Review Article

Proton therapy for non-small cell lung cancer: the road ahead

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Abstract: Proton therapy is an evolving radiotherapy modality with indication for numerous cancer types. With the benefits of reducing dose and sparing normal tissue, protons offer a clear physical and dosimetric advantage over photon radiotherapy for many patients. However, its impact on one type of disease, non-small cell lung cancer (NSCLC), is still not fully understood. Our review aims to highlight the data for using proton therapy in NSCLC, with a focus on the clinical data—or lack thereof—supporting proton treatment for early and advanced stage disease. In evaluating these data, we consider how future directions and advances in proton technology give rise for hope in defining a role for protons in improving NSCLC outcomes. We close with considerations for next steps and the challenges ahead in using proton therapy for this unique patient population.

Keywords: Proton; policy; lung cancer; radiation oncology; particle therapy

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Introduction

Proton therapy is an evolving radiotherapy modality with indication for numerous cancer types. With the benefits of reducing dose and sparing normal tissue, protons offer a clear physical and dosimetric advantage over photon radiotherapy for many patients. However, its impact on one type of disease, non-small cell lung cancer (NSCLC), is still not fully understood.

Our review aims to highlight the data for using proton therapy in NSCLC, with a focus on the clinical data—or lack thereof—supporting proton treatment for early and advanced stage disease. In evaluating these data, we consider how future directions and advances in proton technology give rise for hope in defining a role for protons in improving NSCLC outcomes. We close with considerations for next steps and the challenges ahead in using proton therapy for this unique patient population.

Clinical evidence for protons

To date, both retrospective and prospective reports demonstrate a potential advantage of protons (1-15) over photon radiotherapy in the NSCLC setting (16-30). This potential advantage persists despite the bias that patients receiving proton therapy are likely older (and potentially more toxicity-prone) owing to a proportionally higher degree of proton approval by Medicare. For early-stage I–II disease, single-arm phase I/II trials and retrospective data since the early 2000s have generally shown that proton therapy results in <5% grade 3 pneumonitis (18), the ability to dose-escalate (9,11,14,17), and variable degrees of local control, with better control in more recent trials, possibly attributable to advances in proton delivery (7,10,12,14,16-18). While these studies are promising, they were mainly done in the beginning stages of proton treatment, and their limitations include failure to utilize a

randomized approach, less-conformal passive scatter proton therapy, and utilizing conventionally fractionated or hypo-fractionated regimens which are no longer employed for early stage disease. Instead, with recent results from CHISEL showing an overall survival advantage of stereotactic ablative radiotherapy (SABR) over conventional radiotherapy (31), SABR is currently the preferred therapy for such early stage tumors (32-34). Thus, those early proton studies utilizing conventional regimes now have limited relevance.

More relevant is a meta-analysis evaluating protons versus SABR for early-stage NSCLC, which suggests that utilizing protons offers an overall survival advantage and a decrease in toxicity, including pneumonitis and grade 3–5 events (albeit not reaching statistical significance after accounting for potential confounding variables) (18). As might be expected, chest wall pain and dermatitis appear higher in proton therapy, likely attributable to the dosimetric profile of beam entry or end-ranging into thoracic chest wall anatomy, but these are factors which can be modified in today's practice based on treatment techniques and/or technical planning/equipment (discussed below). To date, there is only one report of a randomized trial of protons in early-stage NSCLC (1), a study by MD Anderson on 9 patients with photon SABR compared to 10 patients with proton SABR. The trial closed early due to concerns about lack of volumetric image-guided RT (IGRT), as well as poor accrual. The poor accrual was primarily attributable to a lack of insurance coverage, a major recognized barrier to conducting proton therapy trials and offering timely and appropriate patient access to proton therapy (35-37). Thus, overall the studies to date provide insight into the potential of proton therapy in early-stage NSCLC, but given the advances and changes in the early-stage NSCLC approach, modern randomized studies are greatly needed.

A similar conclusion is suggested for using proton therapy in advanced stage III NSCLC. Early prospective reports and retrospective matched analyses show acceptable local-regional control with proton therapy used with chemoradiation (CRT) for advanced NSCLC (19-30). They also show the potential for reduced pneumonitis and other toxicity (19-21,23), as well as the possibility of dose escalation given the ability of protons to spare dose to the heart and central structures (21-23). High doses to the heart and, to a lesser degree, the lungs, is what was thought to account, in part, for the negative effects of dose-escalated photon therapy in RTOG 0617 (38-40). With protons, a dose escalation may be possible (and beneficial) because the heart and central structures might be spared. While protons are unlikely to have an effect on OS from a cancer-specific standpoint given that (I) the rates of distant metastasis were still on the order of 40–45% in these trials (21,22,25), and (II) advanced disease is a systemic problem, local control in the mediastinum and lung is highly desired, and a great source of potential morbidity/mortality reduction (41-43). Further, since CRT is a toxic treatment, reducing side effects and/or dose might reduce long-term effects from radiotherapy and that, in the long-term, may translate into a survival benefit (44). This question is discussed further below.

Still, despite these potential advantages, the only randomized phase II trial to date was negative for a benefit of protons over photons in advanced NSCLC (28). In this MD Anderson-based study, protons did not improve the primary endpoint of local control or grade 3 pneumonitis in patients with stage IIB-oligometastatic disease who were candidates for CRT. However, on evaluation of this trial, the negative finding was likely due to its design and not necessarily attributable to the modalities themselves. Firstly, the trial used a very heterogeneous group of patients with a broad spectrum of disease states (from advanced to metastatic) and treatment strategies (from postoperative CRT to definitive CRT). Such heterogeneity limits interpretation of endpoints such as overall survival, disease specific survival, toxicity, and locoregional control. Due to the variability in target coverage, normal tissue exposure, and patterns of failure, all of which differ according to disease state and extent, the resulting interpretation remains guarded.

Secondly, and perhaps most importantly, patients were only deemed eligible for randomization after initial screening with generation of comparative intensity-modulated photon radiotherapy (IMRT) and proton treatment plans. Therefore, only patients with acceptable plans for both modalities were included. This inherently defeats the purpose of demonstrating superiority of one modality over another even if, prior to randomization, dosimetric profiles were generally good for both modalities for all patients. This is a major limitation because it requires that any signal of benefit had to be based on fine tuning points in the dosimetric profile for a given modality, so that patients who may have benefited tremendously from protons were outright excluded.

Lastly, since the trial was conducted during the early phase of proton therapy at the center, the proton technology and delivery were not fully developed. Indeed, the authors state that there was a large learning

curve for proton treatment planning and delivery in NSCLC treatment during the course of that study (45), as reflected by the fact that, for patients receiving protons, the rate of pneumonitis decreased by half (31% *vs.* 13%) from the first years of enrollment to the second half of enrollment (28). Furthermore, the trial used passive scatter proton therapy which, with its lesser conformality, cannot be fairly compared to the highly conformal IMRT therapy of today. Pencil beam scanning with robust image-guidance should have been employed, but was limited by availability at the time. This highlights the fact that a great tool inadequately applied will lead to inadequate results, a notion supported by a recent report finding that NSCLC patients treated with protons at academic centers have improved outcomes (46). While these results can be due to a number of reasons, they speak to how greater experience in proton planning and delivery could lead to better outcomes, and such experience is a requisite to achieving desired results.

The overall lesson learned from utilizing the suboptimal design and execution of the phase II study will be hard-felt throughout the coming years. The results exacerbate the conundrum faced by those attempting to test proton therapy in NSCLC: insurance companies want trial data before they authorize a modality (protons), yet to generate that data, they must authorize use of that modality for patients on trials. With the results of this trial showing a preliminary, but arguably inappropriate, conclusion that there is a lack of benefit, it will be exponentially more difficult to accrue patients for ongoing studies testing protons in this setting. Yet, we must have more randomized results in order to understand whether proton therapy does provide a benefit in the advanced NSCLC setting.

The promise of protons in NSCLC

Reducing toxicity

Although there are currently no prospective clinical data demonstrating a clear benefit of proton over photon therapy, there are numerous reasons such data are likely to emerge, chief among them being that numerous reports have shown a dosimetric advantage. Both in using proton SABR for early-stage NSCLC and as the radiotherapy element of CRT for advanced stage NSCLC, overall dose to the lungs in the form of mean, V5, V10, V15, and V30, as well as esophageal dose, heart dose, and spinal cord dose, all have been reduced with protons over photons (2,5,6,47-49). For SABR, proton therapy allows for enhanced potential sparing of difficult to treat tumors near the mediastinum centrally, the spinal cord posteriorly, or those located more superiorly near the brachial plexus. When using ablative doses in this range, any advantage to reducing maximum dose, and other dosimetric parameters, enables better confidence in safe treatment delivery. In particular, the prevention of late debilitating side effects such as hemorrhage, fistula, and paralysis are potential benefits. This superior dose profile with protons has been demonstrated in at least one report evaluating intensity modulated proton therapy (IMPT) *vs.* IMRT photon therapy in the SABR setting (50).

Furthermore, given the recent evidence for its similar outcomes compared to lobectomy in operable patients (32,51,52), SABR, which was traditionally reserved for only inoperable patients, is now being used to treat more individuals with early-stage NSCLC. New data on the effectiveness of low-dose CT for lung cancer screening will also lead to the earlier detection of early-stage tumors, which will be amenable to procedures such as SABR (53,54). In light of that data, more patients are expected to be treated with SABR, and, in fact, there has been a tripling of SABR use just from 2008 to 2013 (55). Because of this, and given the more favorable survival outcomes with early-stage NSCLC patients, using a SABR technique that minimizes dose to any normal tissue is preferable. This is largely because the effects of radiation on normal tissues, including low doses, increase over time. Proton therapy in this setting would be potentially advantageous given its better dose profile and native-tissue sparing effects compared to photon therapy. This would be particularly true for younger, healthier operable SABR patients, who are anticipated to live longer.

However, an additional caveat to using SABR for treatment of early-stage NSCLC is that up to 1 in 7 patients can have isolated local-regional failure (32,34,56,57). The reason is that SABR does not remove the entire lobe of the lung or treat lymph nodes. However, these potentially curable failures are highly salvageable (58). As more patients are treated with SABR, more patients will invariably be treated for these recurrences. Using proton over photon SABR may offer a significant advantage for these patients moving forward where re-irradiation is often considered and performed in the salvage setting. Sparing normal tissues upfront, including elimination of a low dose bath to surrounding lung parenchyma, could enable safer and more effective salvage for the up to 1 in 7 patients who need it. From a forward-thinking perspective, and considering the NSCLC population being treated, proton SABR offers a

potential significant advantage when considering patterns of failure and the potential need for additional treatment in this patient population.

From a concurrent CRT standpoint, advanced stage NSCLC patients are also poised to benefit from proton therapy instead of conventional photon therapy. As with SABR, a number of reports have found significant dose reductions to organs at risk by using IMPT over IMRT for advanced stage tumors (5,19,23,59,60). Since patients with advanced stage disease have much larger volumes to treat, a substantial amount of lung and central structures often are unnecessarily bathed in radiation. It has been shown that lung alveoli can be damaged by even low doses of radiation (61), and that each 1 Gy to the heart raises the chance of a cardiac event by 7.4% (62). As such, minimizing doses to these structures is paramount, particularly for NSCLC patients who often present in their elderly years and have other competing risks for mortality, chief among them a substantial smoking history. Most of these patients have other cardiopulmonary health problems including chronic obstructive pulmonary disease (COPD), heart failure, coronary artery disease, and emphysema (63-65). Thus, eliminating unnecessary radiation for these patients by sparing already damaged organs and not exacerbating the toxicity they endure, may have profound benefits in the long term. This is particularly true as significant advances have been made in prolonging survival in advanced stage NSCLC. With novel biologics, and most notably anti-PD1/L1 immunotherapy (i.e., PACIFIC trial), advanced stage patients are now living much longer than before (66,67), making reduction in late-term effects a timely, and now newly energized priority for those patients.

Furthermore, *long-term* side-effect reductions are not the only potential benefit for using protons in the CRT setting. CRT itself is a toxic treatment that is made more difficult because of the collateral radiation dose spillage into organs at risk. Since side effects such as esophagitis, dyspnea, and fatigue occur because of radiation exposure to at-risk organs, reducing dose all around could also reduce *short-term* side effects during treatment. Reducing side effects is important to patients being able to complete radiation in order to achieve tumor control and cure. It is also important because concurrent CRT, versus sequential or staged chemotherapy and radiation, has a survival benefit (44) but often treating physicians do not pursue it due to concerns that it will be too toxic for these often frail and elderly patients (68-71). Using proton therapy to reduce short-term side effects through normal tissue sparing, may allow more patients to better tolerate, and be treated with, concurrent CRT. Thus, proton therapy to reduce acute side effects from treatment can have a profound effect [and potential survival benefit (44)] on the population of advanced stage NSCLC patients as a whole.

Biologic tumoricidal rationale

The tissue sparing effects of protons are not the only proposed mechanistic advantage. With NSCLC patients living longer, owing mainly to improvements in screening and systemic therapies, durable control of treated disease is imperative. Protons, compared to photons, have a higher biologic effectiveness [termed relative biologic effectiveness (RBE)]; many accept this increase in tumor kill effectiveness to be on the order of 10% over photons, although there remains no clinical evidence supporting this increase in tumor killing. However, such effectiveness predictions are based on limited *in vitro* cell line data (72,73), and we now know that the biologic effectiveness with protons is variable—predicted to be much higher—and greatest just at or beyond the Bragg peak (72,73). Thus, if we were to view radiation as a drug, protons compared to photons would be a much more biologically effective agent. There is ongoing investigation on how to optimize placement of this enhanced effectiveness [such as linear energy transfer (LET) property] into the tumor directly (74-76). When choosing a given agent, it would make sense to use the option that is more biologically effective, particularly if that agent also carries the demonstration or suggestion of reduced side effects. Such an advantage in therapeutic ratio may lend itself well in the CRT setting, where loco-regional failure (including in and out of field) can approach 50% for advanced stage disease (40), but >95% local control of the treated tumor is already achieved with SABR (32,56,57).

Finally, although highly speculative, proton therapy may also be able to spare circulating lymphocytes from radiation by reducing the volume of blood that is irradiated, thereby preventing lymphopenia, which has been correlated to worse outcomes in some studies (77). This is particularly true of advanced NSCLC, where mediastinal irradiation is common, and for which subsequent immunotherapy is now standard of care for appropriately selected patients. For those patients, it is desirable to spare immune effector cells from radiation since they are the moderators of immunotherapy's anti-tumor response and the drug's (durvalumab) survival effect (66).

Advancing proton therapy to the next level

The reality is that we are still in the infancy stages of proton therapy. Many advances are on the horizon, and to realize the full potential of proton therapy in the NSCLC setting, innovation will be required. Yet already there are general advances for the modality (protons) and specific advances pertaining solely to NSCLC and thoracic tumors.

General advances are being made on all levels of proton therapy planning, delivery, and evaluation; many of these have been reviewed elsewhere. However, for planning purposes, one advance that will undoubtedly improve proton treatment for NSCLC is the employment of dual energy CT (DECT) or other techniques that reduce range uncertainty for treatment delivery (74-76,78-80). Indeed, the range uncertainty with proton stopping estimation may be improved by up to 50% with DECT. Currently, algorithms using single energy CT photon to proton stopping power calculations implement a 3–3.5% uncertainty for each centimeter (cm) of beam path length. That means the uncertainty as to how protons interact and deposit dose in tissue, compared to traditional photons, requires an extra dose cloud expansion around the target in order to ensure therapeutic radiation is robustly delivered to the full tumor. For short beam path lengths, such as in the brain or head and neck, this extra dose added around the proton treatment volume to account for uncertainty is less. But when treating tumors deep in the chest, such as for NSCLC, a beam with 10–20 cm of path length could result in an additional 3–6 mm of dose all around (3–3.5% margin for uncertainty), and that translates into a significant amount of extra dose volume delivered solely because of uncertainty. As such, DECT or other techniques to improve uncertainty can lead to profound improvements in the ability to sculpt proton radiation to NSCLC targets. This would lead to much enhanced tissue sparing and the ability to treat tumors near critical structures to potentially higher doses or with more confidence. Conformality can thus be greatly improved with these techniques. Although potentially dangerous with regard to marginal miss and density changes from anatomical changes (inter- and intra-fractional), high-quality image guidance can greatly assist in attenuating these concerns.

Another general advance will come with continued improvements in computational power. With IMRT, a major limitation in its development and clinical implementation was the computer power needed to generate the inverse planning algorithms to perform the complex and time-intensive dose calculations (81-83). The same will be true for proton therapy. Currently, Monte Carlo and fast Monte Carlo techniques are being developed for use with commercial treatment planning software (TPS) (84-86). Such techniques have the ability to more accurately depict where proton particles will travel and deposit energy for a given plan. The end result will be greater confidence that the visual treatment plan generated for review by dosimetry and physicians will match what will actually be received by the patient. Along this vein, other computational modeling, including LET modeling (being able to adjust a plan to put more "biologic effectiveness" with protons directly into the tumor and away from normal tissues) is also being developed. For NSCLC and moving thoracic tumors, incorporating the breathing cycle (4D) into the robustness optimization for a given patient is also being investigated (87,88). This will significantly help to accurately model where a dose is going within a part of the body, such as the thorax, that is continuously moving. Yet, all these examples of enhancements in complex treatment planning to improve certainty with proton therapy and to exploit their biologic advantages over photons require substantial computational power that is not routinely supported by current systems and that requires significant time and resources. As TPS system vendors and proton centers invest in the development of these programs and the computer resources to support them, we can expect important advances in proton planning that will lead to improved tissue sparing, target coverage, and plan delivery.

Finally, from a delivery and evaluation stance, further reductions in spot size will improve dose painting with normal tissue sparing/dose sculpting. Whereas the "historical" technique for proton therapy has been passive scattering, the newest technique involves pencil beam scanning (89,90). The latter has the chief advantage of increased target conformality by means of intensity-modulation. However, these come at the expense of technical concerns such as "overconformality" (marginally missing the tumor owing to unforeseen tumor changes and/or motion) and the "interplay effect" (referring to the degradation in dose distribution based on the simultaneous relative motion between a tumor and the beam). However, with technical advances, these limitations may be attenuated. Gantry/accelerator/vault modifications will reduce cost and treatment time, and will broaden the scope of delivery and, therefore, proton planning options (91-93). In addition to

robustness optimization at the treatment planning step, robustness evaluation both for target coverage and normal tissue avoidance will continue to improve. Depending on the methods utilized to calculate the dose, evaluation of only the nominal DVH for protons is often inadequate. Dose heterogeneity (mean dose, min, max, variability around the DVH curve) is often weighted against tumor coverage and OAR avoidance. Beam angle placement is vital: evaluating so as not to aim at critical structures is a basic principle. Adjusting beams throughout treatment in order to spread out the LET and RBE when this is unavoidable can be attempted, but with consideration of the impact of adding more radiation with additional beams. With increased experience and better planning algorithms these decisional aspects can be further optimized. Also, trusting dose representation near metal alloys, and considering artifact effects on what is being delivered versus what is predicted, remains a challenge but provides room for improvement.

As demonstrated by the points made above, the need for complex proton planning and delivery, with the advances that can be made there, is matched by the importance of a treating physician taking the time to carefully and completely evaluate a final plan. To that end, advances in our understanding of proton characteristics and treatment modeling will also advance our abilities to judge plans for their safety and efficacy. Our abilities to determine which features on a printed plan are clinically relevant to evaluate, and how to adjust these variables iteratively in order to optimize a final product, will continue to improve. With volumetric imaging, we also will be able to help determine when and how often to adapt plans based on tumor and normal tissue changes throughout treatment (90), something that protons are exquisitely sensitive to.

Considerable research is taking place on all these fronts, and the end result of our improved understanding and confidence in plan evaluation will undoubtedly translate into safer and more effective proton treatment (94). The bottom line, as revealed through some of the data already gathered, is that the importance of funding clinical research testing proton versus photon therapy is matched by the need to invest in efforts to improve the modality (95). Failure to advance on both fronts could lead to suboptimal results and, ultimately, a premature and inappropriate conclusion that protons may not provide benefit in NSCLC. But forging ahead with significant, coordinated effort offers the potential for developments in proton therapy that will benefit many NSCLC patients.

Conclusions

Early investigations of proton therapy for NSCLC have taught some difficult but important lessons. Most notable of which is the recognition that there is a substantial learning curve for using protons and much room for significant advances. Yet, we also have learned that there are notable clinical and preclinical rationales for proton therapy in providing advantages over photon therapy when treating lung cancer. This is particularly the case for a population of patients who are living longer and could drastically benefit from side effect reductions in radiation therapy, not only for long-term effects, but also improved tolerance to the curative modality that is prescribed.

IMPT offers many advances, but can be suboptimal if not appropriately employed. Trials testing IMPT versus photons in NSCLC require excellent quality control to ensure study results are a product of the treatments, and not the trial execution. Since dosimetric planning, simulation, and setup is entirely different for protons than for photon therapy, having a physics staff trained in proton therapy is key to success. The new proton centers emerging across the globe must provide appropriate levels and types of staff that have the requisite training and experience with this unique modality, or IMPT could hold as much risk of harm as it does benefit.

The coming years will be exciting as more advances are made in proton therapy. Perhaps no cancer type is better suited to reap benefits from these advances than NSCLC, in light of the tissue heterogeneity, depth of tumor sites, and motion issues encountered. We encourage NSCLC patients considered for proton therapy to also be enrolled on trial whenever possible, as we evaluate the potential life-changing improvements in NSCLC treatment with this advanced RT modality.

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Footnote

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