Proton Therapy for Thoracic Malignancies: A Review of Oncologic Outcomes

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Abstract

Introduction: Radiotherapy is an integral component in the treatment of the majority of thoracic malignancies. By taking advantage of the steep dose fall-off characteristic of protons combined with modern optimization and delivery techniques, proton beam therapy (PBT) has emerged as a potential tool to improve oncologic outcomes while reducing toxicities from treatment.

Areas covered: We review the physical properties and treatment techniques that form the basis of PBT as applicable for thoracic malignancies, including a brief discussion on the recent advances that show promise to enhance treatment planning and delivery. The dosimetric advantages and clinical outcomes of PBT are critically reviewed for each of the major thoracic malignancies, including lung cancer, esophageal cancer, mesothelioma, thymic cancer, and primary mediastinal lymphoma.

Expert opinion: Despite clear dosimetric benefits with PBT in thoracic radiotherapy, the improvement in clinical outcomes remains to be seen. Nevertheless, with the incorporation of newer techniques, PBT remains a promising modality and ongoing randomized studies will clarify its role to determine which patients with thoracic malignancies receive the most benefit. Re-irradiation, advanced disease requiring high cardio-pulmonary irradiation volume and younger patients will likely derive maximum benefit with modern PBT.

Introduction

Radiotherapy is an integral part of the multi-modality approach to treating thoracic malignancies. Conformal dose distribution from techniques like intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) allows dramatic reduction in dose and subsequent toxicity to nearby organs-at-risk (OAR). However, due to the dosimetric properties of photon-based treatment, significant volumes of normal tissue are still exposed to intermediate and low doses of radiation. This undesired, but inevitable, irradiation of normal organs including the heart, lungs, and esophagus results in excessive acute and late toxicities.

In this context, proton beam radiotherapy (PBT) with its unique physical characteristics of relatively insignificant exit dose have emerged as a promising modality to improve local control while maintaining toxicity, or conversely, maintain oncologic outcomes while reducing toxicity. Technological advancements in treatment delivery systems have allowed for an increase in the adoption and affordability of PBT. Nonetheless, high-level data supporting the use of PBT as a superior treatment technique compared to photon therapy are limited and have been accumulating relatively slowly.

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In this review, we seek to present the current data regarding the use of PBT in thoracic malignancies. Following a brief discussion on the physical properties and treatment techniques of PBT, the dosimetric advantages, clinical outcomes, and toxicity data will be reviewed for PBT in thoracic malignancies including lung cancer, esophageal cancer, mesothelioma, thymic malignancies, and mediastinal lymphomas.

Physics of proton beam therapy

In contrast to X-rays, PBT dose deposition utilizes the Bragg Peak property of heavy charged particles (e.g., protons, carbon ions), where the majority of the radiation energy is deposited within a narrow spatial range as the particle comes to a stop resulting in virtually no exit dose distal to the location of the peak [1]. This advantageous characteristic of PBT makes the modality particularly appealing in cases where critical structures, such as the uninvolved lung, heart, esophagus, spinal cord, kidneys, liver, central airways, or great vessels, lie in close proximity to the target volume.

The clinical delivery of PBT begins with extraction of protons from an accelerator to produce a single, monoenergetic proton beam (approximately 250 MeV) with a cross-sectional diameter (spot size) of 3–4 mm. Next, the beam is modified in order to treat tumors with varying depths, shapes, and sizes by one of two methods: passive scattering (PS) or pencil beam scanning (PBS), also referred to as active scattering or spot scanning. In passive scattering a wedge energy selection system reduces the proton energy to the specific energy that allows for protons to stop at the distal edge of the tumor. Next, a range-modulator wheel spreads out the monoenergetic proton beam into a beam containing protons with many different energies (i.e. Spread-Out Bragg Peak). This generates protons with varying energies that stop at different depths. A physical material is then introduced to widen the beam in the plane perpendicular to the direction of the beam and thereby allow treatment of a larger surface area. In order to shape the beam to the target and limit the scattered dose to normal tissue outside of the treatment field, a custom-made physical device called an aperture is placed in the beam path. A custom-made compensator is also fabricated and used for treatment delivery to shape the distal edge of the field by varying the amount of material the beam passes through. An important limitation of PS PBT is the inability of the compensator to conform and modify entrance dose on the proximal edge of the beam, possibly resulting in greater dose to normal tissue residing proximal to the target volume [2,3].

In contrast to PS PBT, PBS is a modern technique that utilizes magnets to steer the spatially narrow, monoenergetic proton beam to deliver discrete ‘spots’ of dose across the entire cross-section of the target volume. The energy selection system is used to degrade the energy of the beam, and therefore reduce the depth of the Bragg Peak, so the steering magnets can place ‘spots’ of dose throughout the target layer by-layer. As a result, PBS obviates the need for apertures and compensators that are individually fabricated for each patient that result in increased labor and cost to PS treatments. By allowing each layer to have an independent number of spots, this approach also allows for improved proximal dose conformality and intensity-modulated proton therapy (IMPT) within the target.

While PBS allows for improved shaping of the dose to the tumor volume, the potential disadvantage is the increased uncertainty with dose deposition [4–8]. Whereas PS treats the entire volume of the tumor simultaneously, PBS 'paints' radiation into the desired dose distribution and is therefore time-consuming and consequently more sensitive to motionrelated changes in target location relative to the beam which can result in differences in actual dose delivery including overdosing normal tissue and underdosing tumor. This phenomenon has been coined the 'interplay effect' due to the relationship between tumor motion and motion of the proton beam as it delivers the planned 'spots'. Further, treatment planning algorithms can underestimate or overestimate the depth of the Bragg Peak for a particular energy contributing to range uncertainty, which must be accounted for in the treatment planning process. Similarly, the location of the Bragg Peak is dependent upon the density of tissue being traversed. Thoracic RT involves considerable changes in tissue heterogeneity as beam traverses through subcutaneous and chest wall tissue to enter lung before reaching solid tumor. These significant changes in tissue density compounded by variations due to respiratory motion, setup error, and inaccurate stopping power modeling can alter the location of dose deposition using the highly conformal PBS delivery technique for treating thoracic malignancies [9].

Various methods have been implemented to combat these potential limitations of PBS. Reducing respiratory motion with the use of external immobilization, breath-hold, or respiratory gating to only turn on the beam during specific phases of the respiratory cycle are some of the approaches. In addition, to reduce the net interplay effect, using larger number of smaller doses per fraction or use of single-field optimization to improve robustness may negatively impact conformality of dose and result in excess dose to nearby structures. In addition, respiratory gating, breath-hold, and repainting provide desirable motion management techniques but increase treatment duration and may be logistically challenging, particularly in busy centers with a single proton accelerator and multiple treatment rooms and in patients with poor lung function. With access to PBT also being limited and associated with higher cost than photon therapy, implementation of these techniques may further impact costeffectiveness.

Lung

Introduction

Radiation therapy remains an integral part of the multimodality approach to treatment of locally advanced non-small cell lung cancer (NSCLC) and has an increasing role in the management of patients with early-stage, metastatic, and recurrent NSCLC.

Despite improvements in radiotherapy techniques with the advent of IMRT/VMAT, incorporation of daily image guidance, and enhancement in motion management techniques, delivery of adequate dose to tumor while respecting normal tissue constraints remains a challenge in thoracic malignancies [12,13]. This is of particular concern in a patient population that often has significant smoking history and cardiopulmonary comorbidities that make them particularly susceptible to treatment-related toxicities. The risk is further exaggerated in the current era of immunotherapy, which carries an independent risk of pneumonitis or cardiac toxicity.

More recently, PBT has emerged as an exciting modality with dosimetric advantages that may allow for improved clinical outcomes by reducing dose to surrounding OARs. In fact, a large propensity score-matched analysis utilizing the National Cancer Database (NCDB) to compare outcomes using photon-based versus proton-based treatments found that PBT was associated with an improvement in OS at 5 years though the nature of data is unable to demonstrate a causal relationship [14]. In a prospective series of patients with unresectable or recurrent NSCLC treated with proton or photon-based radiotherapy with concurrent chemotherapy, patients treated with PBT were also found to develop less severe symptoms based upon patient reported outcomes [15].

Summary dosimetric data

Data regarding the dosimetric benefits of PBT have been reviewed in multiple reports wherein a reduction in the dose to the lungs, spinal cord, heart, esophagus, and integral body dose was all achieved using PBT compared to photon therapy (3D-Conformal or IMRT) for both early and advance-staged NSCLC patients [16–20]. Figure 1 shows example treatment plans of IMPT to the lung in various settings.

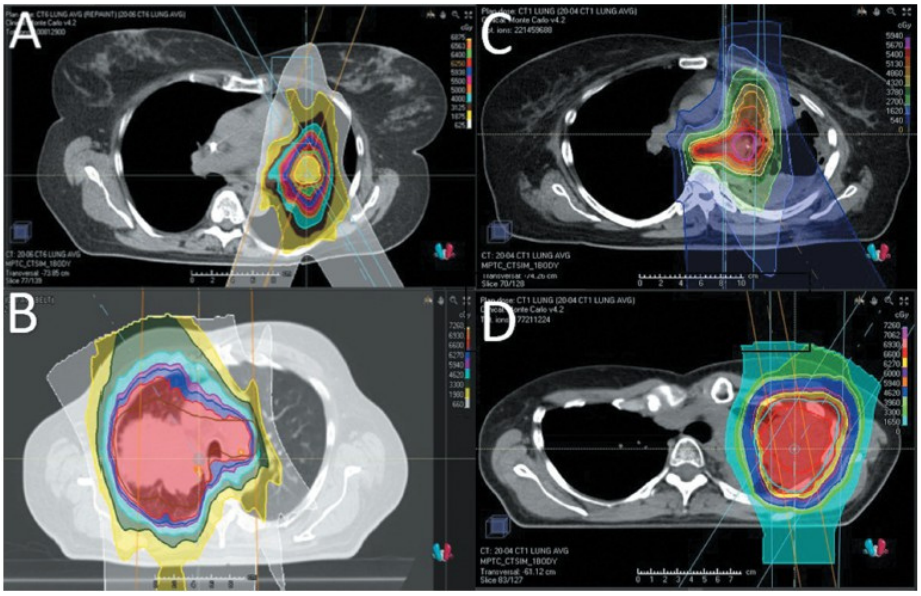

Figure 1. Examples of IMPT for lung. A) A 63 year-old female with history of extremity sarcoma was treated for a centrally-located left hilar sarcoma oligometastasis o 62.5 Gy in ten fractions with IMPT B) 80 year-old male with locally-advanced NSCLC treated definitively with IMPT to 66 Gy with concurrent chemotherapy; the target volume represents the CTV. C) 59 year-old female cT2N2M0 left hilar adenocarcinoma s/p neoadjuvant chemotherapy x6 cycles left pneumonectomy (ypT0N2) treated post-operatively with IMPT to 54 Gy; the target volume represents the CTV. D) 53 year-old female originally with cT3cN2 IIIB NSCLC, s/p chemoradiation (63 Gy), later received immunotherapy for progression complicated by pneumonitis, one year later treated for in-field recurrence with re-irradiation with IMPT to 66 Gy in BID fractionation and concurrent chemotherapy; the target volume represents the CTV.

PBT for early-stage lung cancer

Stereotactic body radiotherapy (SBRT) that utilizes higher dose of radiotherapy per fraction to a precisely defined target is an excellent alternative to surgery in patients who are medically inoperable or decline surgery, which has been demonstrated to result in more favorable toxicity profiles and improved oncologic outcomes [21–23]. Even

with using multiple arcs or beams, SBRT-based techniques are limiting when tumor diameter is greater than 5 cm or for central tumors within 2 cm of the proximal bronchial tree due to the increased risk for significant toxicity and mortality from treatment [24,25]. By taking advantage of the sharp buildup and fall-off region of PBT, sufficient tumoricidal dose may be delivered while limiting OAR toxicity as a planning objective.

Clinical outcomes data for PBT in early-stage lung cancer are limited to retrospective studies or single-arm prospective analyses. The phase II experience from Loma Linda offers some of the most mature evidence for use of high-dose and hypofractionated PBT in patients refusing surgery or considered medically inoperable with central or peripheral Stage I NSCLC [26,27]. In an analysis of 111 patients, a statistically significant 4-year overall survival (OS) benefit was detected with dose escalation at 18%, 32%, and 51% using 51 Gy, 60 Gy and 70 Gy, respectively [26]. 19.8% of patients had tumors greater than 5 cm and 33% of patients had central tumors. Treatment with dose escalation to 70 Gy was well tolerated and there were no reports of grade 2 or greater toxicity. This study has established 70 Gy in 10 fractions PBT as a safe and effective regimen even for larger and centrally located tumors.

MD Anderson Cancer Center and Massachusetts General Hospital also performed a phase I/II prospective doseescalation study including 35 patients with inoperable T1 tumors (central or superior location) or T2-T3 tumors (in any location) treated with PBT to a dose of 87.5 Gy at 2.5 Gy/fraction [28]. The majority of patients included in this study would not have met current indications for SBRT with 25 patients (71.4%) having tumors >5 cm and 8 patients (22.9%) having tumors abutting critical structures. At a median follow up of 83 months reported 5-year local control (LC) and OS were 85% and 28%, respectively. Toxicity outcomes were excellent without any grade 4 or 5 events. Only one case of grade 3 radiation pneumonitis occurred in a patient with significant COPD at baseline. The most common adverse event was dermatitis likely due to the use of passive-scatter PBT which typically generated higher entrance dose proximally. Additional toxicity events included grade 2 esophagitis (one patient), possible grade 2 cardiac toxicity (two patients), grade 2 rib fracture (one patient), and grade 2 chest wall pain (one patient). This study demonstrated that ablative doses of radiotherapy could be delivered to large or central tumors using PBT with minimal toxicity.

In a recently published meta-analysis comparing hypofractionated PBT and SBRT with photons in early-stage NSCLC, hypofractionated PBT was associated with an improvement in 5-year OS and progression-free survival (PFS) on univariate analysis [29]. However, statistical significance could not be reached on multivariate analysis after inclusion of operability. In regards to toxicity outcomes, the incidence of a severe (grade 3–5) adverse events was higher following photonbased SBRT (6.9% vs. 4.8%, $p = 0.05$) without differences in grade 4–5 toxicities. The incidence of grade 3 radiation pneumonitis was significantly increased in the SBRT group (0.9% vs 3.4%, $p < 0.001$), although the rate of grade 3 chest wall toxicity (1.9% vs 0.9%, $p = 0.03$) as well as rib fractures (13% vs. 3.2%, $p < 0.001$) were worse in the PBT cohort. While this meta-analysis failed to demonstrate a clear superiority in oncologic outcomes using PBT, the results suggest they are at least equivalent in terms of LC with reduced risk of severe complications.

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PBT for advanced-stage lung cancer

The majority of locally advanced NSCLC cases are considered inoperable at diagnosis and are treated with definitive chemoradiotherapy. The impact of RT dose-escalation was explored in the RTOG 0617 phase III trial in which patients with locally advanced NSCLC were randomized to receive 60 Gy in 30 fractions versus 74 Gy in 37 fractions. With a survival detriment seen with photon dose escalation, the trial was instrumental in evaluating the impact of radiation dose to normal tissue and provided multiple dosimetric predictors for OS, including heart V5, V30, and V50 [30]. A treatment modality, such as PBT, allowing for increased dose delivery to the tumor while meeting these dosimetric constraints may allow us to further capitalize the potential gains of locoregional control for locally advanced NSCLC therapies. Conversely, PBT could provide an alternative technique to treat the same tumor with conventional doses while reducing OAR doses to improve toxicities for patients who maybe more vulnerable to radiotherapyrelated side effects.

Several published studies, the majority of which are retrospective or single-arm prospective analyses, have examined clinical outcomes with the use of PBT in unresectable locally advanced NSCLC. Authors from MD Anderson Cancer Center published long-term outcomes in patients with stage II–III inoperable NSCLC treated with chemotherapy and PBT (using passively scattered techniques to doses of 60–74 Gy) [31]. In their cohort of 134 patients, 5-year DFS and median OS for Stage II patients were 17.3% and 40.4 months, respectively. For stage III patients, 5-year disease-free survival (DFS) and OS were 18.0% and 30.4 months, respectively. Treatment was tolerable with only one case of grade 4 esophagitis, six cases of grade 3 esophagitis, and two cases of grade 3 pneumonitis. Although data from this study were promising and suggested PBT was safe and efficacious, it is noteworthy to mention that only 57% of patients received dose-escalated radiotherapy to 74 Gy and therefore true toxicity outcomes with dose escalation may be higher than reported.

To address these concerns, the same investigators from the MD Anderson Cancer Center reported the results of their phase II study evaluating long-term outcomes in 64 patients with unresectable Stage III NSCLC treated with PBT to a dose of 74 Gy (using passively scattered beams) with concurrent chemotherapy [32]. At a median follow up of 27.3 months, the median OS, 5-year OS, and 5-year PFS were 26.5 months, 29%, and 22%, respectively. Distant failure was the most common site of failure (48% of patients) compared with local and regional failures of 16% and 14%, respectively, highlighting the need for additional or more aggressive systemic therapy regimens, perhaps with targeted molecular therapy or immunotherapy. Elective lymph node failure was often mentioned as a concern when using PBT instead of photon-based treatment due to the reduction in scatter dose to adjacent regional lymph node regions, but only 3% of patients developed an isolated regional recurrence in this study. Toxicity was favorable when compared to the 74 Gy arm of the RTOG 0617 trial, however, 4-dimensional CT and heterogeneity corrections were not mandated in RTOG 0617 and therefore, further studies should be conducted for a fair, head-to-head comparison between both the photon and proton modalities. Since then, retrospectively, additional data from several institutions have corroborated the above findings and demonstrated that PBT is a safe and effective treatment for locally advanced NSCLC cases [33–37].

In a recently published phase II Bayesian adaptive randomized trial from the MD Anderson Cancer Center and Massachusetts General Hospital patients with inoperable locally advanced NSCLC were randomized to receive IMRT or passive scattering PBT to a dose ranging from 60 to 74 Gy in 2-Gy fractions, with primary endpoints being grade 3+ radiation pneumonitis rate and local failure [38]. While PBT resulted in an improvement in low-dose lung dosimetric endpoints and heart dose, there was no benefit in either grade 3+ pneumonitis rates (10.5% PBT and 6.5% IMRT) or local failure (about 11% for both groups). Both, rate of grade 3+ pneumonitis and local failure were lower than expected in this study, which may have impacted the statistical power. This trial was important, however, in demonstrating the presence of a steep learning curve for PBT, with 31% of patients in the proton arm meeting the primary endpoint (i.e., had a grade 3+ pneumonitis or experienced local failure) prior to the midpoint of the study, compared to 13% after the midpoint- underscoring the potential importance of experience when utilizing this advanced treatment technique. The authors also re-planned six patients who developed radiation pneumonitis in the initial cohort and were able to generate better proton plans, using the experience gained through the study. The high-dose lung volumes were larger with passive scatter PBT in the above study, potentially explaining the high pneumonitis rates. Use of pencil-beam scanning with modern motion management and image-guided radiotherapy (IGRT) that is available at newer proton centers may be able to reduce these margins and otherwise achieve better conformality. Interestingly, prior to randomization, 44 patients were excluded since the plans did not allow randomization (IMRT better in 26 and PBT better in 13). It is unclear if this proportion would be different when using modern IMPT. Finally, even though 181 pts were randomized, due to Bayesian design and detrimental impact of higher pneumonitis rates in the first half of the study, the final randomization was in favor of IMRT (105 vs 76 pts) which may have impacted statistical power. Even further, only 57 of 76 pts randomized to PBT were actually treated with PBT due to insurance denial and other reasons.

As an alternate approach for biological dose-escalation, the Proton Collaborative Group (PCG) completed a phase I/II trial investigating the safety and efficacy of delivering hypofractionated PBT with concurrent chemotherapy in patients with locally advanced NSCLC. In the recently reported phase I portion of the trial, the total prescription dose remained at 60 Gy but the maximum tolerated dose per fraction was established by starting at 2.5 Gy per fraction and escalating to 4 Gy [39]. The trial was closed early due to poor accrual but increased dose per fraction up to 3.53 Gy RBE seemed to be safe.

Post-operative radiotherapy (PORT) with PBT

The role of post-operative radiotherapy in NSCLC continues to be an area of controversy in locally advanced NSCLC. The risks and toxicity from adjuvant treatment must be weighed against the potential benefits in oncologic outcomes. Several retrospective reviews have demonstrated local control benefits at the potential expense of increased mortality/morbidities, with a survival benefit seen in select subgroups such as patients with pN2 disease or positive margins [40–42]. A recent analysis of the LungART study which demonstrated no DFS or OS benefit with PORT noted a significant increase in grade 3–5 cardiopulmonary toxicity (20% vs 7.7%) with PORT [43]. Clearly, any further investigation of PORT will require use of more advanced modalities.

Clinical outcomes data evaluating the use of PBT in the post-operative setting remain scarce overall. The largest study published to date, from the University of Pennsylvania, retrospectively analyzed 61 patients with pN2 disease and/or positive margins treated with PBT (27 patients) or IMRT (34 patients) [44]. Patients in the IMRT arm were treated to a median dose of 54 Gy, and patients treated with PBT received a median dose of 50.4 Gy. This study predominantly included patients treated with double-scatter PBT (n = 22) rather than IMPT (n = 5). One-year OS (85.2% vs. 82.4%) and local recurrence-free survival (92.3% vs. 93.3%) were not statistically significantly different. Grade 3 radiation esophagitis developed in one patient in the PBT arm and four patients in the IMRT arm. Grade 3 radiation pneumonitis was observed in one patient in each arm despite a significant reduction in the V5Gy volume and mean lung dose with PBT, including for that case. Notably, in their analysis, dose to the heart (V30, V45, and Max) was not improved with the use of PBT. Mean heart dose differences were not reported.

Re-irradiating the thorax with PBT

Locoregional recurrence happens in 30–40% of patients with locally advanced NSCLC. Treatment options are often limited compared to the upfront setting due to the increased risks and toxicities associated with treating the thorax again with radiotherapy. Re-irradiation is likely the single most important clinical indication for PBT in lung cancers. The appealing dosimetric properties of PBT can be exploited in this setting to allow for aggressive treatment in patients previously considered too high risk for reirradiation [45].

Multiple retrospective series evaluating PBT in the reirradiation setting have reported median OS of 11–18 months and 1 year OS between 47% and 59% with a limited number of grade 3+ toxicities [46–50]. McAvoy et al. published the results of their single-institutional retrospective analysis of 102 patients receiving reirradiation to a median dose of 60.5 EQD2 Gy in a median of 30 fractions. Overall, definitive intent reirradiation was well tolerated with 97% of patients completing the prescribed course, and limited number of patients developed grade 3+ toxicity. Oncologic outcomes were poor overall due to cancer recurrence, but without significant differences in survival or toxicity between IMRT or PBT. Further data on the actual proportion of patients treated with IMRT vs PBT or differences in patient characteristics by re-irradiation technique were not reported.

More recently, using PBT, a multi-institutional prospective study including 57 patients treated to a median reirradiation dose of 66.6 Gy (RBE) revealed locoregional failure and distant metastasis in 25% and 11%, respectively, and 1-year OS of 58%. Despite 93% of patients completing the reirradiation treatment, 39% of patients developed acute grade 3 or higher toxicity, and 12% developed grade 3 or higher late toxicity. Most notably, grade 5 toxicity was observed in six patients, however, the majority of patients were treated with passive scattering beams (90%) in the study. The authors also noted a significant correlation between grade 3 or higher toxicities and central region overlap along with mean heart dose, mean esophageal dose, and use of concurrent chemotherapy.

Authors from the MD Anderson Cancer Center then reported their outcomes with reirradiation for thoracic malignancies using IMPT [50]. Twenty-seven patients (majority being NSCLC) received IMPT to a median dose of

66 Gy RBE by EQD2. Median OS was 18 months, and 1-year OS was 54% with improved LC using doses ≥66 Gy by EQD2. In their series, reirradiation was overall well tolerated, with only 7% experiencing late grade 3 pulmonary toxicities and no reports of grade 3+ esophagitis or grade 4–5 toxicities of any kind. This study was the first and only report of IMPT for reirradiation in thoracic malignancies and demonstrated excellent local control could be achieved with minimal toxicities.

The largest series to date evaluating outcomes for recurrent NSCLC treated with PBT was recently reported from a multiinstitutional prospective registry [51]. Of the 79 patients included, 68% were treated with conventionally fractionated radiotherapy (median 60.2 Gy by EQD2 in 2 Gy fractions) and 32% were treated with hypofractionated/stereotactic body radiation therapy (median 83.3 Gy by EQD2). At a median follow-up of 10.7 months, median OS and PFS were 15.2 months and 10.5 months, respectively. Acute grade 3 toxicity developed in 6% of patients and late grade 3 toxicity developed in 1% of patients with three patients dying after PBT possibly due to treatment-related toxicity.

Esophageal cancer

Introduction

Concurrent chemoradiation is a standard of care for esophageal cancer both neoadjuvantly prior to definitive surgery and definitively for medically inoperable or unresectable patients though associated with significant acute and late morbidity including post-operative complications and cardiopulmonary toxicities [52]. IMRT has demonstrated reduction in cardiopulmonary toxicity risk and mortality when directly compared to three-dimensional conformal RT [53,54]. Although IMRT is the current standard of care, there is significant interest in PBT to reduce dose to surrounding organs-at-risk thereby theoretically further improving outcomes.

Summary of dosimetric data Multiple studies have evaluated the dosimetry of PBT and established the advantages over IMRT [55–57]. Passive-scatter PBT (PS-PBT) improves the V5-30 Gy of lung, V5-40 Gy of the heart, and mean doses to the heart, lungs, and liver [55–57]. In a single institutional experience, the mean heart dose was improved with PS-PBT (11.6 Gy vs. 19.9 Gy) and the heart V30Gy was improved with PS-PBT (18.9% vs. 24.4%) when compared to IMRT [55]. Additionally, active-scanning PBT has demonstrated improved dosimetric outcomes when compared to IMRT in terms of dose to the heart as well as dose to the substructures of the heart when utilizing a 3-field approach. Figure 2 shows example proton treatment plans for three patients with esophageal cancer receiving either preoperative radiotherapy or reirradiation using IMPT.

ClinicaleEvidence for PBT as treatment for pre-op and definitive esophageal cancer

Numerous studies have suggested that the dosimetric advantages of PBT translate into improved toxicity profiles and clinical outcomes when compared to photon-based RT [55,58–61]. The University of Texas MD Anderson Cancer Center demonstrated that PBT was associated with significantly reduced cardiac, pulmonary, postoperative, and wound complications when compared to photon-based RT [58]. PBT, when compared to IMRT, was associated with reduced post-operative hospitalization length of stay (8 vs. 10 days) as well as

diminished 90-day post-operative mortality rate (0.9% vs. 3.9%) [58]. In another study of a 211 patient cohort treated with either PBT or IMRT, PBT was associated with decreased mean RT dose to the heart and lungs and ultimately improved OS [55]. Surprisingly, on multivariate analysis, PBT also was associated with improved disease control in terms of local recurrence-free survival and PFS. Additionally, PBT has been correlated with decreased risk of clinically severe lymphopenia during chemoradiation. After adjusting for clinical factors that predict for grade 4 lymphopenia in a cohort of over 500 patients, PBT was associated with a reduced risk of severe lymphopenia when compared to IMRT; grade 4 lymphopenia is also a strong prognostic indicator for overall survival and disease-free survival [59]. These findings suggest a potential role for therapies that preserve host immunity to impact long-term disease control.

Lastly, early phase prospective data also support the use of PBT for esophageal cancer [61]. In a randomized phase IIB trial for locally advanced esophageal cancer, 145 patients were randomized to either PBT or IMRT (50.4 Gy in 28 daily fractions) and with approximately half of evaluable patients undergoing surgical resection [61]. Notably, 80% of the PBT cohort received treatment via a passive-scatter technique. Although the 3 year PFS and OS were similar, the total toxicity burden and postoperative complication rates were improved with PBT [61]. This is the first randomized trial that suggests that PBT is safer than IMRT for esophageal cancer. Importantly, as surgical technique was at the discretion of the surgeon, the improvement in postoperative complication rates can be applied broadly amongst a variety of surgical practices. Additionally, as this trial was completed at a high-volume academic surgical center, the differences in postoperative complication rates and therefore the benefit of PBT may be greater in the community setting. Ultimately, there is no clinical evidence that PBT improves toxicity profile when directly compared to IMRT in both the definitive and neo-adjuvant setting.

Reirradiation for esophageal cancer

Re-irradiation is being increasingly considered in locally recurrent esophageal cancer. In a retrospective study of 87 recurrent esophageal cancer patients, reirradiation was associated with improved OS despite a higher rate of treatment-related toxicities including tracheoesophageal fistulas, pericardial/pleural effusion, and pneumonitis [62]. PBT is an attractive modality for reirradiation of recurrent esophageal cancer. Although limited by small subject number and short-term follow-up, a single-institutional experience of 17 patients who underwent reirradiation with pencil-beam scanning PBT for recurrent esophageal cancer demonstrated an encouraging rate of LC (75% at 1 year) and OS with an approximate 28% risk of grade ≥ 3 toxicity and 17% risk of grade ≥ 4 toxicity [63]. A prospective study of 14 patients with recurrent esophageal cancer treated with PBT reirradiation (median 54 Gy RBE) also demonstrated encouraging outcomes and toxicity profile (29% grade 3 toxicity risk) [64]. The single grade 5 toxicity was an esophagopleural fistula most likely attributable to disease progression rather than RT [64]. While high-level randomized data are unlikely in this population due to limited patient numbers and inherent heterogeneities in prior treatments for patients undergoing re-irradiation; the limited data do support that outcomes are likely at least equivalent to IMRT.

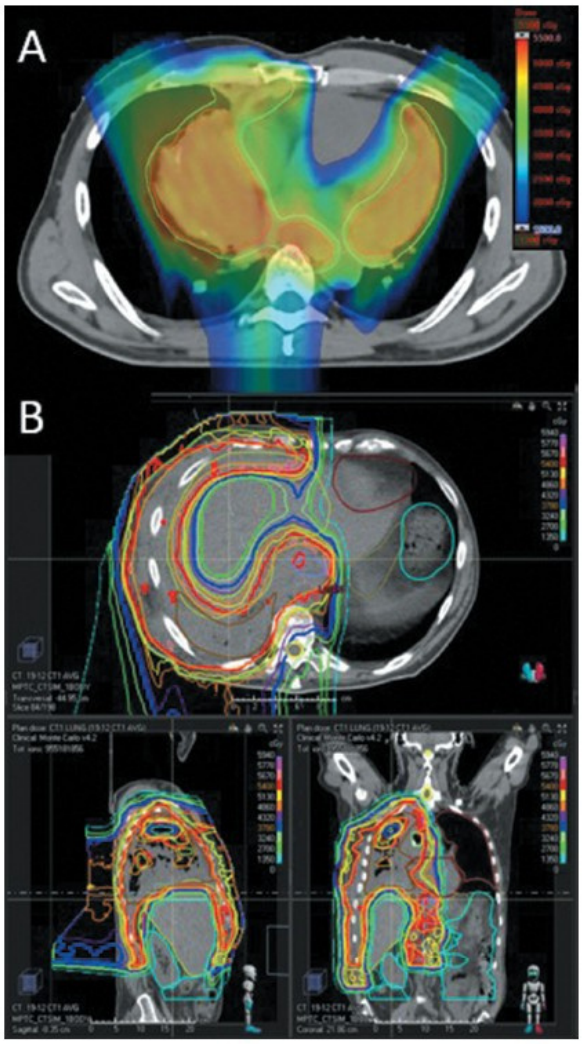

Figure 2. (A) An axial comparison of IMPT (left) vs. IMRT (right) dose distribution for a 74 year old with Siewert II classification Stage IB adenocarcinoma of the esophagus who received 50.4 Gy in 28 fractions preoperatively with concurrent carboplatin and paclitaxel. The gross tumor volume (bright red), optimization target volume (cyan) and planning target volume (magenta) are identified above. (B) An 82 year old male with a distal esophageal adenocarcinoma receiving definitive IMPT reirradiation with 50

Gy in 25 fractions for an unresectable recurrence. Target volumes include gross tumor volume (smallest), clinical target volume (intermediate), and optimization target volume (largest). (C) A 56 year old male with a Stage IIIA adenocarcinoma of the thoracic esophagus who received preoperative IMPT with 50 Gy in 25 fractions. Target volumes include gross tumor volume (red) and optimization target volume (cyan).

Mesothelioma

Introduction

Malignant Pleural Mesothelioma (MPM) is a relatively rare but highly aggressive malignancy. Despite advances in surgical techniques, systemic therapy, and radiotherapy, MPM remains a difficult malignancy to treat and portends a poor prognosis with median OS of only one year [65]. Treatment of MPM often requires a multi-modality approach, with the majority of patients being medically inoperable or unresectable at diagnosis [66,67].

Due to the high rates of recurrence after surgery alone, adjuvant treatment with chemotherapy is recommended [68,69]. The role of definitive or adjuvant radiation, however, has been significantly limited by the risks associated with treating a large radiation field encompassing the entire hemi-thorax with radiotherapy was historically reserved solely for palliative purposes. Improvements in delivery techniques have expanded indications for use, with more recent evidence supporting treatment after both types of surgical techniques namely extrapleural pneumonectomy (EPP) as well as extended pleurectomy and decortication (EP/D) [70–75]. PBT has the potential to further expand radiation use.

Summary of dosimetric data

Multiple studies in MPM patients have established the dosimetric benefits of utilizing PBT over IMRT. In one dosimetric analysis from Switzerland, eight patients treated with IMRT after EPP were replanned for passive-scatter PBT [76]. When utilizing PBT, dose coverage (V95) and dose homogeneity improved for the planning target volume. Doses to the contralateral kidney, ipsilateral kidney, contralateral lung, liver, heart, and spinal cord were also significantly reduced with PBT. A similar analysis from Italy confirmed similar dosimetric advantages in seven patients initially treated with adjuvant IMRT after EPP and re-planned using active-scanning PBS [77]. In this study, normal tissue complication probabilities were modeled and a significant reduction in risk of liver complications, kidney injury, and acute esophagitis were identified with PBS as compared to IMRT. Figure 3 shows the treatment plans for two patients with mesothelioma treated in the adjuvant setting using IMPT.

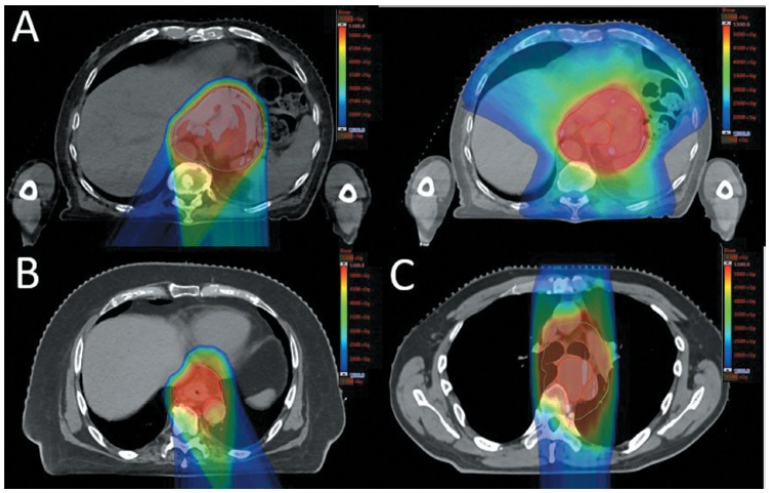

Figure 3. (A) A 54 year old male with mesothelioma of the pericardium s/p R2 resection who received 46 Gy in 23 fractions with intensity-modulated proton therapy. Gross tumor volume (red) and optimization target volume (light green) are identified above. (B) 68 year-old male with pT4N2 malignant pleural mesothelioma s/p EPD treated with adjuvant right hemi-thoracic IMPT to 50.4 Gy to the entire right-sided pleura with sequential boost to a total 54 Gy to gross disease; the target volumes represents the respective CTV's. Note the proximity of numerous intrathoracic and intra-abdominal OARs, a unique challenge of hemithoracic RT.

Clinical evidence for PBT as treatment for mesothelioma

Despite compelling dosimetric rationale for PBT in MPM, there is a paucity of clinical outcome data. The first published series came from the MD Anderson Cancer Center with their experience for using IMPT in lung-intact mesothelioma patients [78]. Of the seven patients included, six underwent P/D and one underwent biopsy alone;

four of them received IMPT, and the other three patients received IMRT. Similar to other studies, IMPT improved mean dose to the contralateral lung, heart, esophagus, liver, and ipsilateral kidney on dosimetric analysis. All patients receiving treatment with IMPT were able to complete the course without breaks, although clinical outcome was not reported for this study.

The largest series to date assessing PBT for MPM was presented by investigators from the University of Pennsylvania. Radiation therapy was delivered as adjuvant therapy following lung sparing radical pleurectomy (eight patients), progression on systemic therapy (eight patients), or as an upfront definitive treatment (one patient). Median dose was 51.75 GyE with a median of 2-GyE daily fractions. Median OS had not yet been reached and there were no reports of grade 3+ toxicity [79].

Investigators from the University of Pennsylvania also conducted a prospective study with PBT and photodynamic therapy including 10 patients with Stage III to IV nonmetastatic MPM [80]. PBT was delivered adjuvantly (eight patients) or as salvage (two patients) following P/D to a median dose 55 GyE in 1.8–2.0 GyE daily fractions. Two-year LC was excellent at 90%, with distant and regional failure rates being 50% and 30%, respectively. Median survival was 19.5 months since completion of RT, and 1- and 2-year survival rates were 58% and 29%, respectively. Most notably, there were no grade 2+ acute or late toxicities.

A smaller series from the University of Washington reported on outcomes after EPP for three patients treated with IMPT to a dose of 54–66 Gy (RBE) [81]. No radiation pneumonitis was seen with the only toxicity observed was grade 2 nausea and dermatitis. Investigators noted that OAR dose profiles were significantly better than the photon-based VMAT and IMRT plans, particularly in regard to contralateral lung and heart dose.

Thymic malignancies

Introduction

Thymic malignancies are the most common primary malignancy in the anterior mediastinum [82]. Although primarily a surgically managed disease, RT plays a significant role in both the postoperative setting for advanced stages especially with positive margins and/or thymic carcinoma histology and for inoperable patients [83].

RT for thymic malignancies is particularly challenging due to large treatment fields and the close proximity to vital structures including the heart, lungs, esophagus, and breast tissue. Treatment-related toxicity is particularly given relatively young median age at diagnosis with good long-term disease control. PBT may especially play an important role in reducing cardiac and lung dosing which is a major limitation when offering radiotherapy for thymic tumors [84]. As a result, there is significant interest in PBT for thymic malignancies.

Summary of dosimetric data

A dosimetric study of 10 thymoma patients comparing 3Dconformal RT (3DCRT), VMAT, TomoTherapy, PBT, and

carbon ion RT demonstrated that target coverage was superior with PBT when compared to VMAT or 3DCRT [85]. Additionally, charged particle therapy reduces mean dose to the heart, lung, breast, and esophagus when directly compared to photon therapies suggesting a theoretical reduction of longterm toxicities and secondary malignancy risk [85,86]. Figure 4 shows an example proton treatment plan of a patient with a thymoma treated in the adjuvant setting using IMPT.

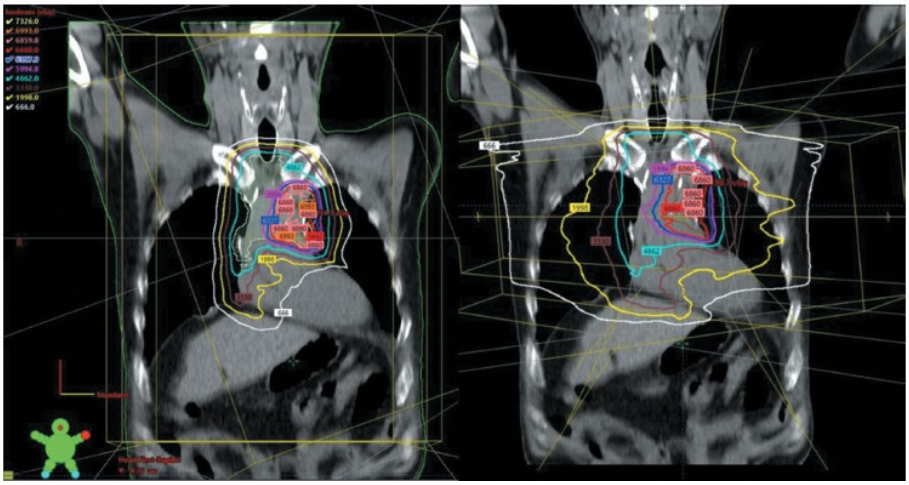

Figure 4. Comparison of IMPT (left) and VMAT (right) techniques for adjuvant RT for high-risk thymoma. A 55 year-old male with Stage III A pT3N0 Masaoka IVA Type B1 thymoma s/p R2 resection (residual disease on left phrenic nerve), also with noted invasion of the lungs, phrenic nerves, pericardium, and myocardium, treated with adjuvant IMPT to 50.4 Gy to the post-operative bed with a sequential boost to a total 66.6 Gy to the high-risk post-operative bed; the target volumes represents the respective CTV's.

Clinical data for PBT as treatment for thymic malignancies

Institutional experiences have demonstrated the safety and efficacy of both adjuvant and definitive PBT for thymic carcinoma and thymoma [87–90]. The PCG experience of 30 patients with thymic malignancies treated with PBT (22 thymoma and 8 thymic carcinoma) demonstrated no grade ≥ 3 toxicities without jeopardizing disease control rates [87]. Additionally, the first prospective cohort of double-scattering PBT for twenty-seven patients with thymic malignancies demonstrated a 100% 2 year local control rate with no grade ≥ 3 toxicities [90]. We await long-term data from this study, especially pertaining to cardiopulmonary toxicities.

Mediastinal lymphomas

Introduction

The overall use of RT for lymphomas, including those involving the mediastinum, has undergone 'de-escalation' over-time, with reduction in treatment volumes and in total delivered dose. This has been primarily driven by late radiation toxicity data of Hodgkin's lymphoma (HL) survivors treated with older techniques. These late toxicities include, among others, cardiac disease, decreased pulmonary function, and secondary malignancy [91,92]. Secondary malignancies represent the leading cause of death in long-term survivors of HL and include breast, lung, and other primary cancers [91,93]. PBT offers the opportunity to mitigate these long-term toxicities – representing a natural next phase in the historical sequence of RT de-escalation.

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Summary of dosimetric data

Dosimetric data comparing proton and photon-based techniques are limited by the multiple variations of both techniques (passive scatter vs intensity-modulated proton techniques, use of deep inspiratory breath hold (DIBH), use of incline board or butterfly IMRT/VMAT techniques). Dosimetric data in the modern era have shown increased OAR sparing with the use of PBT over IMRT and 3D-CRT- namely, of the heart, lungs, and breasts especially with targets extending below the takeoff of the left main steam coronary artery (LMSCA) and on both sides of the heart. This benefit likely derives from decrease in low-intermediate dose, as photon-based techniques are able to effectively spare high dose to OARs. Effective cardiac sparing for a target above the takeoff of the LMSCA can also be achieved with VMAT when using DIBH, breath-hold, and inclined board techniques [94,95]. Expectedly, modern IMPT techniques can also further optimize the dosimetric benefits when using breath-hold approach [96]. Further, the dose to coronaries, is highly dependent on the target configuration with an overall decrease in mean dose with PBT, though at the cost of possible end-range effects on the coronary vessels [94]. Guidelines provide important factors to consider when considering different techniques [97].

An overall reduction in mean breast dose is seen with PBT with volumes receiving low dose are lower though those receiving high dose are higher. This is in contrast to VMAT which can limit higher doses at the expense of more low-dose spread [98]. Reduction of low dose with PBT may be most pronounced with an axillary component of the target-a situation historically precluding consolidative RT- as well as with bulky disease [94,97]. While posteriorly oriented proton beam configurations or butterfly technique maximize sparing of breast tissue these come at the expense of increased cardiac dose, both for photon and proton-based techniques [95].

Lastly, reduction in lung mean dose and V20 is often achievable with PBT, especially using DIBH, and is an important consideration in patients receiving pulmonary-toxic chemotherapy. Comparative studies predict significant decrease in second malignancies with the use of modern IMPT as compared to VMAT [99].

Clinical data for PBT as treatment for of mediastinal lymphomas

Clinical outcomes using PBT are limited by relatively short follow-up, but nevertheless are comparable to historical photon data [100]. Patterns of care studies have demonstrated that mediastinum/hilum, either alone (27%) or with nodal head-neck region (28%) were the most common anatomical sites treated with PBT [101]. Additionally, there has been no evidence to suggest marginal failures due to PBT conformality [102]. Recent reports are exploring IMPT with breath-hold techniques [103]. Further maturation of data will quantify long-term cardiac and secondary malignancy toxicity.

Due to need for higher dose of radiation, there is interest regarding the use of PBT in patients with relapsed/refractory (R/R) lymphoma receiving definitive radiotherapy. Concern for toxicity, especially pneumonitis in the peri-transplant setting, use of prior cardiotoxic and pulmonary toxic drugs in extensively treated patients and marrow toxicity has limited use of radiotherapy, despite known effectiveness. The PCG reported an

experience of 51 R/R lymphoma patients with mediastinal disease who received PBT. In a heavily pre-treated population with a median follow-up of 21.2 months, grade 2 pneumonitis was reported in 12% of patients. No grade 3 or higher late toxicity was noted. Two-year OS and PFS were 87% and 69%, respectively [104].

Conclusion

Radiotherapy is an integral component in the treatment of the majority of thoracic malignancies. By taking advantage of the steep dose fall-off characteristic of protons, PBT has emerged as a tool to potentially improve oncologic outcomes while reducing toxicities from treatment. Despite clear dosimetric benefit with PBT in many scenarios, randomized data comparing clinical outcomes between proton and photon radiation are limited to a small number of studies in lung and esophageal cancer with most evidence is based upon retrospective analyses or single-arm prospective trials. More recent trials have also incorporated newer PBT techniques, which may allow for more dramatic improvements in tumor control and toxicities. As additional proton centers develop and the clinical data matures, the role of PBT in thoracic malignancies will be better understood but it will be important to clarify which subsets of patients receive the most benefit to optimize the cost-benefit ratio.

Expert opinion and future directions

Lung

Treatment of NSCLC remains challenging due to the close proximity of multiple critically vital organs that limit the ability to provide optimal doses of radiation. The physical and dosimetric advantages of PBT offer the benefit of allowing for hypofractionation and dose-escalation in early-stage, locally advanced and re-irradiation cases. PBT also has the potential to limit the detrimental impact of post-operative radiotherapy especially in pneumonectomy patients or those in whom standard radiation would deliver high cardiac dose. Nonetheless, the appeal of PBT with its high level of precision may have a counterproductive effect due to uncertainties in dose delivery due to IGRT limitations, robustness issues, and interplay effect that are more profound in thoracic RT than other locations. Advancements in treatment planning and delivery techniques with IMPT may allow overcoming these limitations thereby allowing translation of dosimetric benefits to clinical improvements.

In early-stage disease, available data suggest that PBT is a safe and effective treatment modality for early-stage lung cancer, especially with larger (>5 cm) or central tumors where photon-SBRT has limitations. For smaller peripheral tumors, photon-SBRT continues to be a preferred modality. Investigators from the University of Florida are conducting a single-arm trial evaluating hypofractionated image guided PBT to a dose of 48 Gy in 4 fractions for peripheral lesions and 60 Gy in 10 fractions for central lesions (LU03; ClinicalTrials.gov identifier: NCT00875901).

In advanced NSCLC, use of PBT has demonstrated feasibility for safe dose-escalation with no increase in marginal nodal failures. Survival and toxicity outcomes seem to be unchanged with passive scattered PBT. Whether differences will be seen with modern IMPT technology remains to be seen from analysis of ongoing clinical trials. The RTOG 1308 trial [ClinicalTrials.gov Identifier: NCT01993810] is a phase III multiinstitutional randomized trial

comparing OS in patients with locally advanced NSCLC using proton versus photon radiotherapies to a dose of 70 Gy in 35 fractions given concurrently with chemotherapy. The ongoing German PRONTOX trial (ClinicalTrials.gov Identifier: NCT02731001) is a single-center phase II trial also randomizing patients with locally advanced NSCLC to photon versus proton radiotherapies with concurrent chemotherapy. Patients are treated to a total dose of 66 Gy using an accelerated regimen of 6 fractions per week (2 Gy per fraction). Investigators from the Mayo Clinic are also currently conducting a phase II trial (ClinicalTrials.gov Identifier: NCT03132532) and comparing PFS in patients with unresectable locally advanced NSCLC treated with chemotherapy and PBT to two-dose levels (60 Gy in 30 fractions versus 70 Gy in 35 fractions).

The authors believe that clinical benefit is most likely in patients with multi-station nodal disease, contralateral mediastinal/ hilar disease and large treatment volumes where IMPT can allow delivery of therapeutic doses while meeting normal tissue constraints. Hypofractionation may also be safer with IMPT which may be a preferred strategy to derive the biological benefit against accelerated repopulation while also creating possibility of immunological benefit of larger dose per fraction that could potentiate immunotherapy. Reduced excess irradiation of regional uninvolved nodal tissue and circulating blood volume around the target region with PBT could translate into lower risk of cytopenia, further allowing a robust immune response.

Although initial clinical data for use of PBT in the postoperative setting show treatment is well-tolerated with similar survival rates compared to conventional IMRT, longer followup data will reveal if PBT provides a benefit over photon therapy. In the authors' experience and based on dosimetric comparisons, PBT is most likely to be of benefit in patients who undergo pneumonectomy or in lower lobe lesions where IMRT can deliver considerably excess dose to cardiac structures. Use of PORT itself, however, will now be called into question with the presentation of results from the LungART study [43].

Esophagus

The role of PBT in the management of primary and recurrent esophageal cancer is promising with data demonstrating significant reduction in toxicity with PBT. We anticipate results from NRG-GI006 (ClinicalTrials.gov Identifier: NCT03801876), a phase III randomized trial of PBT vs. IMRT for the treatment of esophageal cancer that may provide level I evidence that PBT benefits patients with esophageal cancer in terms of overall survival, treatment-related toxicities, and quality of life.

Mesothelioma

The delivery of definitive or adjuvant radiation therapy after lung-sparing surgery in MPM is particularly challenging due to the significant risks of toxic events and the large, complexshaped target volumes. PBT, and in particular PBS, provides a dosimetrically superior technique to better spare surrounding OARs, especially contralateral lung, heart, and abdominal viscera. While, initial reports appear to show the relative safety of using

PBT in the adjuvant and definitive settings, the use of PBT in MPM is still investigational. Additional studies are necessary to determine the benefit of utilizing this advanced modality in the treatment of MPM especially as immunotherapy becomes standard of care for these patients [105]. Even with IMPT, dose to ipsilateral lung is a key issue with possible risk of serious acute radiation pneumonitis. This is especially relevant with increasing use of immunotherapy in the management of mesothelioma, which increases concern for risk of additive pneumonitis. The advancements in technology and treatment delivery with PBT may thereby expand the role of radiotherapy in this challenging and aggressive disease. Given the rarity of this disease, this may be best performed in the context of a national or global clinical outcome registry for newly dragonized mesothelioma patients. The ongoing NRG-LU006 trial (ClinicalTrials.gov Identifier: NCT04158141) is a phase III randomized trial evaluating OS in patients treated with P/D and chemotherapy with or without adjuvant hemithoracic radiotherapy delivered using either IMRT or IMPT.

Thymic malignancies

Utilization of PBT may improve the therapeutic ratio in thymic malignancies by reducing cardiopulmonary toxicities particularly for young thymoma patients with a favorable prognosis. The lower integral dose to critical structures also has the potential to translate into lower risk of second malignancies. Given the rarity of thymoma and thymic carcinoma, we encourage continued retrospective and prospective studies of PBT through multi-institutional groups.

Mediastinal lymphoma

PBT is an important modality in the treatment of mediastinal lymphoma, with marked dosimetric benefit in patients with complicated target geometries adjacent to/overlapping the heart, bulky disease, and axillary involvement. Benefits will likely be maximized with the use of breath-hold IMPT, though even free-breathing IMPT can provide benefits comparable to breath-hold VMAT. Early clinical data indicate no compromise in disease control with the use of PBT. Though late toxicity data are short in follow-up, the aforementioned indicate it is safe to use, effective, and estimated to reduce potentially lifelimiting long-term toxicities. Expected benefits will likely be higher in patients with R/R mediastinal lymphoma who are at a higher risk of cardiopulmonary and marrow toxicity due to extensive history of systemic therapy including stem cell transplant.

Re-irradiation

Concern for radioresistance and normal tissue toxicity has conventionally limited use of re-irradiation. However, advent of modern technology which provides dosimetric superiority has allowed increased use of re-irradiation, both with photon and proton-techniques. In this setting, altered dose fractionation may provide additional benefit to allow radiobiological benefits both against resistant tumor clones and organs-atrisk. When dosimetry allows, photon-based IMRT/VMAT/SBRT techniques might allow safe re-irradiation especially with longer time gap from prior treatment. For other cases, PBT may offer superior dosimetric benefit with the additional benefit of delivering a higher RBE that may overcome radioresistance and translate to improved tumor control. Data from multiple

institutions have demonstrated safety in the setting of lung and esophageal cancers with ability to deliver definitive doses of PBT resulting in encouraging local control. Despite the potential dosimetric advantages of PBT, toxicity is not completely negligible, especially when combined with systemic therapy. Hence, proper patient selection is of paramount importance. With the development and incorporation of newer techniques such as IMPT, better IGRT and robustness evaluation techniques, and also a more thorough understanding of the radiobiology of thoracic structures, aggressive treatment of locoregional recurrences may become more feasible and is an important area for future research and clinical studies. Due to significant patient heterogeneity related to target volume, time from previous irradiation, and history of prior systemic therapy, a randomized trial comparing PBT with photon-based approaches is unlikely to be feasible. As such, data derived from institutional experiences will help shape the clinical indication and dosimetric guidelines for PBT-reirradiation.

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