Review Article

A proton primer to stereotactic lung radiotherapy

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Contributions: (I) Conception and design: All authors; (II) Administrative support: CB Simone 2nd, MV Mishra; (III) Provision of study material or patients: None; (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: Stereotactic body radiation therapy (SBRT) is regarded as a safe and effective treatment for early stage non-small cell lung cancer (NSCLC). However, the safety of SBRT has been questioned, specifically in the treatment of central tumors abutting critical organs at risk (OARs), when treating large or multiple tumors or when re-irradiating. Due to these concerns, radiation with stereotactic body proton therapy (SBPT) has emerged as a possible alternative due to its potential to decrease dose to OARs. The Particle Therapy Cooperative Group (PTCOG) recommends consideration of SBPT for large or multiple tumors, central tumors and those close to critical OARs. However, proton irradiation can be associated with significant uncertainty due to tumor motion, tissue heterogeneity, set up error, or changes in patient anatomy, as well as variations in distal range linear energy transfer values. In this review, we discuss clinical outcomes data from prospective and retrospective studies evaluating the benefits and risks of SBPT, methods to address uncertainties associated with PBT, and future directions for research.

Keywords: Lung cancer; stereotactic body radiation therapy (SBRT); stereotactic ablative radiotherapy; proton therapy; stereotactic body proton therapy (SBPT)

Received: 27 January 2019; Accepted: 25 February 2019; published: 15 May 2019.
doi: 10.21037/tro.2019.04.01
View this article at: http://dx.doi.org/10.21037/tro.2019.04.01

Introduction

Stereotactic body radiation therapy (SBRT), or stereotactic ablative radiotherapy as it is otherwise known, is defined as "an external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions" (1). Although surgical resection is still widely viewed as the gold standard for curative treatment in early stage non-small cell lung cancer (NSCLC), SBRT is being utilized more commonly, especially in patients who refuse surgery or are deemed to be non-operative candidates (2). Phase I data in this setting showing acceptable safety and toxicity profiles were first published in 2003 by Timmerman *et al.* (3). Since then, convincing data showing excellent local control rates of 85–97.6% using this technique have been reported (4-7), which have also led to favorable direct comparisons of SBRT to surgical resection (6,7).

Conventionally, SBRT is delivered in early stage NSCLC using photon beams. Although this method has proven to be safe and effective in many cases, there are still technical and toxicity-related concerns, particularly when treating tumors located near critical organs (8). Central tumors are commonly defined as being within 2 cm of the proximal bronchial airways or immediately adjacent to nearby critical organs including the heart, esophagus, and spinal cord (9,10). Serious SBRT toxicities such as pericardial effusion, pneumonitis, pneumonia, hemoptysis, bronchial stenosis, fistula and death have been reported when treating central tumors (10-13). Other critical organs at risk (OARs) can include the brachial plexus and chest wall. The treatment of large tumors, multiple tumors simultaneously and re-

irradiation are additional clinical scenarios associated with increased risk of toxicity when utilizing SBRT.

The use of proton radiotherapy has become increasingly common as a means to potentially reduce toxicity associated with SBRT. Historically, stereotactic body proton therapy (SBPT) was delivered using passive scattering techniques, but in recent years more modern and conformal active scanning techniques are being utilized. Protons possess a dosimetric advantage compared to photons in which the target dose is delivered to a specific depth, or "Bragg Peak", followed by a rapid dose fall off which results in little or no exit dose. This allows for sparing of OARs located close to lung cancer target volumes (14) and therefore has the potential to reduce acute and chronic toxicities when compared to conventional photon SBRT. Proton therapy also allows for a significant reduction in integral dose to patients which can further reduce late toxicities.

Purpose

The purpose of this review is to explore the currently available literature relating to stereotactic radiotherapy in early stage NSCLC in order to compare the use of SBPT to SBRT and to highlight future directions for research.

Dosimetry and feasibility studies

Several studies have demonstrated a potential dosimetric advantage favoring SBPT over SBRT (15-22). SBPT plans significantly decreased mean lung doses and $V5_{Gray}$ to the ipsilateral and contralateral lungs (16-18,20-22). Many of these studies have also demonstrated lower doses delivered to critical OARs such as the heart and esophagus (17-20,22). Although some of the dosimetric SBPT advantages seen were modest, it must be noted that the vast majority of patients in these studies were treated using passive scattering techniques. The dosimetric advantages of SBPT over SBRT could have been underestimated by the use of passive or double scattering techniques rather than pencil beam scanning, which allows for the most conformal dose distribution with protons (23).

Westover *et al.* reported their experience of 15 patients with 20 stage 1 NSCLCs who were generally high risk for treatment, most of whom had interstitial lung disease, multiple primary tumors, or prior thoracic RT. These patients were treated with SBPT to a median dose of 45 cobalt gray equivalent (CGE) in 14 fractions. They reported 3 cases of rib fracture and 1 case of grade 3 pneumonitis. They also reported 2-year overall survival and local control rates of 64% and 100%, respectively (24). Nakayama *et al.* reported their experience of 55 patients treated with double scattering, most commonly to 66 CGE in 10 fractions with 2-year overall survival and local control outcomes reported at 97.8% and 97%, respectively. Only 2 patients had deterioration of lung function and another 2 patients developed grade 3 pneumonitis (25).

The oldest and largest clinical experience was reported by Bush *et al.* at Loma Linda (26). This 12-year experience included 111 patients treated with 1 of 3 dose levels: 51, 60 or 70 CGE in 10 fractions. The authors reported increased 4-year overall survival rates with each progressive dose level (18%, 32% and 51% respectively). Peripheral T1 tumors showed local control rates of 96% at 4 years. This clinical experience also reported excellent safety outcomes with none of the patients suffering from significant treatment-related pneumonitis or decreased pulmonary function. There were, however, 4 patients who developed a rib fracture, all of whom had tumors in close proximity to the chest wall (26).

A large meta-analysis was also recently conducted that compared particle beam stereotactic radiotherapy to SBRT using photons, however, this analysis included studies in which patients were treated with carbon ion therapy, which has somewhat different dosimetric properties than protons. Chi *et al.* compared 72 SBRT studies to 9 hypofractionated particle therapy studies and reported 3-year local control rates favoring particle based therapy on multivariate analysis and a decreased rate of severe (grade 3+) toxicity with particle therapy (0.9% *vs.* 3.4%, P=0.001). While overall and progression free survival were statistically better in the particle studies on univariate analysis, these differences did not remain significant on multivariate analysis. This analysis was limited given that most studies included were single arm, single institutional, observational studies with heterogeneous patient populations and treatment planning and delivery techniques, which could have introduced a significant selection bias (27).

Randomized evidence

One randomized trial attempted to compare SBRT to SBPT in early stage NSCLC, however, it closed early due to poor accrual (28). Reasons for premature closure included lack of 3D volumetric imaging in the SBPT arm, lack of insurance coverage in the SBPT arm, strict inclusion of only "high risk patients" in the trial and patient treatment preferences

(28,29). For the 21 patients successfully enrolled, median survival time was not reached in the SBPT group and was 28 months in the SBRT group. The 3-year local control was similar in both groups (90% *vs.* 87.5%). Three-year overall survival in the SBPT group was 90% *vs.* 27.8% in the SBRT group, but this difference was not statistically significant given the small patient numbers in the trial. Only one patient in the study experienced a grade 3 toxicity (skin fibrosis in the SBPT arm) with no grade 4 or 5 toxicities being reported in either arm. The authors concluded that if a similar study were to be attempted in the future, it would require improvements in volumetric imaging for SBPT and improved cooperation with insurance companies (28).

Uncertainties and cost

Due to the physical characteristics of protons, there is a significant amount of dose delivery uncertainty just distal to the Bragg Peak. Therefore, clinicians attempt to orient beams to avoid end-ranging into critical OARs. This end range uncertainty can arise due to a variety of factors which include inaccuracy in the CT Hounsfield unit conversion to proton stopping power, treatment set up uncertainties and inter-treatment changes in patient anatomy (30-32).

The effect of these uncertainties becomes magnified with the high doses per fraction and reduced number of fractions delivered with stereotactic lung radiotherapy. Particularly relevant to lung cancer, tumor motion due to normal physiologic respiration adds another degree of uncertainty. Motion management strategies for proton therapy include the use of 3-dimensional volumetric on-board imaging to ensure beam delivery accuracy and utilization of breath hold techniques which have been shown to be feasible (33,34). Uncertainty of tumor motion is further compounded by the fact that the use of active scanning proton delivery can introduce a second dimension of complexity known as the "interplay effect." This is further defined when "relative motion between a tumor and a scanning proton beam results in degradation of the dose distribution" (35,36). Strategies to account for this include utilization of Monte Carlo and robust optimization algorithms (36,37). As the interplay effect is understood to be a random error, another successful strategy is the use of "dose repainting." This is defined as splitting the delivered dose into 2 or more fractions delivered sequentially during a single treatment (as opposed to conventional twice daily fractions that are typically delivered at least 6 hours apart). This process effectively increases the number of fractions, which is more likely to smear out the interplay effect by negating the random error, ultimately reducing treatment planning uncertainty (38).

Robust optimization can also be used to account for inter-treatment changes in patient anatomy, which can have significant dosimetric and clinical consequences. Proton radiotherapy is especially sensitive to these changes compared to photon radiotherapy (39). A clinical example of this is shown in *Figure 1*. Another unique issue when treating lung tumors is the drastic change in density from lung to tumor tissue. This density gradient has a greater effect on proton particles than photons. It can also be accounted for by utilizing Monte Carlo simulations which account for sudden changes in tissue density (30,31). Finally, the lack of volumetric on-board imaging has been cited as an obstacle for the use of SBPT in lung cancer (28), however, as proton treatment gantries with cone beam CAT scan capabilities become more widely available this will likely be less relevant going forward (33).

The financial cost of delivering proton treatment has been a major hurdle in treating patients using protons, especially in privately funded health care systems. Theoretically, if proton treatment is able to decrease dose to OARs, this could potentially lead to decreased costs associated with the clinical management of radiation-induced toxicities. However, proton therapy is currently significantly more expensive compared to conventional photon therapy at most centers, and its' use in individual cases must be clinically justified. Peeters *et al.* conducted an in depth cost effectiveness analysis comparing conventional photon treatments to proton treatments and found that the cost of running a proton facility was 2.6 times higher than that of running a photon facility, and that the cost per fraction of proton treatment was 3.2 times higher than photon therapy. Interestingly, and particularly relevant to this discussion, the authors found that the cost difference between proton and photon therapy was smallest when treating stage 1 NSCLC and they observed a linear increase in treatment cost as the number of fractions increased. This could suggest that the use of fewer fractions, as is delivered in stereotactic radiotherapy, would offer a potential cost benefit with the use of protons (40). Additionally, the potential for acute and late toxicity reduction with SBPT may prove it to be more cost effective in the long term.

Treatment recommendations

The use of SBPT in the management of early stage NSCLC should be considered on an individual patient basis and should account for tumor and non-tumor related

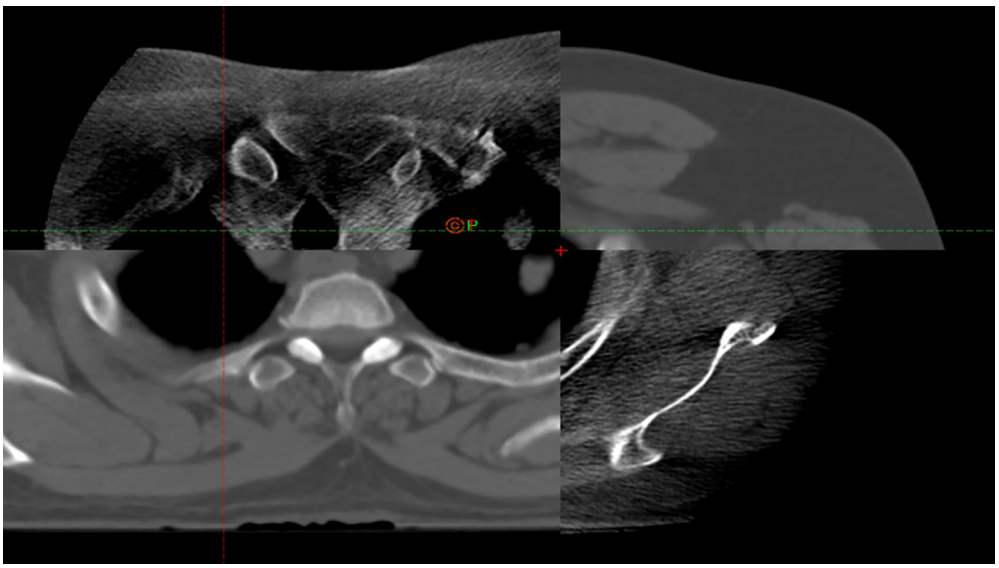

Figure 1 Images of a 62-year-old smoker with left sided, apical, cT1a NSCLC treated with proton radiotherapy. Shown is an axial slice in which the top right and bottom left panels show the initial CT simulation scan images and the top left and bottom right panels show offline cone beam CT imaging taken during treatment. The location of the tumor has shifted superiorly and medially, despite several attempts to reposition the patient for optimal matching. In this instance, treatment re-planning was required. NSCLC, non-small cell lung cancer.

factors such as medical comorbidities. The Thoracic Subcommittee of the International Particle Therapy Co-operative Group (PTCOG) published treatment guidelines in 2016, which outline specific tumor characteristics which could warrant the use of SBPT (41). They recommend that small, peripheral tumors not be treated with SBPT, as the potential benefit compared to SBRT is marginal at best. They do, however, recommend consideration of SBPT for larger tumors due to dosimetric advantages and possible reductions in chest wall and rib toxicity. There is also a recommendation for consideration of SBPT in patients with multiple tumors based on a case report by Shi *et al.* (42).

The PTCOG recommendation also suggests consideration for proton therapy for central tumors which abut critical OARs such as the esophagus, heart, major vessels, spinal cord or airways in order to reduce potential toxicity. They also recommend that tumors close to the brachial plexus be considered for SBPT in order to reduce treatment-related neuropathies (41).

Outside of the PTCOG recommendations, other treatment scenarios in which SBPT may be considered include cases in which dose reductions to the chest wall and ribs are desired. Welsh *et al.* demonstrated SBPT's ability to achieve superior dosimetry and similar PTV target while reducing chest wall dose. They concluded that the dosimetric reduction seen with SBPT versus SBRT could result in fewer adverse clinical outcomes such as chest wall pain and rib fracture (43). SBPT can also be considered in patients with poor lung function, as measured by low pulmonary function testing, as there can be significant reductions in mean lung dose and low dose lung volumes with SBPT compared to SBRT (16-18,20-22). Proton therapy may also be helpful in patients with oligo-metastatic or oligo-progressive disease who are actively receiving or have recently received systemic therapy in an attempt to reduce the dose to the lungs and other critical OARs, thus potentially reducing toxicities that may be additive or synergistic when combining radiotherapy and systemic therapy. Finally, SBPT can be considered in re-irradiation scenarios where sparing dose to OARs is critical.

Conclusions and future directions

Currently, consideration for the use of SBPT in early stage NSCLC should be limited to certain complex treatment scenarios, including central tumors close to OARs, large or multiple tumors and re-irradiation cases. Additional randomized trials comparing SBRT directly to SBPT are needed to fill current knowledge gaps but are unlikely in the immediate future. Future trials should evaluate the

effectiveness of SBPT with pencil beam scanning delivered with on-board volumetric imaging (23). Further work is also needed to better understand the inherent uncertainties associated with proton therapy. Finally, more cost-effectiveness research is required to determine whether the use of protons can significantly reduce the costs of treatment-related toxicities and establish proton therapy as a cost effective treatment modality. This, in turn, could result in increased cooperation and willingness to cover treatment costs by insurance companies. SBPT in early stage NSCLC shows great promise in certain clinical scenarios, but its ultimate value as a treatment modality in radiation oncology is yet to be established.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: MV Mishra and CB Simon 2nd receive a speaker's honorarium from Varian Medical Systems. CBS serve as an unpaid editorial board members of *Therapeutic Radiology and Oncology* from Aug 2018 to Aug 2020. MVM serve as an unpaid editorial board members of *Therapeutic Radiology and Oncology* from Sep 2019 to Aug 2021.The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/tro.2019.04.01
Cite this article as: Sharma AM, Simone CB 2nd, Remick J, Kowalski E, Mishra MV. A proton primer to stereotactic lung radiotherapy. Ther Radiol Oncol 2019;3:16.