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Particle beam therapy for lung cancer

Feasibility of proton beam therapy for reirradiation of locoregionally recurrent non-small cell lung cancer

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ABSTRACT

Background and purpose: Options are limited for patients with intrathoracic recurrence of non-small cell lung cancer (NSCLC) who previously received radiation. We report our 5-year experience with the toxicity and efficacy of proton beam therapy (PBT) for reirradiation.

Materials and methods: Thirty-three patients underwent PBT reirradiation for intrathoracic recurrent NSCLC at a single institution. All patients had had RT for NSCLC (median initial dose 63 Gy in 33 fractions), with median interval to reirradiation of 36 months. Median reirradiation dose was 66 Gy (RBE) in 32 fractions. Toxicity was scored with CTCAE v4.0, and survival outcomes were estimated using Kaplan–Meier.

Results: Thirty-one patients (94%) completed reirradiation. At a median 11 months' follow-up, 1-year rates of overall survival, progression-free survival, locoregional control, and distant metastasis-free survival were 47%, 28%, 54%, and 39%. Rates of severe (grade $\geqslant 3$) toxicity were 9% esophageal, 21% pulmonary; 1 patient had grade 4 esophagitis, and 2 had grade 4 pulmonary toxicity. Nine patients experienced a second in-field failure.

Conclusions: PBT is an option for treating recurrent NSCLC. However, the rates of locoregional recurrence and distant metastasis are high and the potential for toxicity significant. The risks and benefits of PBT must be carefully weighed in each case.

External-beam radiation therapy (RT) is a common treatment modality for non-small cell lung cancer (NSCLC), with 70% of patients receiving radiation to the thorax as part of definitive or adjuvant treatment. Despite advances in treatment techniques over the past decade, the rates of locoregional relapse (LRR) and subsequent death remain high [1]. Many patients who experience LRR after prior radiation and are not considered candidates for surgery are offered systemic therapy. However, the generally low response rates to second-line chemotherapy [2,3] have prompted interest in using repeated radiation therapy (reirradiation) as a method for controlling local disease and palliating symptoms with a more durable response. Reports of outcomes after reirradiation are limited. The published studies tend to have heterogeneous patient populations with respect to tumor histology and treatment intent (palliative vs. definitive), technique, and dose-fractionation schemes [4–16]. Thus, predicting toxicity and prognosis in this setting can be difficult.

For the past 5 years, our institution has been referring selected patients with locoregionally recurrent NSCLC who are not candidates for surgery to undergo definitive reirradiation with proton beam therapy (PBT) in light of the favorable dose distributions that PBT can provide. Our purpose in reporting survival and toxicity outcomes for these patients is to help guide clinicians as to the feasibility of this approach, to identify patients who are candidates for definitive reirradiation, and to provide preliminary data regarding the use of PBT in this setting.

Patients and methods

Patients

This retrospective study was approved by the appropriate institutional review board. Subjects were all patients receiving PBT for reirradiation of recurrent NSCLC from November 2006 through September 2011 at a single institution. All patients had had thoracic RT for histologically confirmed NSCLC. Definitive intent reirradiation with PBT was considered for patients with recurrent disease noted radiographically, who did not have a surgical option. This cohort comprised 33 patients; patient, tumor, and treatment characteristics are shown in Table 1. The most common primary tumor was adenocarcinoma. *KRAS* and *EGFR* mutation status was analyzed in 10 patients, of whom 2 had *KRAS* mutations and 1 had an *EGFR* mutation. Patients had good performance status at time of reirradiation, with 67% ($n = 22$) having an Eastern

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Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Eight patients (24%) received concurrent chemotherapy with PBT reirradiation; the most common agents were carboplatin with paclitaxel ($n = 4$), and other patients received carboplatin alone ($n = 1$), etoposide ($n = 1$), etoposide and cisplatin ($n = 1$), or pemetrexed ($n = 1$).

All patients had completed an initial course of radiation for NSCLC, either at our institution or at an outside facility, delivered via conventional fields, 3D conformal RT, intensity-modulated radiation therapy (IMRT), stereotactic ablative RT (SABR), or PBT. The initial course of RT had been completed in 1979 through June 2010, and consisted of an initial median dose of 63 Gy (range 40–74 Gy) in a median 33 fractions (range 4–59 fractions), median dose per fraction was 2 Gy (range 1.18–12.5 Gy). The 4 fraction patients were treated with SABR. Given the wide range of dose and fractionation schemes, biologically effective dose (BED) and equivalent dose in 2 Gy fractions (EQD2) were also calculated. For BED calculations an α/β ratio of 4, corresponding to late pneumonitis reactions, was used (designated as Gy_4). Median BED for initial radiation therapy was 93 Gy_4 (range 62–206 Gy_4) while median EQD2 was 62.2 Gy (range 39–155 Gy). The median time to tumor recurrence was 19 months (range 0–375 months). Thirty-two of 33 patients had diagnostic FDG-PET/CT restaging of their recurrent disease. Recurrence was confirmed by biopsy in 27 patients (82%). Most failures (15; 45%) were in the same lobe of the lung, followed by nodal failure (13; 39%), contralateral lung (8; 24%), and ipsilateral lung different lobe (6; 18%). Most patients received other therapies prior to reirradiation; 15 patients (45%) were treated with chemotherapy, 2 (6%) underwent surgery, and 2 (6%) had both surgery and chemotherapy.

In-field failure was defined as the geometric center of the recurrent mass lying within the 50% isodose line. Nineteen patients (57.5%) underwent PBT reirradiation for in-field failure, 2 (6%) for marginal failure, and 12 (36%) for out-of-field failure after the initial RT course. Central location was defined using RTOG criteria as tumor within or touching the zone of proximal bronchial tree or immediately adjacent to mediastinal or pericardial pleura. Twenty-eight of 33 patients (85%) received PBT for a centrally located tumor ($n = 26$ within the proximal bronchial tree and $n = 13$ adjacent to mediastinal or pericardial pleura with $n = 11$ meeting both criteria).

Table 1
Patient, tumor, and treatment characteristics.

Characteristics at time of initial diagnosis	
Age	
Median	64
Range	42–85
Ethnicity	
White	29
Black	2
Asian	1
Hispanic	1
Sex	
Female	15
Male	18
Current smoker	
Yes	10
No	21
Histology	
NSCLC	4
Squamous	14
Adenocarcinoma	15
T-stage	
T1	7
T2	9
T3	8
T4	6
Unknown	2
N-stage	
N0	14
N1	1
N2	14
N3	4
M-stage	
M0	32
M1	1
Stage group	
IA	4
IB	3
IIA	2
IIB	3
IIIA	12
IIIB	8
IV	1
Characteristics at time of recurrence	
Age	
Median	69
Range	47–85
Current smoker	
Yes	2
No	31
ECOG performance status at time of reirradiation	
0	7
1	15
2	9
3	1
4	1
Area of failure after initial RT	
In field	19
Marginal	2
Out of field	12
Interval between initial RT and reRT (months)	
Median	36
Range	1–376
Concurrent chemotherapy with proton beam therapy	
Yes	8
No	24

Radiation treatment simulation and target volume delineation

Patients were positioned supine with arms overhead and immobilized with custom Vac-LOK cradles (CIVCO Medical Solutions, Kalona, IA). Four-dimensional computed tomography (4D CT) was used to account for tumor motion. FDG-PET simulation was not used, however for patients with available diagnostic PET/CT imaging of recurrence (32 of 33 patients) these images were used for target delineation. Targets were delineated as described elsewhere [17,18]. Briefly, the internal gross tumor volume (iGTV) was defined as the envelope of motion on a reconstructed maximum intensity projection image verified across all phases of the 4D CT dataset. Internal target volume (iTV) included the iGTV plus an 8-mm expansion to cover microscopic disease. ITV contours were reproduced on other respiratory phases and then edited by the attending radiation oncologist. For each beam, the iTV projection in the beam's-eye view was expanded laterally by 5 mm to account for day-to-day variations in setup. Target volume included gross nodal disease only. For PBT, median iGTV volume was 30.7 cc (range 3.1–271.5 cc) and median iTV volume was 95.8 cc (range 16.8–489.3 cc). Fifteen patients had data available to calculate median total iGTV (from initial and PBT radiation), for these patients median total iGTV was 106.4 cc (range 13.4–312.6 cc).

Passive scattering proton therapy planning and delivery

Compensators and apertures were custom-designed for each patient to account for tumor motion. Treatment plans were