Preface

Proton therapy in non-small cell lung cancer

Radiation therapy has undergone tremendous evolution over the past few decades, from two-dimensional radiation treatment fields based on surface landmarks and bony anatomy, to three-dimensional radiation treatment using cross-sectional anatomy to identify tumor and organ locations. Further advancements such as inverse planning, imaging guided radiation treatment, and adjustments for organ motion with technology such as respiratory motion-gated treatment, have enabled dose escalation to tumor targets while maintaining an acceptable level of toxicity. Although photon-based radiation treatment can now deliver high doses of radiation that are tightly conformed to complex target volumes, the penetrating nature of photon radiation means a significant volume of normal tissue will also be subject to a low-dose radiation bath.

Proton radiation has been under investigation for cancer treatment since the 1950s. The physical characteristics of the proton beam, with most of the dose deposition occurring in the Bragg peak without exit dose, was thought to be advantageous over photon-based radiation in certain scenarios. It could improve the therapeutic ratio of radiation treatment by delivering a high dose of radiation to a tumor target, with minimal dose to normal tissues distal to the target. Similar to photon-based radiation treatment, proton radiation technology has also evolved over the past decades. Older proton therapy machines employ passive scattering technology, using patient-specific beam-modifying devices to conform the dose to the treatment volume. Newer proton therapy machines often employ scanning beam technology, such as pencil beam scanning. The article by St. James *et al.* in this issue compares the advantages and disadvantages of both technologies, specific to the treatment of lung cancer. Dose calculation algorithms have also been improving, especially in the era of increased computing power. The articles by Maes *et al.* and Saini *et al.* look at the increased dosimetric accuracy of Monte Carlo dose calculations compared with standard algorithms for scanning beam technology in the treatment of lung cancer. Another technologic advancement that has improved photon-based treatment has been image-guided radiation treatment; for example, using a cone-beam CT to localize a lung tumor prior to performing stereotactic ablative radiotherapy (SABR) for lung cancer. Image guidance for proton therapy has lagged behind photon-based machines, but the article by Zhang *et al.* detail the current developments in image guidance for proton treatment.

Radiation therapy for lung cancer has seen exciting developments as well as disappointments over the recent years. For early stage lung cancer, the development of SABR has produced local control rates of >95% with minimal toxicity for patients with small, peripheral tumors (1,2) However, central tumors and larger tumors remain a management challenge, and the article by Gomez *et al.* reviews the role of proton therapy in early-stage lung cancer. For resectable stage III non-small cell lung cancer (NSCLC), the role of post-operative radiation therapy (PORT) has long been a topic of controversy, with older clinical series showing the toxicity of treatment was potentially detrimental to patient survival (3). Shepherd *et al.* review the role of proton therapy in this patient population, and the potential for decreasing treatment toxicity with proton radiation. For patients with unresectable stage III NSCLC, RTOG 0617 showed that uniform dose escalation over an unselected patient population was detrimental to survival (4). It also showed that normal tissue dose (heart dose) and toxicity (maximum esophagitis grade) are highly correlated with survival. Liao *et al.* review the potential advantages of proton radiation in the definitive chemoradiation setting, including the possibility of lower normal tissue dose with advanced proton treatment planning, such as with intensity-modulated proton therapy (IMPT).

With improvements in and intensification of systemic therapy for lung cancer, radiation therapy is increasingly important to establish local control of disease as well as limit toxicity. The recently published PACIFIC trial has established a year of adjuvant checkpoint-inhibitor therapy as standard of care for patients after chemoradiation for locally advanced NSCLC (5). One toxicity of checkpoint inhibitor immunotherapy is pneumonitis, and the most frequent cause of treatment discontinuation in the PACIFIC trial was pneumonitis or pneumonia. Advanced proton therapy techniques, such as IMPT, can decrease radiation dose to the lung in some patients, which could become increasingly important in the era of immunotherapy. Proton therapy may also work synergistically with immunotherapy, perhaps above and beyond what could be achieved with photon radiation, as reviewed in Lee *et al.* As systemic therapy improves for lung cancer with both targeted agents as well as immunotherapy, some patients have long term systemic control of disease, and isolated local lung tumor recurrence is increasingly common. Chao *et al.* review the data for proton therapy in this challenging clinical scenario, where reirradiation is often impossible to perform with photon radiation.

Beyond NSCLC, proton therapy also has a potential role in the treatment of other thoracic malignancies, such as small cell lung cancer, which often has similar treatment volumes as locally advanced NSCLC. Verma *et al.* review the rationale and evidence of proton therapy in this population. The dosimetric advantages of proton radiation in treating the mediastinum while sparing the heart and lungs make it attractive for the treatment of thymoma, which often has an indolent course with long patient survival, and this is reviewed by Zhu *et al.* For mesothelioma, the toxic nature of the radiation treatment means proton therapy could potentially reduce side effects of treatment to improve outcomes, as reviewed by Badiyan *et al.* While evaluating the implementation of technologies, multiple factors must be considered including the cost of treatment, expected increase in efficacy, as well as potential decrease in long- and short-term toxicity. An exploratory analysis is presented for proton therapy in locally advanced NSCLC in the paper by Smith *et al.*

In conclusion, we present in this issue articles that show proton therapy is an important tool in the era of precision oncology, where the goal is for personalized radiation therapy that achieves the right dose to the tumor, with the minimum possible toxicity, and maximal efficacy. Proton therapy is not expected to be uniformly superior for all patients in all scenarios, but it is expected to provide dosimetric advantages that translate into superior clinical outcomes for the right patient, at the right time.

Acknowledgements

None.

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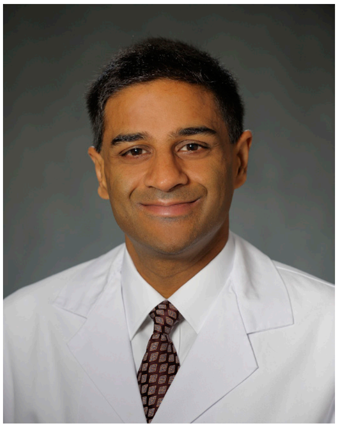

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doi: 10.21037/tlcr.2018.04.13
Conflicts of Interest: The authors have no conflicts of interest to declare.
View this article at: http://dx.doi.org/10.21037/tlcr.2018.04.13

Cite this article as: Rengan R, Zeng J. Proton therapy in non-small cell lung cancer. Transl Lung Cancer Res 2018;7(2):103-105. doi: 10.21037/tlcr.2018.04.13

