Review Article

Proton therapy for thoracic reirradiation of non-small cell lung cancer

Hann-Hsiang Chao, Abigail T. Berman

Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA, USA

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Correspondence to: Abigail T. Berman, MD, MSCE. Assistant Professor of Radiation Oncology, University of Pennsylvania School of Medicine, Hospital of the University of Pennsylvania, TRC 2-West, 3400 Civic Center Boulevard, Philadelphia, PA 19104, USA.
Email: abigal.berman@uphs.upenn.edu.

Abstract: Lung cancer is a leading cause of cancer death with frequent local failures after initial curative-intent treatment. Locally recurrent non-small cell lung cancer represents a challenging clinical scenario as patients have often received prior radiation as part of a definitive treatment regimen. Proton beam therapy, through its characteristic Bragg peak and lack of exit dose is a potential means of minimizing the toxicity to previously irradiated organs and improving the therapeutic ratio. This article aims to review the rationale for the use of proton beam therapy for treatment of locally recurrent non-small cell lung cancer, highlight the current published experience on the feasibility, efficacy, and limitations of proton beam reirradiation, and discuss future avenues for improved patient selection and treatment delivery.

Keywords: Proton beam therapy; reirradiation; non-small cell lung cancer (NSCLC); intensity-modulated proton therapy (IMPT)

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Introduction

Lung cancer today remains one of the leading causes of cancer-related mortality worldwide with an estimated 222,500 new cases and 155,870 deaths expected in the United States in 2017 (1). Non-small cell lung cancer (NSCLC) is the most common histological subtype of lung cancer, accounting for roughly 85% of all lung cancers (2). Radiation therapy is commonly utilized as part of a definitive treatment regimen, and it has been estimated that >70% of lung cancer patients may derive benefit from receiving radiotherapy at initial presentation (3). Radiation can be employed with curative intent as single-modality treatment in the setting of early stage disease (4), or as part of combined modality treatment for locally-advanced NSCLC with bimodality (5-11) or trimodality regimens (12,13).

Despite advances in the management of NSCLC, treatment outcomes remain disappointing, with median survival of 20–28 months for unresectable stage III patients with good performance status in the modern era and 5-year overall rates of 15–20% (14). Treatment failures remain quite common, with distant failure being the typically observed pattern of failure. However, there is also an estimated ~25% risk of isolated locoregional failure (6) and these failures often occur in prior radiation fields, given the high likelihood of having received radiotherapy as part of definitive treatment at initial presentation (3). Because of these factors, the presentation of isolated locoregional failure without evidence of distant metastatic disease presents a unique clinical challenge. Retreatment using systemic chemotherapy results in suboptimal response rates (15,16), although there have been more recent promising experiences utilizing

immunotherapy (15,17). The developing potential for durable survival in a subgroup of recurrent patients then further highlights the importance of effective local control of disease. Salvage surgery may result in favorable control outcomes (18), but is also associated with prohibitive risks (19), leading many to explore reirradiation as an option for durable locoregional control. Thoracic radiation is inherently challenging due to the presence of adjacent critical structures such as the heart, normal lung, spinal cord and esophagus. This challenge is heightened in the reirradiation setting given the potential for radiation dose overlap to these critical structures from the original radiation plan, and resultant treatment-related toxicities. Many groups have published their experiences with NSCLC reirradiation in the past (20-27), using a variety of radiation techniques, but only more recently have proton reirradiation protocols been explored and reported. In this article, we review the current published experiences on the use of proton beam therapy for thoracic reirradiation of lung cancer.

Rationale for proton therapy

Proton therapy has been explored as a means of improving the therapeutic ratio for thoracic malignancies in both the initial and reirradiation treatment settings. In contrast to conventional forms of radiation, where the energy delivered to the patient falls off gradually with depth, proton therapy allows energy to be deposited at a specific depth that is known as the Bragg peak (28,29). This physical property of proton therapy allows for rapid falloff of radiation dose at the distal end of the target, which can result in normal tissues beyond the tumor depth to receive little or no radiation (30-32).

Proton beam delivery is typically delivered using either passive scattering or pencil beam scanning techniques. In passive scatter therapy, the tumor volume is irradiated as a whole with lateral beam shaping achieved through the use of apertures. The dose is conformed to the target using collimators and compensators. Conversely, in pencil beam scanning, the proton beam is magnetically scanned across the patient and the target volume is treated spot-by-spot with a narrow proton beam. Both methods allow for complete sparing of tissue distal to the target but higher target conformality can be achieved using pencil beam scanning as it allows for improved dose sculpting and the delivery of intensity-modulated proton therapy (IMPT) (31,33).

By taking advantage of the rapid energy fall off with protons, normal tissue sparing can be maximized regardless of treatment technique (31). The benefits of normal tissue sparing in the initial treatment setting are apparent (34), but gain added importance in the reirradiation setting due to the potential of avoiding normal tissues that may have previously received high-dose radiation (25,27). The use of proton therapy in the reirradiation setting is an active area of investigation (35), with published experiences on its use in central nervous system (36), head and neck (37,38), and gastrointestinal recurrences (39,40). Lung cancer is no exception, with multiple institutions now reporting their experience with proton reirradiation (24,25,27,41).

Proton reirradiation for NSCLC

The earliest large published series on proton therapy for reirradiation of locoregionally recurrent NSCLC is from MD Anderson Cancer Center (25), where the authors report on their experience with 33 cases. Patients were treated exclusively using a passive-scatter technique and largely received full dose radiation at both the initial and retreatment courses (median 63 and 66 Gy, respectively). Ninety-four percent (31 patients) of patients were able to complete the full reirradiation course. The median time interval from the completion of the initial course to reirradiation was 36 months in this series. With a median follow-up of 11 months, the 1-year locoregional control, progression-free survival and overall survival were 54%, 28%, and 47%. Median overall survival was 11.1 months and median progression-free survival 4.5 months. No patients experienced grade 5 toxicities, while three patients developed grade 4 toxicities (tracheoesophageal fistula, tracheal necrosis). There was a 9% rate of grade 3 esophagitis and a 21% rate of grade 3 pneumonitis. Concurrent chemotherapy was given with proton beam reirradiation in 24% of cases in this series.

A subsequent series was published by the MD Anderson group examining definitive reirradiation of locoregionally recurrent NSCLC with either proton beam therapy or intensity modulated radiation therapy (IMRT) in 102 patients (24). However, the exact numbers of patients treated with either proton *vs.* IMRT is not provided, making it infeasible to comment on the proton reirradiation experience in this series. The study period overlaps with the prior MD Anderson report (2006–2011 *vs.* 2006–2013), making it likely that the combined proton beam and IMRT experience includes many patients on the previously

reported MD Anderson proton reirradiation experience. This series is notable however for including 19 patients (19%) who received proton beam therapy for their initial definitive course of radiation.

Chao *et al.* (27) subsequently published the only multi-center prospective study to date of definitive reirradiation for locally recurrent NSCLC, examining 57 cases treated at the University of Pennsylvania, Procure Oklahoma City, and the Northwestern Medicine Chicago Proton Center. The majority of cases were treated using a passive scatter technique, with another six patients (11%) treated using pencil beam scanning, making this series both the first multi-institutional prospective experience and the first to report on patients treated with pencil beam scanning. A comparison is not made between patients treated using passive scatter or pencil beam scanning however, so it is not possible to judge the relative performance of intensity modulated proton therapy from this experience. In this series, 52 patients (91%) were able to complete the full reirradiation course to a median dose of 66.6 Gy. The interval between radiation courses was a median of 19 months and 67% of patients received concurrent chemotherapy. Locoregional control was 75%, with 1-year overall survival and progression free survival of 59% and 58% respectively. Median overall survival was 14.9 months. Six grade 5 toxicities were observed in this series, and 24 (42%) patients developed grade ≥3 acute and/or late toxicity.

In each of these series, passive scatter proton therapy was the predominant form of proton beam delivery. More recently, a retrospective analysis of 27 patients treated exclusively using IMPT techniques at MD Anderson was reported (41). This series included patients who received prior thoracic radiation for any malignancy excluding breast cancer and the use of IMPT was chosen at the discretion of the treating physician. Twenty-two patients (81%) were treated for NSCLC, with the others histologies including neuroendocrine, small cell, thymoma, and mesothelioma with a median follow-up of 11.2 months. The authors do not report any failures to complete the full reirradiation course, with a median dose of 66 Gy. The median interval between radiation courses was 29.5 months and 48% of patients received concurrent chemotherapy. The 1-year freedom from locoregional failure, progression-free survival, and overall survival were 61%, 51%, and 54% respectively, with a median overall survival of 18.0 months. Reirradiation was well tolerated in this series, with no grade 4 or 5 toxicities and only 2 patients (7%) experiencing late grade 3 pulmonary toxicity.

Limiting toxicities of proton reirradiation

From the published proton reirradiation series to date, we observe that patients are largely able to tolerate and complete their radiation course, but there is variability in the incidence and degree of subsequent toxicity experienced. This is likely reflective of the differing populations that were including in the series, with variation in factors such as concurrent chemotherapy usage and reirradiation interval. The multi-institutional experience encountered the most severe toxicities with six grade 5 toxicities and 42% grade ≥3 acute and/or late toxicity. In this series, the authors initially included all patients regardless of tumor volume, but did stratify patients into a high-volume [clinical target volume (CTV) ≥250 cm^3] and low-volume (CTV <250 cm^3) group. The high-volume group was subsequently suspended to further enrollment in August 2012, accounting for two of the grade 5 toxicities, and with all but one of these patients experiencing a grade ≥3 event. Tumor size comparisons across the three series are difficult to make as granular data was not provided, but the median tumor volume treated was marginally higher in the multi-institutional series (median CTV: 107.9 cm^3) as compared to the two MD Anderson Cancer Center series [median internal target volume (iTV): 95.8 cm^3 and median CTV: 98 cm^3]. However, the actual range of tumor sizes varied widely (range, 6.4–695.7, 16.8–489.3, and 13–1,081 cm^3 respectively).

In the multi-institutional experience, the rate of grade 5 events also dropped off over time, suggesting a possible learning-by-doing improvement in patient selection and treatment planning/delivery. Another source of increased toxicity in this experience was that this series also had the highest rate of concurrent chemotherapy use. The grade ≥3 included many incidents of neutropenia and other systemic chemotherapy related toxicities, which were likely exacerbated by the concurrent therapy.

The IMPT series from MD Anderson Cancer Center showed very low rates of toxicity, with two grade 3 toxicities being the highest level of toxicity reported. The authors report only the rates of toxicity for pulmonary, esophageal, dermatitis, fatigue, pain, and hemoptysis symptoms, and so it is unclear if events such as neutropenia directly related to chemotherapy were not observed or not reported. Nonetheless, no grade 4 or 5 events directly attributable to therapy were observed in this series, which could be attributable to the technical improvements achievable with

IMPT, and the knowledge gained from prior reirradiation experience at the same institution (25).

Patient selection for proton reirradiation for recurrent NSCLC

It is evident from the published literature on proton reirradiation that its delivery is technically feasible (25,27), especially as improvements continue to be made in plan robustness and motion management techniques to allowing for better dose conformality through the use of IMPT (31,33,41). However, the variability in the rate and degree of toxicity observed, suggests that patient selection remains an important factor in the careful and considered use of proton reirradiation. Though continued improvements in delivery technique may help mitigate toxicity, appropriate identification of the factors likely to predispose towards higher toxicity will help isolate those patients with a favorable therapeutic ratio and likely to benefit from reirradiation.

Predictors of toxicity that have been posited in the current literature include time to reirradiation, tumor location, tumor volume, and dose delivered to critical organs. A longer interval between initial RT and reirradiation was non-significantly associated with lower rates of grade 3 ≥ toxicity (25), while other series showed no association (24). Central tumor location, defined as within 2 cm of the proximal bronchial tree, has been shown in multiple cases to be associated with greater toxicity (25,27). McAvoy *et al.* (25) showed that central tumor location was statistically significantly associated with greater rates of cardiac toxicity, and a trend towards increased pulmonary toxicity, while Chao *et al.* (27) showed significantly higher rates of any grade ≥3 event with increasing volume of central region overlap (<41 *vs.* ≥41 cm^3). The actual contribution of tumor volume to outcomes and toxicity is unsettled. McAvoy *et al.* (24) showed that iGTV volume was not associated with increased risk of toxicity. However, the later IMPT experience by Ho *et al.* (41) from the same institution showed that iGTV and CTV volume had a significant association with overall survival as discussed below, although here the authors did not comment specifically on toxicity. As previously mentioned, the high-volume arm on the multi-institutional series was closed due to excessive toxicity, and increased central region tumor volume was found to be associated with increased toxicity. Although the data is conflicting on the relationship between toxicity and tumor volume, it is likely that greater tumor volume reflects other contributory factors such as likelihood of central region involvement, dose delivered to normal critical structures, and extent of disease at initial presentation and recurrence, which can affect toxicity in the short term and survival in the long-term.

Indeed, higher mean doses delivered to the heart and esophagus are found to be associated with increased grade 3 or higher toxicity, with an additional association with worse overall survival with higher esophageal mean dose (27). There is also evidence in the proton and IMRT reirradiation experience that higher maximum point dose to the esophagus and larger esophageal volume irradiated (V60) had greater rates of grade 2 or higher esophageal toxicity (24). Similarly, greater volume of reirradiated lung, specifically the V10, V20, and mean lung dose parameters, had greater risk of grade 2 or higher pulmonary toxicity (24).

Concurrent chemotherapy is another potential contributor to toxicity in the reirradiation setting, though analysis is confounded by the inherent heterogeneity in patient selection and the chemotherapy agents used. Two of the four reported series suggest increased risk of toxicity with concurrent chemotherapy with reirradiation (24,27). The early MD Anderson Cancer Center experience (25), however, did not show a significant association with esophageal or pulmonary toxicity with concurrent chemotherapy, and the IMPT experience (41) did not comment on the association of chemotherapy with toxicity, only on overall survival. This suggests that careful and considered use of chemotherapy with reirradiation is critical, as it has potential for increased toxicity, but can be employed in well-selected patients due to potential disease control benefits.

Outcomes of proton reirradiation for recurrent NSCLC

The outcomes from proton reirradiation experiences are largely similar, with published median overall survival between 11.1–18.0 months and 1-year overall survival between 47–59% (25,27,41). Progression-free survival exhibited greater variance, ranging from 1-year rates of 28% to 59%. It is notable that the progression-free survival rates tracked with the usage rate of concurrent chemotherapy. This is reflected in analyses that show concurrent chemotherapy was associated with improved distant metastases-free survival in one series (24), and improved overall survival in two series (24,27). No association was seen with survival and concurrent chemotherapy in the

IMPT reirradiation series (41). Notably, performance status was also associated with improved survival (24) and concurrent chemotherapy is the only factor that showed differential effects on toxicity and survival outcomes, highlighting the tradeoff to be made between aggressive disease eradication and treatment related toxicity.

Other factors that the literature suggests may be associated with improved survival outcomes are similar to those associated with decreased toxicity. Ho *et al.* showed a significant association with iGTV <32 cm^3 and CTV <100 cm^3 with improved overall survival on univariate analysis (41). The same analysis also showed that a more advanced original T-stage (3–4 *vs.* 1–2) was associated with worse overall survival. Likewise, McAvoy *et al.* (24) found that a cutoff of iGTV <27 cm^3 was associated with improved overall survival. In the same vein, Chao *et al.* found that a greater volume of tumor overlaps with the central region (≥41 cm^3) showed a trend towards worse overall survival, suggesting location and size both play important roles (27).

There is conflicting evidence on the importance of dose delivered to the target volume. Ho *et al.*, showed patients who received 66 Gy or higher had improved freedom from local failure, freedom from loco-regional failure, and progression-free survival (41), and increased dose at reirradiation is also suggested to play a role in overall survival in a separate series (24), but an earlier series found no association between dose delivered and survival. Higher normal tissue dose may nullify the potential higher tumor dose, as Chao *et al.* found that higher mean esophageal dose was associated with worse overall survival (27). Consequently, the benefits of higher dose to the tumor may be canceled out if the dose to adjacent critical structures is not adequately limited. Dose to the tumor may also serve as a surrogate to other factors such as tumor volume and tumor location, since a large central tumor is less likely to be treated with dose escalation than a small peripheral tumor.

Future directions

The current published experiences highlight the potential of proton therapy in the realm of retreatment for recurrent NSCLC. Proton therapy provides the capability to treat patients previously felt to be too high risk for reirradiation due to dose overlap with critical organs. IMPT represents a continued evolution of proton therapy, and its potential for improved dose shaping may further increase the safety of proton reirradiation. IMPT can further minimize high-dose overlap with central structures (42), thus limiting treatment-related toxicity, as evidenced by the fact that the published IMPT reirradiation series has the lowest reported toxicities to date. Thus, with wider adoption of IMPT, proton reirradiation may be safer and more accessible, and be able to treat some patients who could not be safely treated with a passive scattering plan. Other technical advancements such as reductions in respiratory motion, estimation of range uncertainty, and improvements in functional imaging to allow for reductions of target volumes are additional ways that can improve the ability to achieve adequate dose, overall efficacy, and improved therapeutic ratio for proton therapy in recurrent NSCLC.

In addition, the optimal systemic therapy to be combined with reirradiation is also an area of active investigation. Immunotherapy has shown potential in locally-advanced NSCLC: the recently-published PACIFIC trial demonstrated that the immunotherapy durvalumab, given in the consolidation setting after chemoradiation, had an 18-month progression-free survival benefit of 44.2% *vs.* 27.0% compared to placebo (43). Therefore, a similar benefit may exist in the reirradiation setting. The University of Pennsylvania currently has an open phase II trial (NCT03087760) investigating "Consolidation Pembrolizumab After Concurrent Chemotherapy and Proton Reirradiation for Thoracic Recurrences of Non-Small Cell Lung Cancer", with the primary endpoint of progression-free survival. Even beyond the results of this study, further questions regarding the sequencing and duration of systemic therapy with reirradiation will need to be addressed.

Conclusions

The challenge with reirradiation remains proper patient selection and identifying the pertinent factors that will allow clinicians to mitigate treatment-related toxicity and improve disease outcomes. Thus, proton reirradiation should be employed in a discriminating manner, and the ideal reirradiation candidate would be one with a relatively small, peripherally located tumor, not abutting the heart or esophagus, with a long interval from initial retreatment, and good performance status capable of receiving concurrent chemotherapy. As advancements in care continue to progress, including areas such as improved imaging and treatment delivery, the outcomes achievable with an ideal reirradiation candidate, as well as those who can be classified as a higher-risk reirradiation candidate

will continue to improve. It is imperative that structured reports of proton reirradiation experiences and techniques continued to be published in order to expand the knowledge base and facilitate future improvements.

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Footnote

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