endpoint; however, because this is a national trial, and because IMPT is not as readily available as PSPT, most proton treatment will likely be delivered with PSPT. A prospective phase I/II study of IMRT versus IMPT with an SIB for locally advanced NSCLC (NCT01629498) is currently taking place at our institution. The phase I portion of the study established 72 CGE as the highest planned dose for the phase II portion [27]. We await the results of these and other prospective randomized trials to confirm the results of our own study with larger numbers of patients to establish the clinical benefit of IMPT for the treatment of inoperable locally advanced NSCLC.

## Conflicts of interest

The authors declare no conflicts of interest.

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