Lung Cancer

12

Daniel Gomez, Heng Li, Xiaodong Zhang, and Steven Lin

Contents

12.1 Introduction

Lung cancer is one of the most common malignancies, accounting for approximately 225,000 new cases and 160,000 deaths per year [1]. Treatment of lung cancer is dependent on stage, with early stages treated by surgery or radiation alone and more advanced tumors receiving bi- or trimodality therapy.

Several studies have demonstrated a dosimetric benefit of particle therapy over intensity-modulated radiation therapy (IMRT) in select cases of lung cancer [2–4]. This dosimetric superiority has been shown in cases of early-stage and locally advanced disease, as well as when comparing 3D conformal therapy and IMRT with

D. Gomez (✉) • S. Lin
Department of Radiation Oncology, MD Anderson Cancer Center, Houston, TX, USA
e-mail: dgomez@mdanderson.org

H. Li • X. Zhang
Department of Radiation Physics, MD Anderson Cancer Center, Houston, TX, USA

N. Lee et al. (eds.), *Target Volume Delineation and Treatment Planning for Particle Therapy*, Practical Guides in Radiation Oncology,
https://doi.org/10.1007/978-3-319-42478-1_12

proton beam therapy (PBT). Notably, the improvement in normal tissue dose has primarily been present in the low-dose regions, such as the volume receiving 5 and 10 Gy(RBE) (V5 and V10, respectively). This selective benefit is due to the sharp dose buildup with PBT. The "low-dose bath" advantage of PBT is not present with advanced photon techniques.

With regard to clinical outcomes, particle therapy has been reported both for early-stage and locally advanced NSCLC [5–9]. In these studies, clinical outcomes appear to be similar to improved compared to that observed with advanced photon modalities such as IMRT and VMAT. One randomized trial has recently been reported comparing particle therapy to photons in the setting of locally advanced NSCLC. Specifically, MD Anderson Cancer Center and Massachusetts General Hospital performed a phase II randomized study comparing IMRT with passive scattered PBT in locally advanced NSCLC. The results have recently been reported in abstract form, and no statistical differences were found between the two modalities with regard to recurrence or grade ≥ 3 pneumonitis. Future analyses from this study are focusing on comparing imaging data, blood samples, further toxicity endpoints, and quality of life to determine how these factors may impact outcomes.

The dosimetric and clinical reports of particle therapy in lung cancer can thus be summarized as follows. There appears to be a dosimetric benefit for proton therapy in certain clinical scenarios, but there is not strong evidence that "all comers" with lung cancer benefit clinically from this treatment compared to advanced photon techniques. Thus, selection of patients is of critical importance, particularly when a passive scattering technique is used. These selection criteria will be discussed further below.

Small cell lung cancer (SCLC) almost always presents as locally advanced or metastatic and therefore has similar simulation, target delineation, and planning principles that apply in PBT. However, experience is very limited. In one report of six patients with a median follow-up time of 12 months, 1-year overall survival and progression-free survival rates were 83% and 66%, respectively [10]. Thus, while much of the discussion on NSCLC with regard to particle therapy techniques can be extrapolated to SCLC, more investigation is needed on outcomes with PBT, including rates of local control and the benefit of such modalities as IMPT.

12.2 Simulation, Target Delineation, and Radiation Dose/Fractionation

Patients should be simulated with their arms above their head for beam arrangement selection not dissimilar to proton techniques. An immobilization device of the upper body should be used in conjunction with 4D image acquisition to capture respiratory motion. If patients cannot raise their arms above their head, the simulation can be done with the arms at the side, though this setup may markedly limit the potential for a dosimetric benefit, particularly if passive scattering PBT is being used.

For both node-negative and node-positive disease, involved field techniques are used with 4D planning regardless of whether a photon or proton technique is utilized.

The gross tumor volume (GTV) is contoured using the CT scan of the chest with contrast and PET scan for guidance, along with histologic findings on the mediastinoscopy or endobronchial ultrasound.

There are two potential approaches for expanding on the GTV to capture both internal motion and microscopic disease. The first involves an expansion of the GTV to the CTV, followed by a further expansion to the ITV to account internal motion, followed by a PTV expansion for daily variations in patient position and movement. The second technique, which is often utilized at our institution, is performed by delineating the GTV and then assessing for internal motion. We then define a structure called the iGTV, which is then expanded to create the iCTV (which is very similar to the ITV). The advantage of the latter approach is that internal motion is being assessed on gross disease, the motion of which may be easier to delineate.

For early-stage lung cancer/SBRT, per RTOG standards, no distinct CTV margin is included, and only a PTV is delineated. For locally advanced disease, standard GTV to CTV treatment margins from the GTV (or iGTV) to CTV are 0.6–0.8 cm to control for microscopic disease, as have been defined on prior pathologic studies [11].

With regard to expansion to a planning target volume (PTV) for proton therapy, note that there is not a standard uniform PTV as exists with photon planning, which is secondary to patient setup error and is typically fixed (e.g., at 0.5–1.0 cm). Rather, the PTV includes two components: (1) *setup margin*, which takes into account day to day setup errors and is dependent on the image-guided radiation therapy (IGRT) method that is used, and (2) *dosimetric margin*, which is field-specific and encompasses proximal, distal, and lateral margins for that particular field (due to dose uncertainty in the beam path).

The PTV setup margin for PBT is 0.5 cm for photon techniques and is an extension directly from the GTV. However, this setup margin presumes that CBCT is available for daily localization. If daily CT imaging is not available, we would recommend strong consideration of fiducial placement, with daily kV imaging during treatment and a 0.5–1.0 cm PTV setup margin.

For locally advanced lung cancer (NSCLC or SCLC), the following PTV margin is utilized: 1.0–1.5 cm without daily image-guided radiation therapy (IGRT), such as kV imaging or cone-beam CT scan; 0.5–1.0 cm for either 4D CT planning or CBCT, but not both; 0.5 cm for 4D CT planning and daily kV imaging; and 0.3 cm for 4D CT planning and CBCT guidance.

The field-specific dosimetric margin is dependent on the water-equivalent range relative to the most proximal and distal points of the CTV from a specific beam angle and typically ranges from approximately 0.5 to 1.0 cm.

There are several 1–10 fraction dose regimens which have been reported and that are acceptable for PBT. In our institution, proton doses are reported with RBE = 1.1, and we routinely utilize a dose of 50 Gy in 4 fractions for peripheral disease and 70 Gy(RBE) in 10 fractions for central disease [12–14]. For locally advanced NSCLC treated with chemotherapy and radiation, the standard dose is 60 Gy(RBE) in 30 fractions, based on the recently published RTOG 0617 trial demonstrating no

benefit to dose escalation to 74 Gy [15]. For SCLC, the standard-dose regimen remains 45 Gy(RBE) in 30 fractions delivered twice daily based on the results of a randomized trial comparing once daily to twice daily radiation [16]. However, the ongoing trial RTOG 0538/CALGB 30610 is currently comparing this standard regimen to a 7-week daily course of 70 Gy(RBE) in 35 fractions.

Simultaneous integrated boost regimens have been applied to the lung cancer setting as well [17–20], and multiple studies are ongoing evaluating the safety and efficacy of this approach.

12.3 Patient Positioning, Immobilization, and Treatment Verification

As noted above, patients should be simulated with the arms above their head if feasible and with upper indexed body immobilization.

For daily treatment verification, most patients undergo daily kV imaging and at least one verification simulation to ensure that there have not been substantial changes in tumor volume or differences in patient anatomy that would warrant replanning. This midtreatment verification is particularly important with particle

Table 12.1 Key definitions in PBT, dosing recommendations for locally advanced NSCLC, and SCLC

	SABR	Locally advanced NSCLC	SCLC
Prescription dose/ fractions	Many 1–10 fraction regimens in use. MDACC regimen: peripheral, 12.5 Gy(RBE) × 4 fractions; central, 7Gy(RBE) × 10 fractions	Standard regimen 60 Gy(RBE) in 30 fractions with concurrent chemotherapy	Standard regimen 45 Gy(RBE) in 30 fractions twice daily with concurrent chemotherapy
iGTV to CTV margin	0 cm	0.6–0.8 cm	0.6–0.8 cm
CTV to PTV setup margin	0.5 cm (GTV to PTV) if daily CT available. If not available, 0.5–1.0 cm, ideally with fiducial placement	1.0–1.5 cm without daily IGRT 0.5 cm with daily kV imaging 0.3 cm with daily CBCT	1.0–1.5 cm without daily IGRT 0.5 cm with daily kV imaging 0.3 cm with daily CBCT
Daily treatment verification	CT scanning (e.g., CBCT, CT-on-Rails) if available and strongly recommended. If not available, strongly consider fiducial placement and then daily kV imaging with 0.5–1.0 cm setup margin	Daily kV imaging, weekly CBCT if available	Twice daily kV imaging (with each fraction), weekly CBCT if available
Verification simulation	None	At least 1 time during treatment (week 3–4), more if significant tumor changes are observed	Consider after first week of treatment if bulky disease

Table 12.2 Dosimetric constraints for PBT in standard fractionated radiation delivered once daily

Normal structure	Dose constraint
Spinal cord	Maximum dose ≤45 Gy
Heart	V30 ≤ 45 Gy(RBE), mean dose <26 Gy(RBE)
Esophagus	Mean dose < 34 Gy(RBE), V50 < 50%
Total lung	Mean dose < 20 Gy(RBE), V20 < 35%
Kidney	20 Gy(RBE) < 33% of bilateral kidney
Liver	V30 ≤ 40%

therapy, where seemingly minor differences in these parameters can have pronounced dosimetric effects.

If in-room CT capability is present, we recommend weekly cone-beam CT scans in addition to the midtreatment verification scan (Table 12.1).

12.4 Dose Constraints

Many constraints exist for PBT, which are based upon the number of fractions being delivered; constraints are from photon therapy. These constraints can be found through the National Comprehensive Cancer Network guidelines (www.nccn.org). For standard fractionated radiation delivered once daily, Table 12.2 depicts our institutional constraints. For twice daily regimens, such as that given in SCLC, similar constraints are used with the exception of the spinal cord dose, which should be limited to a maximum dose of <40 Gy(RBE).

12.5 Proton Beam Therapy Planning

12.5.1 Passive Scattering PBT Planning

12.5.1.1 Patient Selection

Patient selection for passive scattering is of importance because a non-negligible percentage of patients will have superior plans with advanced conformal techniques, such as IMRT. There are several reasons why some photon plans may be improved compared to PBT. First, there are some limitations in beam angles with passive scattering PBT due to uncertainty of dose in the beam path. Second, passive scattering PBT requires a "backstop" in order to provide much of the sharp dose falloff, which can be difficult in the context of early-stage, parenchymal lung tumors. Without high-density tissue distal to the target, dose "spikes" can occur that can then substantially affect the dosimetry. The high-dose spikes may contribute to more dose to the normal tissues than necessary and thus lead to toxicity.

With these limitations in mind, from a dosimetric standpoint, the following patients are thus good candidates for passive scattering PBT compared to IMRT: (1) location of tumor in tissue that can provide a suitable backstop that utilizes the dose falloff properties of proton therapy; (2) IMRT not feasible due to inability to meet low-dose constraints, such as V5, V10, or V20; and (3) anterior mediastinal tumors in that are proximal to the heart, lung, spinal cord, and esophagus.

12.5.1.2 Treatment Planning

A review of the passive scattering planning approach at MDACC can demonstrate several key principles of this modality, as well as its relative benefits and limitations. An example of this process is as follows. First, the physician contours the appropriate GTV and CTV and specifies the setup margin for PTV that should be used. Second, in order to provide adequate coverage of the target, all iGTV contours that overlap with lung parenchyma are overridden to represent solid tissue. If not overridden, the proton beam may "undershoot" the intended target. However, it should also be noted that doing so also creates the dosimetric disadvantage of potentially "overshooting" the tumor in certain phases of the respiratory cycle [21]. Third, the tissue in the diaphragm is overridden so that the diaphragm does not enter the treatment field, producing an inadequate distal margin (with again the risk of overshooting the target in specific cycles).

The fourth step is beam selection using several criteria. Beams are generally avoided that traverse through breast tissue, to maximize reproducibility and stability. For similar reasons, beams also aren't placed through the edge of the couch. Next, for all beams that range into the spinal cord, adequate margin is ensured through the ETV so that the spinal cord is not overdosed. At our institution, we typically utilize at least one beam that is off-cord, for similar reasons. Finally, a beam is selected that minimizes the aperture size, to reduce the dose to normal tissues. These features of beam selection are demonstrated below (Fig. 12.1).

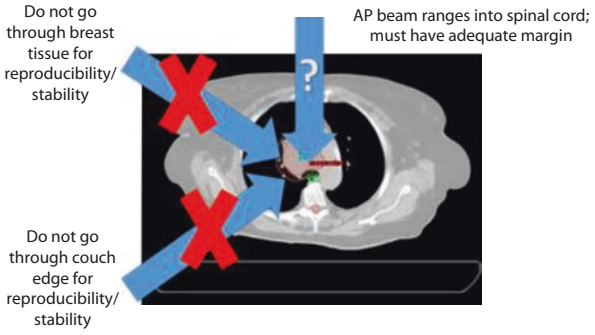

Fig. 12.1 Beam selection in passive scattering PBT

After beam selection, the compensator and aperture are edited to optimize the plan. Then, the weighting of the beam is adjusted as needed to further improve target and normal structure dose. Finally, the robustness of the plan is verified on both the T0 and T50 breathing phases. This consistency verification is again particularly important in PBT, due to the dose sensitivity to changes in tissue heterogeneity [21].

If dose constraints cannot be met at the desired dose with either photon techniques or passive scattering PBT, consideration can be given to implement pencil-beam scanning/intensity-modulated proton therapy (IMPT).

12.5.2 IMPT Treatment Planning

12.5.2.1 Patient Selection

IMPT offers the following benefits over passive scattering PBT: (1) improved conformality and (2) reduced influence of beam placement because dose can be supplemented where necessary through the technique of "patching," which also can reduce the magnitude of hot spots.

IMPT could be suitable for simultaneous integrated boost regimens because by placing the proton Bragg peak in the target, the target dose could be escalated while contributing very little dose to normal tissue. A comparative clinical trial is undergoing at our institution using IMPT and IMRT SIB techniques.

Limitations of IMPT include (1) higher dose sensitivity to changes in anatomy and tumor size due to the lower number of beams and very high conformality and (2) risk for reduced local control due to interaction between respiratory motion and spot-scanning delivery, leading to target miss through certain phases of the respiratory cycle. Two specific scenarios where this reduced dose to the target has been found in lung cancer are in the development (or reduction) of atelectasis and in changes in tumor size, the former of which is demonstrated in Fig. 12.2.

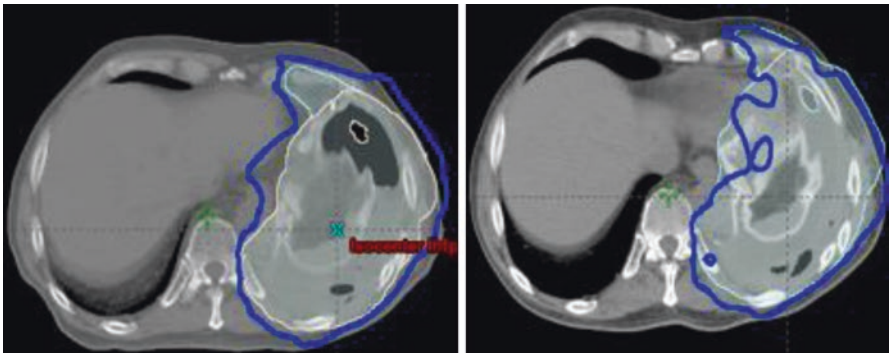

Fig. 12.2 Reduced target dose due to changes in lung volume that occurred approximately midway through a 5-week course of radiation therapy to the lung

IMPT has often been utilized in the following scenarios: (1) mediastinal but laterally displaced tumors in which there is an improved dose distribution to the lung and esophagus, (2) extremely challenging cases where the dose constraints can't be met with other techniques (e.g., large bilateral mediastinal masses), and (3) the re-irradiation setting, where the goal is to almost completely avoid dose to one or more normal structures. However, with the increased availability and experience with IMPT, more patients have been selected for this approach, particularly in locally advanced lung cancer. Several trials are ongoing examining the safety and efficacy of this approach, with particular attention being paid to local control given the concerns with respiratory motion interplay.

IMPT planning differs substantially from that of passive scattering PBT, in several ways: (1) beams are selected largely based on the minimal excursion of the proton beam path length covering the target throughout the respiratory cycle; (2) 4D treatment planning, where multiple phases from the 4DCT were used instead of the average CT, to further reduce the impact of respiratory motion on treatment planning, could be used to further reduce the impact of respiratory motion; (3) given that the technique is sensitive to changes in anatomy and tumor size, robustness optimization is often used to reduce this sensitivity; and (4) robustness evaluation of the treatment plan ensures the dose distribution and dose to target, and OARs remain acceptable with setup and range uncertainty under consideration.

Figure 12.3 shows an example of beam angle selection with water-equivalent thickness (WET) analysis, where the WET change between T0 and T50 were examine. Beam angles including one at 160° were selected for this patient because

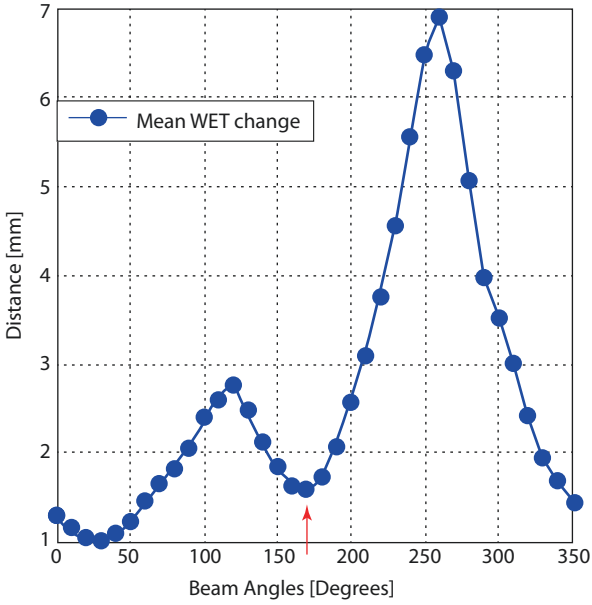

Fig. 12.3 Change in water-equivalent thickness required to cover the target volume between T0 and T50 as a function of beam angle (from Chang 2014)

of the small WET change indicating less impact from the respiratory motion, along with other considerations including patient anatomy and tumor location.

4D treatment planning [22], along with fractionation and delivery techniques such as re-scanning and optimization of the delivery sequence [23], could be used to reduce the impact of intra-fractional respiratory motion for IMPT.

Robustness optimization could lead to reduced sensitivity of the dose distribution in patient to inter-fractional setup and range uncertainties or anatomy change [24] and could be combined with 4D treatment planning [22].

The following Figs. 12.4 and 12.5 shows a sample workflow for IMPT treatment planning [25].

Robustness evaluation is crucial to IMPT planning. For lung cancer cases, we consider a difference of $\leq 5\%$ between the worst-case dose distribution and the nominal dose to be acceptable [25]. If the plan was found to be not robust (quantified by $a > 5\%$ difference), then the plans are typically re-optimized.

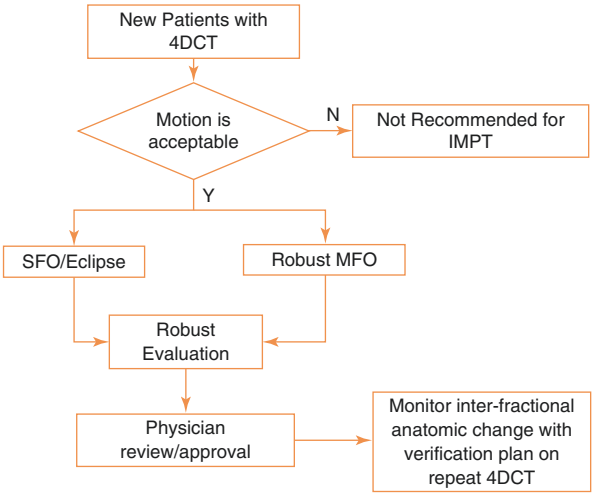

Fig. 12.4 Procedural flow chart for intensity-modulated proton therapy (IMPT) quality assurance. 4D CT Z four-dimensional computed tomography; MFO Z multifield optimization; SFO Z single-field optimization (Chang 2014)

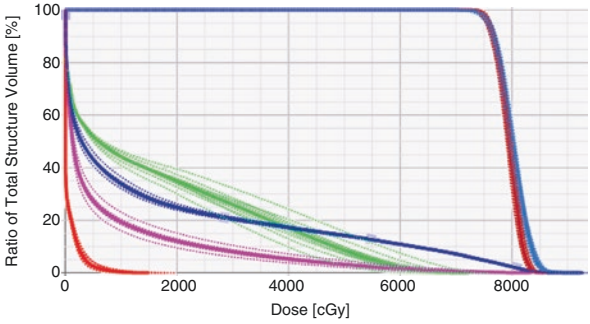

Fig. 12.5 Robustness evaluation of an IMPT plan. *Solid lines* indicate nominal DVH calculated from the time-averaged CT scan; *dotted lines*, DVH calculated from the iso- or relative stopping-power-ratio-shifted scenarios (from Chang 2014)

12.6 Clinical Outcomes of Proton Beam Therapy for Lung Cancer

Several retrospective and prospective single-arm studies have reported outcomes of proton beam therapy for lung cancer. With regard to early-stage cancer, several studies have been published that have demonstrated analogous results to SBRT, with high rates of local control and low toxicity [9, 26–28]. For instance, investigators from Loma Linda examined outcomes for hypofractionated radiation doses of 51–70 Gy(RBE) in 10 fractions over 2 weeks for stage T1/T2N0M0 biopsy proven NSCLC. They reported disease-specific survival rates of 88% and an overall survival of 60% at 4 years. No patient of the 111 reported required steroids for radiation pneumonitis, and central versus peripheral location did not correlate with survival outcomes. The authors therefore concluded that this regimen achieved excellent outcomes, possibly warranting the exploration of further dose escalation [28]. Of course, the primary obstacle in the setting of early-stage disease is the baseline low rate of toxicity and high local control rates with photon-based SBRT techniques, which can lead to reluctance of both physicians and patients to enroll on comparative effectiveness studies. Indeed, one recent trial from MD Anderson Cancer Center attempted to compare these two techniques in centrally located lesions and was closed due to poor accrual.

There has been more momentum for the study of proton beam therapy in the locally advanced setting, due to higher local failure rates and the common difficulty of achieving dose constraints. Therefore, several trials have reported clinical outcomes in this setting as well [29–34]. Again, in the single-arm and retrospective setting, proton beam therapy appears to hold great promise for improving the standard of care in definitive treatment. For example, investigators from Japan [35] retrospectively studied 57 patients with stage III NSCLC treated with PBT, none of whom had received concurrent chemotherapy. A median dose of 74 Gy(RBE) was administered (range 50–85 GY(RBE)) in 2-Gy(RBE) fractions (range 2–6.6 Gy(RBE)). One- and two-year OS rates were 65.5 and 39.4%. After a median follow-up interval of 22 months (for surviving patients), 2-year progression-free survival (PFS) and local control rates were 24.9 and 64.1%. Distant metastasis was the most common site of initial recurrence. In a phase II study by investigators at MD Anderson Cancer Center, [36] the authors reported outcomes with passively scattered PBT and concomitant chemotherapy (weekly carboplatin and paclitaxel) for 44 patients with unresectable stage III NSCLC. One-year OS and PFS rates were 86 and 63%, and the median OS time was 29.4. In this trial, the most common sites of recurrence were distantly (19 patients, 43%) and isolated local failures (4 patients, 9.1%). This cohort was then expanded to 84 patients by Xiang et al. [37]. In this subsequent study, the median OS time was 29.9 months, and the 3-year OS rate was 37.2%. Three-year local recurrence-free survival, distant metastasis-free survival, and a PFS rates were 34.8%, 35.4%, and 31.2%, respectively.

These outcomes compare favorably to prior studies of concurrent chemoradiation in locally advanced NSCLC, particularly the OS rate of almost 30 months. There are several possible reasons for these excellent outcomes, including improved

patient selection, a higher tumor dose leading to improved disease control, and a direct correlation of reduced normal tissue dose and decreased toxicity. However, the premise of clinical superiority with protons versus photon techniques requires rigorous testing through randomized trials. Indeed, MD Anderson Cancer Center and Massachusetts General Hospital conducted a phase II Bayesian randomized trial of intensity-modulated radiation therapy versus passive scattering proton beam therapy for locally advanced lung cancer. In this trial, 149 patients with locally advanced disease were randomized to one of these two techniques at a dose of 60–74 Gy(RBE), with each patient receiving the highest dose level that could be achieved within this range without exceeding critical dose constraints. The two co-primary endpoints were local recurrence and Grade 3 or higher radiation pneumonitis. The authors found no difference in either co-primary endpoint (or when put together) between the modalities [38]. Currently, the two modalities are being tested in a larger phase III study, with OS as the primary endpoint (RTOG 1308, NCT01993810).

12.7 Discussion and Future Directions

Motion management in IMPT for lung cancer is of critical importance because of the sensitivity of the proton beam to the path length change induced by respiratory motion and the anatomy change over time. Currently most patients treated with IMPT are treated with free-breathing technique. However, due to concerns of the motion induced uncertainty, the range of the acceptable respiratory motion is usually limited. One of the reports limits the respiratory motion range to <5 mm [21, 25]. Advanced motion management techniques are being developed to make IMPT available to more patients. For example, real-time gated proton beam therapy (RGPT) system was recently developed to deliver gated treatment with high efficiency [39]. Another major concern for IMPT in lung cancer is the anatomy change over time. It has been demonstrated that adaptive therapy is necessary for a large proportion of IMPT lung cancer patients even with robustness optimization, and therefore repeating imaging and adaptive therapy is mandatory [24, 25, 40]. It is highly desirable to investigate techniques to reduce the need of or improve the efficiency of adaptive therapy for IMPT.

From a clinical outcomes standpoint, prior studies have demonstrated feasibility with respect to producing similar, if not improved, results when compared to photon-based techniques. When examining early versus locally advanced stages of disease, the most promising outcomes have been generated in the locally advanced setting, where dose constraints are more difficult to meet and locoregional failures can be as high as 50%. Disappointingly, after apparent superiority to 3D-CRT in dosimetric, retrospective, and prospective trials, the only reported prospective randomized comparative effectiveness trial demonstrated no difference in either toxicity or local control. The investigators of that trial have outlined several potential reasons for this lack of benefit, including the treatment of all patients with 3D planning techniques (rather than IMPT), as well as the fact that adequate proton delivery

likely requires a learning curve, a premise that was supported by the results of this trial. And indeed, this concept is being further tested in an ongoing cooperative group trial, with OS as the primary endpoint. However, given these negative results, it is clear that the threshold for justification of proton beam therapy in "all comers" has been elevated. Therefore, future trials are likely to focus on appropriate patient selection, as well as novel delivery techniques such as spot-scanning proton arc (SPArc) therapy [41] and dynamic collimation [42], which could offer robust delivery with further reduce dose to OARs.

References

1. Larsen H, Sorensen JB, Nielsen AL, Dombernowsky P, Hansen HH. Evaluation of the optimal duration of chemotherapy in phase II trials for inoperable non-small-cell lung cancer (NSCLC). Ann Oncol. 1995;6(10):993–7.
2. Zhang X, Li Y, Pan X, et al. Intensity-modulated proton therapy reduces the dose to normal tissue compared with intensity-modulated radiation therapy or passive scattering proton therapy and enables individualized radical radiotherapy for extensive stage IIIB non-small-cell lung cancer: a virtual clinical study. Int J Radiat Oncol biol Phys. 2010;77(2):357–66.
3. Wang C, Nakayama H, Sugahara S, Sakae T, Tokuuye K. Comparisons of dose-volume histograms for proton-beam versus 3-D conformal x-ray therapy in patients with stage I non-small cell lung cancer. Strahlenther Onkol. 2009;185(4):231–4.
4. Chang JY, Zhang X, Wang X, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in stage I or stage III non-small-cell lung cancer. Int J Radiat Oncol biol Phys. 2006;65(4):1087–96.
5. Nguyen QN, Ly NB, Komaki R, et al. Long-term outcomes after proton therapy, with concurrent chemotherapy, for stage II–III inoperable non-small cell lung cancer. Radiother Oncol. 2015;115(3):367–72.
6. McAvoy SA, Ciura KT, Rineer JM, et al. Feasibility of proton beam therapy for reirradiation of locoregionally recurrent non-small cell lung cancer. Radiother Oncol. 2013;109(1):38–44.
7. Ishikawa Y, Nakamura T, Kato T, et al. Dosemetric parameters predictive of rib fractures after proton beam therapy for early-stage lung cancer. Tohoku J Exp Med. 2016;238(4):339–45.
8. Hoppe BS, Henderson R, Pham D, et al. A phase 2 trial of concurrent chemotherapy and proton therapy for stage III non-small cell lung cancer: results and reflections following early closure of a single-institution study. Int J Radiat Oncol biol Phys. 2016;95(1):517–22.
9. Bush DA, Cheek G, Zaheer S, et al. High-dose hypofractionated proton beam radiation therapy is safe and effective for central and peripheral early-stage non-small cell lung cancer: results of a 12-year experience at Loma Linda University medical Center. Int J Radiat Oncol Biol Phys. 2013;86(5):964–8.
10. Colaco RJ, Huh S, Nichols RC, et al. Dosimetric rationale and early experience at UFPTI of thoracic proton therapy and chemotherapy in limited-stage small cell lung cancer. Acta Oncol. 2013;52(3):506–13.
11. Giraud P, Antoine M, Larrouy A, et al. Evaluation of microscopic tumor extension in non-small-cell lung cancer for three-dimensional conformal radiotherapy planning. Int J Radiat Oncol Biol Phys. 2000;48(4):1015–24.
12. Kelly P, Balter PA, Rebueno N, et al. Stereotactic body radiation therapy for patients with lung cancer previously treated with thoracic radiation. Int J Radiat Oncol Biol Phys. 2010;78(5):1387–93.
13. Chang JY, Roth JA. Stereotactic body radiation therapy for stage I non-small cell lung cancer. Thorac Surg Clin. 2007;17(2):251–9.

14. Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2008;72(4):967–71.
15. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16(2):187–99.
16. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med. 1999;340(4):265–71.
17. Zhang W, Liu C, Lin H, et al. Prospective study of special stage II (T2b-3N0M0) non-small-cell lung cancer treated with hypofractionated-simultaneous integrated boost-intensity modulated radiation therapy. J Cancer Res Ther. 2015;11(2):381–7.
18. Weiss E, Fatyga M, Wu Y, et al. Dose escalation for locally advanced lung cancer using adaptive radiation therapy with simultaneous integrated volume-adapted boost. Int J Radiat Oncol Biol Phys. 2013;86(3):414–9.
19. Ji K, Zhao LJ, Liu WS, et al. Simultaneous integrated boost intensity-modulated radiotherapy for treatment of locally advanced non-small-cell lung cancer: a retrospective clinical study. Br J Radiol. 2014;87(1035):20130562.
20. Dirkx ML, van Sornsen De Koste JR, Senan S. A treatment planning study evaluating a 'simultaneous integrated boost' technique for accelerated radiotherapy of stage III non-small cell lung cancer. Lung Cancer. 2004;45(1):57–65.
21. Kang Y, Zhang X, Chang JY, et al. 4D proton treatment planning strategy for mobile lung tumors. Int J Radiat Oncol Biol Phys. 2007;67(3):906–14.
22. Liu W, Schild SE, Chang JY, et al. Exploratory study of 4D versus 3D robust optimization in intensity modulated proton therapy for lung cancer. Int J Radiat Oncol Biol Phys. 2016;95(1):523–33.
23. Li H, Zhu XR, Zhang X. Reducing dose uncertainty for spot-scanning proton beam therapy of moving Tumors by optimizing the spot delivery sequence. Int J Radiat Oncol Biol Phys. 2015;93(3):547–56.
24. Li H, Zhang X, Park P, et al. Robust optimization in intensity-modulated proton therapy to account for anatomy changes in lung cancer patients. Radiother Oncol. 2015;114(3):367–72.
25. Chang JY, Li H, Zhu XR, et al. Clinical implementation of intensity modulated proton therapy for thoracic malignancies. Int J Radiat Oncol Biol Phys. 2014;90(4):809–18.
26. Bush DA, Slater JD, Bonnet R, et al. Proton-beam radiotherapy for early-stage lung cancer. Chest. 1999;116(5):1313–9.
27. Chang JY, Komaki R, Wen HY, et al. Toxicity and patterns of failure of adaptive/ablative proton therapy for early-stage, medically inoperable non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2011;80(5):1350–7.
28. Do SY, Bush DA, Slater JD. Comorbidity-adjusted survival in early stage lung cancer patients treated with hypofractionated proton therapy. J Oncol. 2010;2010:251208.
29. Niho S, Motegi A, Kirita K, et al. Proton beam therapy (PBT) and concurrent chemotherapy using cisplatin (CDDP) and vinorelbine (VNR) for locally advanced non-small cell lung cancer (NSCLC). J Clin Oncol. 2015;33(15):e18525.
30. Nguyen Q, Komaki R, Liao Z, et al. The 5-year outcome for patients diagnosed with locally advanced non-small cell lung cancer treated with definitive concurrent chemotherapy and proton beam therapy. Int J Radiat Oncol. 2014;90:S19–20.
31. Lievens Y, Verhaeghe N, de Neve W, et al. Proton radiotherapy for locally-advanced non-small cell lung cancer, a cost-effective alternative to photon radiotherapy in Belgium? J Thorac Oncol. 2013;8:S839–S40.
32. Koay EJ, Lege D, Mohan R, Komaki R, Cox JD, Chang JY. Adaptive/nonadaptive proton radiation planning and outcomes in a phase II trial for locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2012;84(5):1093–100.

33. Kesarwala AH, Ko CJ, Ning H, et al. Intensity-modulated proton therapy for elective nodal irradiation and involved-field radiation in the definitive treatment of locally advanced non-small-cell lung cancer: a Dosimetric study. Clin Lung Cancer. 2015;16(3):237–44.
34. Kesarwala AH, Ko C, O'Meara WP, et al. Feasibility of proton therapy for elective nodal irradiation in patients with locally advanced non-small cell lung cancer. Int J Radiat Oncol. 2012;84(3):S577–S8.
35. Oshiro Y, Mizumoto M, Okumura T, et al. Results of proton beam therapy without concurrent chemotherapy for patients with unresectable stage III non-small cell lung cancer. J Thorac Oncol. 2012;7(2):370–5.
36. Chang JY, Komaki R, Lu C, et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. Cancer. 2011;117(20):4707–13.
37. Xiang ZL, Erasmus J, Komaki R, Cox JD, Chang JY. FDG uptake correlates with recurrence and survival after treatment of unresectable stage III non-small cell lung cancer with high-dose proton therapy and chemotherapy. Radiat Oncol. 2012;7:144.
38. Liao ZX, Lee JJ, Komaki R, Gomez DR, O'Reilly M, Allen P, Fossella FV, Heymach JV, Blumenschein GR, Choi NC, Delaney T, Hahn SM, Lu C, Cox JD, Mohan R. Bayesian randomized trial comparing intensity modulated radiation therapy versus passively scattered proton therapy for locally advanced non-small cell lung cancer. J Clin Oncol. 2016;34(suppl):abstr 8500.
39. Yamada T, Miyamoto N, Matsuura T, et al. Optimization and evaluation of multiple gating beam delivery in a synchrotron-based proton beam scanning system using a real-time imaging technique. Phys Med. 2016;32(7):932–7.
40. Hoffmann L, Alber M, Jensen MF, Holt MI, Moller DS. Adaptation is mandatory for intensity modulated proton therapy of advanced lung cancer to ensure target coverage. Radiother Oncol. 2017;122(3):400–5.
41. Ding X, Li X, Zhang JM, Kabolizadeh P, Stevens C, Yan D. Spot-scanning proton arc (SPArc) therapy: the first robust and delivery-efficient spot-scanning proton arc therapy. Int J Radiat Oncol Biol Phys. 2016;96(5):1107–16.
42. Smith B, Gelover E, Moignier A, et al. Technical note: a treatment plan comparison between dynamic collimation and a fixed aperture during spot scanning proton therapy for brain treatment. Med Phys. 2016;43(8):4693.