Review Article

Proton therapy for early-stage non-small cell lung cancer (NSCLC)

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: In the setting of early-stage non-small cell lung cancer (NSCLC), defining the optimal clinical context for proton beam therapy (PBT) is challenging due to the increasing evidence demonstrating high rates of local control and good tolerance of stereotactic ablative body radiation (SABR). Given the relatively small percentage of lung and other critical structures treated with SABR, dosimetric studies comparing the two techniques have typically concluded that there are modest advantages to PBT, typically by reducing the low dose volumes, such as volume of lung receiving 5 Gy. This advantage may be more significant in treating larger tumors, multiple tumors, or central tumors. Most of the published studies are based on passive scattering PBT. Dosimetric benefits are likely to increase when pencil beam scanning/intensity-modulated proton therapy (IMPT) is employed, as has been observed in dosimetric reports in the locally advanced setting. More clinical data is needed regarding the safety and efficacy of stereotactic PBT in comparison to SABR. However, the only randomized trial that has been attempted closed early due to poor accrual, thus demonstrating the difficulty in designing trials in this context that incorporate a relevant and focused scientific question that can be extrapolated to clinical practice, yet also accrue sufficiently. The advent and increased use of advanced image-guided radiation therapy (IGRT) techniques in the context of proton therapy, as well as the widespread implementation of IMPT, will increase the potential benefit of PBT. The next 5–10 years will likely yield more appropriate, feasible studies that will help answer the question of patient selection for this advanced technology.

Keywords: Proton therapy; early stage; non-small cell lung cancer (NSCLC)

Submitted Mar 22, 2018. Accepted for publication Apr 09, 2018.
doi: 10.21037/tlcr.2018.04.12
View this article at: http://dx.doi.org/10.21037/tlcr.2018.04.12

Introduction

The role of proton beam therapy (PBT) is being studied in multiple malignancies and clinical scenarios. In the setting of early-stage non-small cell lung cancer (NSCLC), defining the optimal clinical context for PBT is more challenging, particularly with increasing evidence demonstrating high rates of local control and good tolerance of stereotactic ablative body radiation (SABR) (1,2). As a result, it is likely that stereotactic body proton therapy (SBPT) will ultimately be limited to early-stage disease that presents distinct difficulties with SABR, such as central location or in the setting of reirradiation. In this review, we will discuss the present data for PBT in the setting of early-stage NSCLC, and will provide general recommendations for patient selection. We will also provide an overview of our SBPT technique. Overall, we hope to demonstrate that there is indeed rationale for the use of PBT in select cases of early-stage NSCLC, but that this paradigm will continue to be defined over the next 5–10 years.

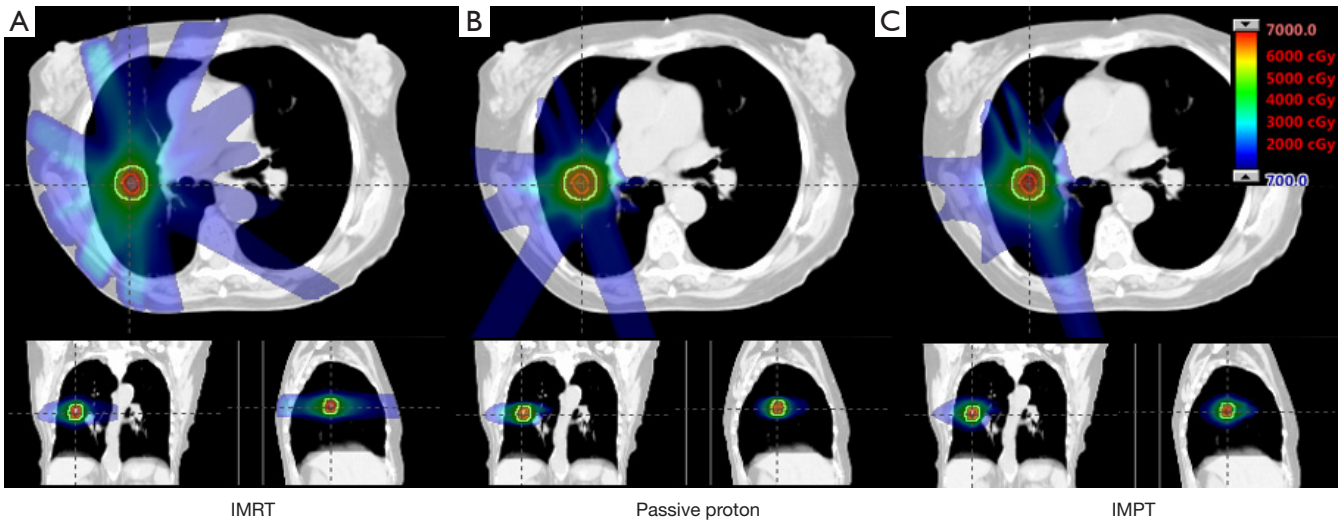

Figure 1 Differences in dose distributions between IMRT (A), passive scattering proton plans (B), and IMPT (C). All three plans are conformal and are effective in sparing normal structures, with the IMPT plan demonstrating a modest improvement over the other two. IMRT, intensity-modulated radiotherapy; IMPT, intensity-modulated proton therapy

Dosimetric rationale for PBT in early-stage disease

Several studies have assessed the dosimetric differences between PBT and SABR in early stage lung cancer. Given the relatively small percentage of lung and other critical structures treated with SABR, studies comparing the two techniques have typically concluded that there are modest advantages to PBT. For example, investigators from Japan assessed 21 patients with stage I NSCLC treated with stereotactic body radiotherapy (SBRT) or PBT, with the primary goal to compare dose-volume histogram (DVH) parameters between the two techniques. Pertinent lung doses for V5, V10, and V20 were 13.2%, 11.4%, and 10.1% for PBT, and 32.0%, 21.8%, and 11.4% for SBRT. The authors concluded that PBT "may be more advantageous" than SBRT for early-stage disease in large or several tumors (3). In an analysis by investigators at MD Anderson Cancer Center, the authors found that V5, V10, and V20 were 31.8%, 24.6%, and 15.8% for SBRT, and 13.4%, 12.3%, and 10.9% for PBT, respectively (4). These studies demonstrate the primary question for clinicians when selecting the optimal modality, that being whether the difference in lower dose volumes (V5, V10) is sufficient to employ this technique when compared to SBRT. It should also be noted that the vast majority of trials that have compared dosimetry in early-stage disease have done so with passive scattering PBT. These benefits are likely to increase when pencil beam scanning/intensity-modulated proton therapy (IMPT) is employed, as has been observed in dosimetric reports in the locally advanced setting (5). It is probable that most future trials examining PBT in early stage NSCLC will do so in the context of IMPT, which have the potential to increase the observed benefit (*Figure 1*).

Retrospective and single-arm prospective clinical studies of PBT for early-stage NSCLC

Much of the clinical experience in the early-stage setting has been reported by Loma Linda Cancer Center, which has been treating early-stage tumors with PBT for over 15 years (6,7). In 2010, this institution published a comorbidity-adjusted survival analysis of 54 patients treated on a single-arm phase II study. Using the Charlson Comorbidity Index, they generated a predicted survival curve, that they then compared to the observed mortality from causes other than lung cancer. With this approach, predicted overall survival (OS) was 67%/50% at 2/4 years, respectively, correlating well with the actual comorbidity-specific survival rates of 64%/45%, respectively (8). This data served to substantiate the investigators' previous reports of survival with PBT in this context.

In this context, 3 years later Loma Linda reported their 12-year experience of hypofractionated PBT for early-stage NSCLC. The largest known series of this nature, this report

warrants a detailed summary. The investigators reported on 111 patients who received dose regimens of 51–50 Gy, then escalated to 70 Gy in ten fractions, over 2 weeks. Consistent with other studies focusing on SBRT for early-stage disease, there was found to be improved OS with increasing dose levels. Indeed, 4-year OS rates were 18%, 32%, and 51% for patients treated to 51, 60, and 70 Gy, respectively (P=0.006). The rate of local control was 96% for peripheral T1 tumors. For T2 tumors, 4-year local control was 45% when treated to 60 Gy, and increased to 74% with 70 Gy (P=0.10). Notably, a multivariate analysis was performed for four outcome measures (OS, disease-specific survival, local control, and distant failure). Note that tumor location (central *vs.* peripheral) was not associated with any of the major outcome measures. The only variable correlated with all four outcomes was tumor size. With regard to toxicity, no patient had clinical radiation pneumonitis that required steroids or hospital admission, and there were no significant declines in pulmonary function, including FEV1 and diffusion lung capacity. Overall, the authors included that PBT for early-stage disease "achieves excellent outcomes" for centrally or peripheral located lesions," while dose escalation may improve survival with larger tumors (9).

While the largest and longest-term series of this nature, other institutions have also reported their outcomes with PBT in early-stage disease. MD Anderson reported on 18 patients treated with a modified, less hypofractionated regimen of proton therapy for medically inoperable and challenging early-stage disease, defined as T1N0 disease located centrally, or T2–T3N0 disease. The dose-fractionation regimen was 87.5 Gy/2.5 Gy fractions. At a median follow-up time of 16.3 months, the only Grade 3 toxicity was dermatitis (17%). Local control was 89%, and regional lymph node failure was 11.1%. Survival remained largely driven by distant metastasis, with a distant metastasis rate of 27.8%. The authors concluded that this regimen was well tolerated and with promising results (10). This study was then updated in 2017, with the patient number increased to 38 and a median follow-up time of 83.1 months. Five-year rates of local recurrence-free, regional recurrence-free, and distant metastasis-free survival were 85.0%, 89.2%, and 54.4%, respectively, rates that are comparable to those with SABR. No further grade 3 events were observed (11). A limitation of this trial is the 30-fraction regimen, which is no longer in routine use for patients amenable to SABR. However, it is likely that many of the patients in this phase II trial would have been dispositioned to receive modified hypofractionated regimens, and it is reasonable to extrapolate similar principles to other ablative doses.

One recent study compared particle beam therapy and SABR through a systematic review, in which 72 SBRT studies and nine hypofractionated PBT trials through searches of PubMed, Medline, Google Scholar, and the Cochrane library database from 2000 to 2016. Interestingly, while PBT was correlated with improved OS (P=0.005) and progression-free survival (P=0.01) in univariate analysis, the benefit compared to SABR was nullified by the inclusion of percent operable tumors in the multivariate model. In fact, operability was the strongest factor affecting survival among all the study characteristics, implying that other factors that are inherent in this variable, such as functional status, substantially affect the results when assessing outcomes in early-stage disease (12). It should also be emphasized that, while this study did not ultimately demonstrate a statistical improvement in survival outcomes in multivariate analysis, the study was still compelling in reporting at least comparable results between PBT and SABR, particularly considering that almost all PBT patients were likely treated with passive scattering techniques and without image guidance, suggesting that it is reasonable to further compare these modalities with more advanced approaches.

Consensus statement on patient selection for PBT in early-stage lung cancer

In 2015, the International Particle Therapy Cooperative Group (PTCOG) published a consensus statement on the utility of PBT in early-stage and locally advanced NSCLC (13). This group concluded that for small peripheral lesions there is no clear role for PBT, particularly if there are disparities in the capability of performing volumetric imaging. For larger tumors, if there are clear dosimetric differences, it would be reasonable to consider PBT instead of SABR. This recommendation also held for peripheral lesions in which the rib or chest wall receives a substantial dose. The strongest recommendation pertained to tumor location, in that the authors acknowledge that there is often a significant improvement in dosimetry to critical central structures, such as the major airways, esophagus, and/or spinal cord. In these circumstances, it was recommended that proton therapy be considered. Finally, the consensus statement addressed two specific scenarios in which patients may benefit from PBT, that of tumors near the brachial plexus and in patients with multiple tumors. In their justification of treatment near the brachial plexus, the

authors cite a study demonstrating improved dosimetry in tumors in the apex (14), as well as the reports of brachial plexus toxicity with SBRT (15). For the setting of multiple tumors, there is again support in a report of a patient that could solely be treated with PBT (16).

Randomized trial of PBT *vs.* SABR for early-stage NSCLC

MD Anderson Cancer initiated a phase II randomized trial of SABR *vs.* SBPT in early stage NSCLC. Under the premise that patients with small, peripheral lesions are less likely to benefit from PBT, only patients with "high-risk" features were enrolled, as defined as follows: (I) centrally located; (II) <5 cm and T3; or (III) isolated lung parenchymal recurrences. The radiation dose was 50 Gy in 4 fractions, as prescribed to the planning target volume (PTV). SBPT was delivered through a passive scattering plan. The primary outcome was treatment-related toxicity, with the hypothesis that PBT would reduce the rate of adverse events in this high-risk patient population.

The study was open from 10/2012 to 6/2014, and closed due to poor accrual, enrolling only 21 patients during that time. No patients on trial demonstrated grade 4/5 toxicity, with one patient experiencing grade 3 skin fibrosis in the SBPT group. Three-year local control rates were similar, at 87.5% and 90% in the SBRT and SBPT groups, respectively. Notably, there was a higher than expected rate of death in the SBRT arm, with one patient dying of unknown causes and 2 of non-treatment related causes. The authors concluded that both techniques appear to have acceptable toxicity, with no indication of inferiority of SBPT (17).

Possibly more meaningful than the toxicity and outcome results, the study highlighted the difficulties with accruing to a randomized study of SBPT *vs.* SABR. In particular, volumetric imaging was not established at the proton therapy center at the time. Therefore, fiducial placement was performed on almost all patients treated with SBPT, which involved an additional procedure that patients were often unwilling to undergo. The logistics and delays of insurance approval were also noted to be a factor in effective enrollment and randomization, as many patients were either ultimately denied treatment with protons or did not want to delay treatment to await this financial clearance. In addition, as is the case with other studies incorporating PBT, patients often expressed a strong preference for one modality over the other, making it difficult to randomize. Finally, the appropriate inclusion of lesions with only high-risk features created additional difficulties with increasing enrollment. While the increasing availability of volumetric imaging is likely to facilitate accrual with regards to the first obstacle, the latter two challenges will likely remain, and for this reason it may be justified to perform future randomized studies in the multi-institutional setting.

Guidelines for treating patients with SBPT

In general, patients treated with SBPT undergo simulation and target delineation that is analogous to that of SABR, provided that similar image guidance is available. During simulation, patients are strictly immobilized with their arms above their head, and four-dimensional images are acquired. At MD Anderson Cancer Center, patients with a tumor motion of >1 cm are treated with a breath-hold technique. The gross tumor volume (GTV) is delineated on the maximum intensity projection (MIP), which incorporates tumor motion [internal GTV (iGTV)]. Per Radiation Therapy Oncology Group guidelines, a 5-mm expansion is then placed on the iGTV to define the PTV.

For proton treatment planning, the GTV/clinical target volume (CTV) were used as targeting structure for plan design, and the PTV was only used for treatment plan evaluation. For proton plans, at least 95% of the PTV had to receive 100% of the prescription dose and 100% of the PTV must have received 95% of the prescription dose (14). Each plan had four or more coplanar beam angles designed in an attempt to minimize both chest wall dose and the exit dose into the lung parenchyma. For passive scattering proton therapy (PSPT) planning, for each beam, we designed aperture block and beamline with proximal/distal margins from the CTV; and a compensator with appropriate smearing margin to shape the distal margin of the spread-out Bragg peak as described in previous publications (18). For IMPT planning, robust optimization was used in order to take into account for setup and range uncertainties (19). The critical structure objectives were prioritized based on the risk that the dose to the structure would exceed the maximum tolerated dose (MTD). Robust evaluation and verification dose distribution calculated on inhale/exhale CTs was used to ensure tumor coverage under the impact of respiratory motion and setup/range uncertainties (20).

Summary

The role of PBT in early-stage NSCLC has not yet been

defined. There is general consensus that PBT is not superior to SABR in small, peripheral lesions, particularly those that do not involve large portions of the chest wall or rib. PBT may be beneficial for complex cases identified as follows: (I) larger tumors (>4 cm); (II) centrally located lesions; (III) tumors that are located in the apex and thus near the brachial plexus; and (IV) cases requiring treatment to multiple sites of disease (e.g., multiple primary tumors). More data is needed regarding the safety and efficacy of SBPT in comparison to SABR. Of note, the only randomized trial that has been attempted closed early due to poor accrual, thus demonstrating the difficulty in designing trials in this context that incorporate a relevant and focused scientific question that can be extrapolated to clinical practice, yet also accrue sufficiently. Certainly, the advent and increased use of advanced IGRT techniques in the context of proton therapy, as well as the widespread implementation of IMPT, will both increase the potential benefit of SBPT, as well as serve to overcome many of the logistical barriers to adequate trial accrual. The next 5–10 years will likely yield more appropriate, feasible studies that will help answer the question of patient selection for this advanced technology.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Gomez DR, Li H, Chang JY. Proton therapy for early-stage non-small cell lung cancer (NSCLC). Transl Lung Cancer Res 2018;7(2):199-204. doi: 10.21037/tlcr.2018.04.12

