

Advances in radiotherapy techniques and delivery for non-small cell lung cancer: benefits of intensity-modulated radiation therapy, proton therapy, and stereotactic body radiation therapy

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Abstract: The 21st century has seen several paradigm shifts in the treatment of non-small cell lung cancer (NSCLC) in early-stage inoperable disease, definitive locally advanced disease, and the postoperative setting. A key driver in improvement of local disease control has been the significant evolution of radiation therapy techniques in the last three decades, allowing for delivery of definitive radiation doses while limiting exposure of normal tissues. For patients with locally-advanced NSCLC, the advent of volumetric imaging techniques has allowed a shift from 2-dimensional approaches to 3-dimensional conformal radiation therapy (3DCRT). The next generation of 3DCRT, intensity-modulated radiation therapy and volumetric-modulated arc therapy (VMAT), have enabled even more conformal radiation delivery. Clinical evidence has shown that this can improve the quality of life for patients undergoing definitive management of lung cancer. In the early-stage setting, conventional fractionation led to poor outcomes. Evaluation of altered dose fractionation with the previously noted technology advances led to advent of stereotactic body radiation therapy (SBRT). This technique has dramatically improved local control and expanded treatment options for inoperable, early-stage patients. The recent development of proton therapy has opened new avenues for improving conformity and the therapeutic ratio. Evolution of newer proton therapy techniques, such as pencil-beam scanning (PBS), could improve tolerability and possibly allow reexamination of dose escalation. These new progresses, along with significant advances in systemic therapies, have improved survival for lung cancer patients across the spectrum of non-metastatic disease. They have also brought to light new challenges and avenues for further research and improvement.

Keywords: Non-small cell lung cancer (NSCLC); stereotactic body radiation therapy (SBRT); proton therapy; intensity-modulated radiation therapy (IMRT)

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Introduction

The 21st century has seen several paradigm shifts in the treatment of non-small cell lung cancer (NSCLC) in early-stage inoperable disease, definitive locally advanced disease, and the postoperative setting. Patients

are increasingly being treated with curative intent rather than palliation. Survival has improved in advanced stages with more aggressive approaches involving combinations of chemotherapy and thoracic radiotherapy (RT) (1). Several chemotherapy agents developed during the 1990s

demonstrated enhanced activity. In addition, the birth of immunotherapy and targeted therapy has revolutionized the treatment of advanced lung cancer. Improved survival rates for inoperable patients with stage III NSCLC have been realized by using “conventional” radiation techniques (2-5) involving the standard dose of 60 Gy delivered over 6 weeks. This dose of radiation was found to be most efficacious in dose-escalation trials in the 1970s and did not change significantly for 20 years. Initial radiation therapy approaches utilized 2-dimensional (2D) imaging for the design of treatment fields. The inherent problems in visualization of tumor and nodal disease on a 2D radiograph necessitated larger radiation fields to cover uncertainty and minimize marginal failures. The tradeoff with these larger fields was an increase in toxicity, which limited use of higher radiation doses.

Local tumor control remained suboptimal in patients treated with conventional RT (even with the addition of chemotherapy) which resulted in renewed interest in strategies to improve local treatment (5). A key driver in the improvement of local control has been the significant evolution in radiation techniques in the last three decades, allowing delivery of more effective radiation doses while limiting doses to normal tissues. With the advent of image-guided radiation therapy (IGRT), techniques have moved from 2D approaches to 3-dimensional conformal RT (3DCRT). The next generation of 3DCRT, intensity-modulated RT (IMRT) and volumetric-modulated arc therapy (VMAT), have enabled even more conformal radiation delivery. Evaluation of altered dose fractionation with these technology advances led to the development of stereotactic body RT (SBRT) for early-stage lung cancer. The recent advent of pencil-beam scanning (PBS) proton therapy has opened new avenues for improving conformity and the therapeutic ratio. SBRT and PBS techniques have placed significant emphasis on motion management, which continues to be among the biggest technical challenges in the use of advanced radiation modalities in lung cancer. Novel monitoring and mitigation strategies have provided the possibility of reducing morbidity/mortality using the standard dose, as well as the possibility of safely escalating the dose to improve oncologic outcomes.

This article reviews the technical advances in RT, their clinical impact, and the associated possibilities for future research in NSCLC. We will focus on progression from 3DCRT to IMRT/VMAT in definitive management of advanced disease, the utility of SBRT in early-stage

inoperable disease, and the advent of proton therapy and its role in early- and late-stage disease.

Technical comparison: 3DCRT and IMRT

3DCRT and challenges

Conventional RT for lung cancer, developed in the 1970s before adoption of computed tomography (CT) for treatment planning, was supplanted by 3DCRT, which uses 3D patient-specific geometry in treatment planning. Despite this progression from conventional RT, limited beam arrangements and uniform dose in each beam in 3DCRT can lead to high doses to organs at risk (OARs) (i.e., normal lungs, heart, spinal cord, and esophagus) because of the simple and relatively large fields (6,7). Several pioneers of the early 3DCRT era published predictors of complications (8-14). Graham *et al.* from Washington University in 1999 demonstrated a correlation between the volume of lung receiving 20 Gy and rates of pneumonitis that remains in use today (8). This analysis demonstrated an 8% rate of grade 3 pneumonitis in patients whose lung volume receiving greater than 20 Gy (V20) was between 22–31%, as compared to 23% for patients whose V20 was >40%. Furthermore, no patients with V20 <32% had grade 5 toxicity. Wang *et al.* performed a retrospective investigation in 223 NSCLC patients treated with concurrent chemotherapy and 3DCRT and found the incidence of grade 3 or higher pneumonitis for patients with V20 >28% was 37% compared to 4% in patients with V20 ≤28% (14). This high risk of complications translated to poor outcomes from increased morbidity and mortality in patients whose disease was controlled. A significant risk of local failures, suggesting a possible utility to dose escalation, was also noted; however, the already high rates of toxicity meant that newer techniques would be required that could change the therapeutic ratio. For these reasons, considerable interest focused on developing and applying treatment planning and delivery techniques that could improve dose conformality (e.g., IMRT).

IMRT is an increasingly common method of lung cancer treatment for both early-stage and locally advanced NSCLC. IMRT treatment plans use advanced technology to modify the intensity of each photon beam via dose-rate alterations and field modulation with multileaf collimators (MLCs). The two main types of IMRT delivery are static and dynamic (or VMAT). Although VMAT has treatment time advantages over static IMRT delivery, no evidence

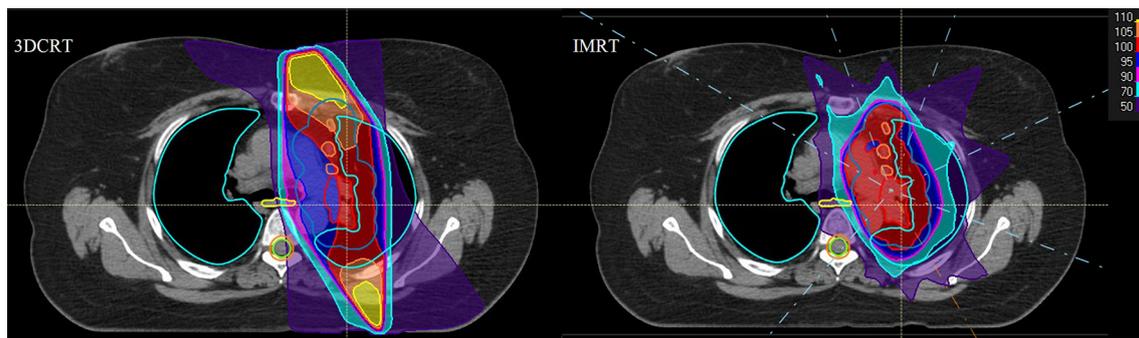


Figure 1 Improved conformity of the high-dose region to the target volume and improved sparing of organs at risk with intensity-modulated radiation therapy compared to 3-dimensional conformal radiation therapy. Gross tumor volume including nodal disease is depicted by the red/orange contour. Spinal cord is depicted by the green contour. Esophagus is depicted by the yellow contour. The relative isodose is depicted in colorwash as per the color scale in the picture.

indicates definitive superiority of one technique over the other (15-18). Regardless of IMRT technique, treatment plans are usually inversely optimized by a treatment planning system and generate conformal dose distributions with sharper dose falloff around treatment structures, thereby theoretically reducing collateral dose to normal tissue and resulting morbidity associated with radiation dose to OARs (*Figure 1*: esophagus and spinal cord) (13,19-21).

To test the hypothesis of reduced OAR dose with IMRT, several studies have compared the dosimetry of 3DCRT and IMRT in treating NSCLC (22-25). Grills *et al.* showed that IMRT can reduce the lung V20 by 15% and esophagus V50 by 40% in node-positive patients (23). Christian *et al.* evaluated five IMRT plans using three, five, seven, and nine equally spaced coplanar beams and one plan with non-coplanar beams and compared them to six-field, inversely planned, 3DCRT plans for 10 patients (26). Their results demonstrated that the ratio of the percentage of the planning target volume (PTV) covered by the 90% isodose line to the percentage of lung volume receiving 20 Gy (PTV 90/V20) was significantly better in all IMRT plans, except those with three fields, when compared with equivalent 3DCRT plans. Regarding the benefit of an increase in the number of beams in IMRT plans for NSCLC, they showed an increase in PTV90/V20 ratio with the increase in the number of equally spaced coplanar beams. They found that nine beams provided the optimal solution in six of the 10 cases; however, they cautioned that increasing setup times, as well as the risk of increased systematic and random errors, may mitigate the marginal increase in benefit (26). More importantly, they also noted that IMRT plans with <5 beams conferred no notable benefit “compared with

beam-angle optimized 3DCRT plans” (26).

Numerous techniques have been developed recently that can leverage the advantages of IMRT with the dynamic motion of MLCs and simultaneous motion of the X-ray source. Intensity-modulated arc therapy (IMAT) is an alternative to tomotherapy proposed by Yu that delivers the radiation dose through single or multiple arcs along with MLC-based modulation to conform the beam to the target and to block critical structures (27). VMAT, as developed by Otto, is a single-arc form of IMAT that also uses a variable dose rate to modulate radiation dose delivery (28).

Motion management and mitigation

These advanced techniques, including VMAT and IMRT, allow delivery of more complex plans while simultaneously decreasing treatment times. In the treatment of NSCLC, however, they heighten concerns about the effects of motion interplay on IMRT delivery. Unlike 3DCRT plans that encompass the entire target through each beam, IMRT plans may block certain regions of the target from certain beams or arc angles (29). These concerns have led to the development of a variety of motion management and mitigation techniques. Breath-hold and abdominal compression are two common methods to reduce tumor motion and, thereby, the average dose to normal lung tissue (30,31). Other management strategies include acquiring 4-dimensional CT (4DCT) to identify tumor motion during breathing cycles and to allow a better estimation of dose delivery to tumors and normal structures (32-37). All of these methods have shown significantly reduced lung V20 (31,38). Finally, significant research exists on beam gating and tumor tracking (39-42). However, inherent

irregularities in patient breathing patterns and the intrinsic delay in dose delivery (i.e., MLC and gantry motion) can lead to increased treatment times and necessitate development of class solutions that are predictive in nature (43-45). Techniques to minimize breathing irregularity including biofeedback and active breathing control may offer additional benefits in improving inter- and intra-fraction reproducibility but additional work to improve reproducibility is needed (46-48). Ongoing research may elucidate techniques that can effectively reduce normal tissue dose without compromising treatment efficiency.

Impact of heterogeneity correction

The increasing complexity of treatment plans results in increasing dependency on accurate dose modeling. One significant advance on this front has been determining the impact of heterogeneous tissue density on dose delivery. Differences in dose calculations with and without heterogeneity corrections for IMRT and SBRT treatments in NSCLC patients have been investigated in several studies that have uniformly demonstrated the necessity for advanced algorithms with heterogeneity corrections to achieve accurate dose calculations (49-54). Vanderstraeten *et al.* compared full Monte Carlo calculations with two different convolution/superposition algorithms and one pencil-beam algorithm for 10 lung cancer patients receiving IMRT (55). They found a better agreement between convolution/superposition and Monte Carlo methods for dose calculation within the target structures. They concluded that none of the dose calculation algorithms could provide results within 5% of the Monte Carlo calculations, and therefore it is imperative to be aware of the impact of the dose calculation algorithm on plan evaluation. Davidson *et al.* determined the accuracy of heterogeneity on dose calculations from two IMRT treatment planning systems against thermoluminescent detectors and radiochromic film measurements positioned in a lung phantom (56). They found that the collapsed cone convolution/superposition dose calculation algorithm provided clinically acceptable results within $\pm 5\%$ of the measurements. They also demonstrated that the pencil-beam algorithm as tested may overestimate the dose to the target. Although Monte Carlo simulations continue to serve as the gold standard for dose calculations, heterogeneity corrections have dramatically improved the accuracy of more efficient but less precise algorithms needed to successfully implement inverse planning IMRT.

Clinical evidence: 3DCRT and IMRT

Although the initial rationales for IMRT and VMAT were largely their dosimetric advantages, numerous retrospective studies have attempted to isolate the clinical benefits of IMRT over conventional external-beam radiation. Some early reports on the benefits of intensity modulation in lung cancer treatment came from the MD Anderson Cancer Center (MDACC) (13,21). Yom *et al.* reviewed rates of toxicity, particularly radiation pneumonitis, in 68 patients with advanced NSCLC treated with concurrent chemotherapy and IMRT from 2002 to 2005 (21). They found that patients treated with IMRT had dramatic and statistically significant decreases in the rate of grade 3 radiation pneumonitis at 1 year compared to 3DCRT patients (8% and 32%, respectively). Liao *et al.* then evaluated an expanded cohort of 496 patients treated between 1999 and 2006, with 318 receiving 3DCRT and 91 receiving 4DCT/IMRT. Their report demonstrated a statistically significant improvement in overall survival (OS), with a hazard ratio of 0.64 (95% CI, 0.41–0.98) when treated with IMRT (13).

The advent of 3DCRT and consequent improvements in toxicity profiles also initiated a series of phase I and II dose-escalation trials that occurred in parallel with development of IMRT. Several authors showed that with the same dose constraints, up to 35% greater RT doses could be given to the target with IMRT than 3DCRT, with the aim of improving local control (23,25,57). Armed with this favorable dosimetric data on toxicity and significant improvements already demonstrated with 3DCRT, several institutions initiated dose-escalation trials in the 1990s and 2000s.

The Radiation Therapy Oncology Group (RTOG) conducted a phase I/II study of dose escalation without concurrent chemotherapy (58) in 177 patients treated using 3DCRT to doses ranging from 70.9 to 90.3 Gy. The results demonstrated that it was safe to escalate radiation dose to 83.8 Gy with a lung V20 of <25% and to 77.4 Gy if the planned lung V20 was between 25% and 36%. Equally important, 90.3 Gy, the highest dose tested, was determined to be too toxic on the basis of two grade 5 toxicities in that population. The safety of dose escalation in the absence of concurrent chemotherapy was also verified by University of Michigan researchers, who escalated the radiation dose from 63 to 103 Gy in 2.1-Gy fractions (59). Most patients (81%) did not receive neoadjuvant chemotherapy. The authors demonstrated improved local control and OS with

higher doses of radiation when patients were divided into three treatment groups (63–69, 74–84, and 92–103 Gy).

The cited studies demonstrated the potential safety and efficacy of dose escalation in lung cancer without concurrent chemotherapy; in the same period, emerging data also indicated a benefit for concurrent chemotherapy. Dose escalation in the setting of concurrent chemotherapy was believed by some to be challenging because of increased risks of cardiopulmonary and esophageal toxicity and the possibility that synergistic effects on tumors could be overshadowed by increased rates of adverse effects. Three phase I/II trials with concurrent chemotherapy were undertaken by RTOG, the University of North Carolina (UNC), and the North Central Cancer Treatment Group (NCCTG) (60–62). RTOG 0117 was designed as a combined phase I/II trial and enrolled 8 patients in cohort 1 of the phase I portion of the trial (60). These patients were treated to a dose of 75.25 Gy in 35 fractions. Two major pulmonary toxicities (grade 3 and grade 5) occurred, leading to a reduction in dose to 74 Gy in 37 fractions. An additional 9 patients were enrolled in the phase I cohort 2, with only one experiencing dose-limiting toxicity (grade 3 esophagitis). The phase II component enrolled a total of 55 patients in the 74-Gy arm, of whom 53 were evaluable (60). This portion of the study showed a median OS of 21.6 months with a more acceptable 10% \geq grade 3 lung toxicity. Similarly, the NCCTG designed a phase I trial to escalate the RT dose from 70 to 78 Gy and found unacceptably high toxicities (50%; 2 of 4 patients) at a dose of 78 Gy (62). Like the RTOG, they concluded that 74 Gy was a safe and tolerable dose. The UNC phase I trial also demonstrated that 74 Gy was a safe dose with concurrent chemotherapy (61).

On the basis of these trials, RTOG launched a phase III trial (RTOG 0617) to determine the benefit of dose-escalated RT utilizing the 74-Gy dose and assessing the benefit of cetuximab (63). The trial was stopped prematurely when results crossed the prespecified boundary for futility. Median OS was 28.7 months in the standard dose (60 Gy) arm and 20.3 months in the dose-escalation arm. Toxicity, particularly severe esophagitis, was more prevalent in the 74 Gy arm (21%) than the 60 Gy arm (7%). Pulmonary toxicity did not differ statistically but marginally favored the standard-dose arm. Despite early termination, this study raised critical questions about dose and toxicity. Of particular importance were questions on rates of completion of prescribed chemoradiation and concerns about volume of disease, adequacy of margins, and heart dose, with

associated cardiac morbidity. A recent secondary analysis of this trial further demonstrated that IMRT was associated with lower cardiac doses and pulmonary toxicities (64). The cardiac dose, particularly V40, was further linked with OS on adjusted analysis (64). Notably, this was despite larger PTV, higher PTV/volume of lung ratio, and more stage IIIB disease in patients receiving IMRT (64). Lastly, there was no difference in OS between IMRT and 3DCRT.

Additional secondary analysis on differences in quality of life (QOL) in the standard- and high-dose arms revealed a correlation between baseline QOL and outcomes (65). The authors also demonstrated that, despite the absence of dramatic differences in physician-graded toxicity profiles, patient-reported QOL was meaningfully and statistically significantly lower in the high-dose arm at 3 months. Participants in the RTOG 0617 trial were stratified by receipt of IMRT or 3DCRT. When the QOL of these two groups was compared using the Functional Assessment of Cancer Therapy-Lung Cancer Subscale, fewer patients in the IMRT arm experienced a decline (21% and 46%, respectively; $P=0.003$). Overall IMRT utilization was similar in the 60- and 74-Gy arms (44.1% and 46.0%, respectively). The difference in QOL, however, occurred despite certain imbalances favoring the 3DCRT group over the IMRT group such as lower PTV volumes [409 and 509 cc, respectively ($P<0.001$)] and fewer stage IIIB patients [31% and 43%, respectively ($P=0.04$)]. Finally, the lower proportion of decline in QOL was persistent for patients receiving IMRT at 12 months, and treatment modality (IMRT or 3DCRT) remained significant in multivariate logistic regression models.

Future directions

Strong emphasis has been placed on determining the cause of decreased survival in the high-dose arm of the RTOG 0617 trial. This is likely to drive further work in not only identifying dosimetric parameters but also innovations in reliably characterizing and quantifying cardiopulmonary toxicity from RT. One increasingly used method is cardiac magnetic resonance imaging, which offers the possibility of evaluating characteristics such as late fibrosis and tissue perfusion. These metrics may help increase sensitivity for detection of radiation-associated cardiac complications beyond frank ischemic changes. Motion management and mitigation will also play a significant role in decreasing dose to surrounding uninvolved lung, and predictive strategies will be integral to minimizing target volumes. Functional

lung imaging may help leverage the inherent heterogeneity of lung function to minimize consequences from normal tissue irradiation. Parallel research into development of radiation toxicity mitigators is underway and may further improve the therapeutic ratio and potentially allow re-evaluation of dose escalation in the future. The next generation of treatment planning is already being investigated and could help further reduce intermediate dose regions despite the potential downside of a larger low-dose bath. One such modality, 4π , involves the use of a highly non-coplanar planning system that utilizes the entire 4π solid angle space in an attempt to improve high-dose conformality at the expense of increased treatment time (66). Much work remains to be done, but dosimetric studies are increasingly highlighting the advantages of 4π treatment planning techniques (67).

SBRT

Introduction

SBRT or stereotactic ablative RT (SABR) is a technique for delivering a high biologically effective dose (BED; usually $BED > 100 \text{ Gy}_{10}$ in contrast to a BED of 72 Gy_{10} with 60-Gy conventional fractionation) to well-localized early-stage NSCLC lesions. SBRT has developed into an excellent option for patients with early-stage NSCLC, especially in cases deemed medically or surgically inoperable. Stereotactic treatment offers the advantage of higher doses per fraction, decreased overall treatment time, and steep dose gradients. However, uncertainty remains over SBRT's superiority to other modes of treatment, such as surgical resection, which remains the standard of care for stage I disease.

SBRT technique

SBRT can be delivered using a 3DCRT, IMRT, or VMAT approach. Typically for the 3DCRT technique, 8–15 static beams are used to generate conformal dose distributions and steep dose gradients. Six megavolt energies are desired over higher energies because of the sharper penumbra resulting from less lateral electron transport (i.e., secondary electrons are lower energy and travel shorter distances). The individual beams are non-opposed, separated by 20° – 30° , and can be coplanar or non-coplanar. Non-coplanar beams have the advantage of increasing the conformality of the

high-dose region but should be used with caution because of inherent shortcomings, including difficulties with portal imaging and associated increase in setup uncertainty, potential for collision and inadequate gantry clearance, possibly longer beam paths, and theoretically longer treatment times.

Beam weighting is adjusted to achieve optimal coverage while minimizing dose to critical structures. The prescription point is also an important consideration for SBRT. In the United States, dose is usually prescribed to between 60% and 90% isodose lines, although the initial Japanese (JCOG 0403) study prescribed to the isocenter (68). Additionally, coverage of the PTV is usually set so that 95% of the PTV is covered by the prescription dose and 99% of the PTV receives at least 90% of the dose. The hot spot is ideally placed in the gross tumor volume (GTV) or should fall within the PTV. To generate rapid falloff, the 50% isodose line can be analyzed to make it conformal around the lesion with few spikes (*Figure 2*). In order to generate the steep gradient, there is very little margin around the target to account for penumbra. Alternative techniques involve prescribing to lower isodose lines, which can also improve dose falloff (69). The dose prescription for SBRT fractionation varies depending on whether the tumor is peripherally located in the chest (25 – $34 \text{ Gy} \times 1$ fraction, $18 \text{ Gy} \times 3$ fractions, 12 – $12.5 \text{ Gy} \times 4$ fractions, or 10 – $12 \text{ Gy} \times 5$ fractions) or centrally located (10 – $12 \text{ Gy} \times 5$ fractions). Because of the high doses involved, tumor size is typically limited to $< 5 \text{ cm}$ in diameter, which prevents overinclusion of treated healthy tissue (70–72).

IMRT/VMAT-based SBRT techniques may have advantages compared with 3DCRT in paraspinal patients in whom motion is limited and where dose constraints to esophagus or spinal cord cannot be achieved. IMRT has the advantage of better coverage of irregular-shaped targets. This approach has also been utilized for peripheral tumors to help reduce dose to the ribs/chest wall. VMAT has the advantage of delivering a beam of radiation over a 358° arc with simultaneous movement of the MLC with varying gantry speed and dose rate. This leads to a reduction in treatment time with increased OAR sparing. And while analyses comparing the impact of technique on normal lung dosimetry are limited, initial results are mixed and warrant careful consideration of the low-dose bath (17,73). Using IMRT/VMAT requires attention to positional misses and uncertainty in dose delivery because of the interplay between MLC movement and respiratory tumor

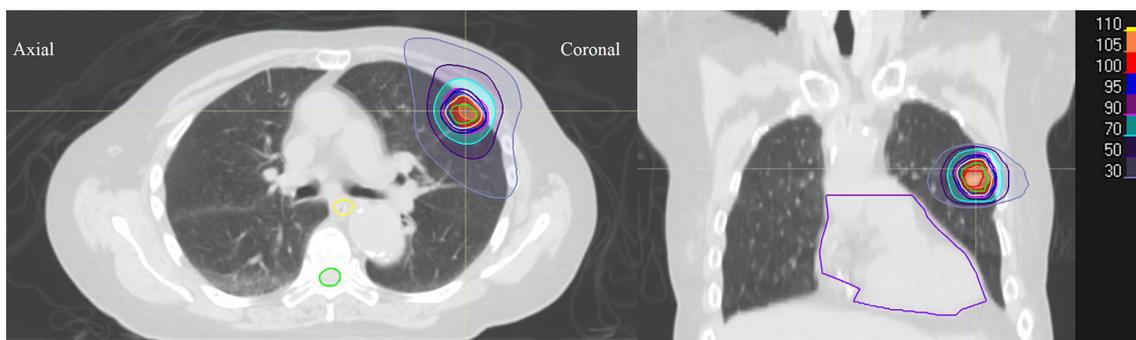


Figure 2 Representative axial and coronal slices demonstrating the dose distribution in a stereotactic body radiation therapy plan. Gross tumor volume including nodal disease is depicted by the red contour. Spinal cord is depicted by the green contour. Esophagus is depicted by the yellow contour. Heart is depicted by the purple contour. The relative isodose is depicted in colorwash as per the color scale in the picture.

motion, as well as dosimetric inaccuracy resulting from tissue heterogeneity and small field sizes. Furthermore, compared with conventionally fractionated therapy, fewer fractions limit the degree of dose-averaging for SBRT regimens. IMRT and VMAT also require significantly more technical resources for planning, quality assurance, and delivery of treatment (74). Lastly, clinical data comparing techniques are limited, and while retrospective data suggest adequate rates of tumor control and toxicity (75), careful consideration of motion mitigation and caution when using modulated beams in tumors with significant (>1 cm) motion are recommended.

The challenges of SBRT treatment planning (i.e., geometric miss, dose heterogeneity, and normal lung dose) are accentuated by the high dose per fraction and low number of fractions. Reliable geometry is of paramount importance in safe and accurate delivery of SBRT, and the regular use of Winston-Lutz tests to check the isocentricity of delivery (<1 mm) and online image guidance to accurately verify tumor and OAR location before and potentially during treatment play significant roles in the reliability of the system (70,76). SBRT dose calculations must also be very precise and, therefore, should include a heterogeneity correction, because lung density can vary up to 0.1× or 0.1 times that of surrounding tissue. This leads to an increased range of photons and secondary electrons that can blur beam edges. Tissue heterogeneity correction depends on beam energy, field size, path length, and lung density and can be calculated accurately using Monte Carlo and superposition/convolution algorithms. The dose calculation grid is frequently set to ≤2 mm for acceptable accuracy (within 1%) (77).

Clinical evidence for SBRT

A number of retrospective reports suggest that conventional RT for early-stage NSCLC results in poor rates of local control and OS. For example, retrospective data from Duke University looked at 156 patients with stage I medically inoperable NSCLC who received a median dose of 64 Gy (range, 50–80 Gy) in 1.2-Gy twice-daily or 3-Gy daily fractions (78). At these doses, deaths were attributed to a high rate of local failure (42%), and the researchers observed that patients with improved local control, which correlated to radiation dose received, also had improved 5-year cause-specific survival (CSS) rates. Population data further validated this; a Surveillance, Epidemiology, and End Results study looked at 4,357 patients with stage I and II NSCLC who did not undergo surgical resection but were treated with conventional RT (79). The researchers concluded that radiation offers a 5–7-month survival benefit but no cure; patients who did and did not receive RT had similar outcomes (5-year OS, 15%). Various literature reviews report 5-year OS to be 30–40% in early-stage NSCLC treated with conventional RT, with doses ≥65 Gy necessary for long-term control (80–82). These data compared adversely with historical surgical series (83–85). Moreover, despite higher doses of conventional radiation, local failure rates remained high (30–70%) (80) and clinicians started exploring the practicality of radiosurgery in treatment of early-stage NSCLC. The use of SBRT for lung cancer was first published in 1991 from clinical work started in Sweden for 42 tumors in 31 cancer patients (86). Various sites, including lung, were treated using a stereotactic body frame for fixation, and prescribed

doses, ranging from 7.7 to 30 Gy/fraction (mean, 14.2 Gy), were given for 1–4 fractions. This early work demonstrated an excellent local control rate (80%) and, more important, revealed minimal complications, suggesting the safety of such an approach. During this time, early studies were also underway in Japan, and the combination of Swedish and Japanese experience spearheaded exploration of SBRT for early-stage NSCLC (87,88).

A phase I dose escalation study from the University of Indiana was conducted on operable but medically ineligible stage IA and IB patients (tumor size <7 cm) (89). For T1 tumors, the maximum tolerated dose (MTD) was not reached (maximum dose =60 Gy), but for tumors >5 cm, the MTD was 72 Gy in 3 fractions. At the time of publication, only one local failure occurred in doses \geq 16 Gy. This work led to RTOG 0236, a phase II trial recruiting resectable but medically inoperable patients whose primary tumor was <5 cm in size and \geq 2 cm from the bronchial tree (because of high rates of grade 5 toxicities seen with centrally located tumors) (69). The radiation dose was 60 Gy in 20-Gy fractions without heterogeneity corrections (18 Gy \times 3 with corrections), and 3-year local control was 90.6%, with survival at 55.8% (90).

In this setting of numerous trials with no clear consensus on optimal dosing, retrospective data published from Japan looked at 245 stage I patients treated with 18–75 Gy targeted at the isocenter, given in 1–22 fractions (87). The group observed a local failure rate of only 8.1% for a $BED_{10} \geq 100$ Gy *vs.* 26.4% when the BED_{10} was <100 Gy. This trend was also seen in survival outcomes, where 3-year OS was 88.4% *vs.* 69.4% with $BED_{10} \geq$ or <100 Gy, respectively.

In this setting of dose escalation, numerous subsequent retrospective analyses began to demonstrate improving local control rates and survival. Grills *et al.* reviewed 124 early-stage NSCLC patients who were not eligible for a lobectomy and underwent either SBRT (n=55) or a wedge resection (n=69) (91). The authors noted better local control with SBRT (recurrence of 4% *vs.* 20%) and similar CSS in both cohorts (93% *vs.* 94%) (91). This equivalence was further supported by data from Onishi *et al.*, who retrospectively evaluated operable stage IA and IB patients treated with a mean BED_{10} of 116 Gy (range, 100–141 Gy) and reported excellent 5-year local control rates of 92%, with OS ranging from 62% to 72%, similar to surgical outcomes (92). A separate group also performed a propensity-matched analysis that compared 64 SABR patients with 64 patients who underwent a video-assisted thoracoscopic surgery lobectomy and determined that post-

SABR locoregional control rates were superior at 1 and 3 years (96.8% and 93.3% *vs.* 86.9% and 82.6%, respectively) with similar OS (93).

Because of this equivalence in survival and improved local control compared with historical surgical data, the STARS trial out of MDACC and the ROSEL trial from The Netherlands attempted to compare SBRT to surgical lobectomy in a randomized trial. Additionally an American College of Surgeons Oncology Group and RTOG combined trial (ACOSOG Z4099/RTOG1021) was also initiated to compare clinical results of SBRT to sublobar resection. Despite early termination, an exploratory QOL analysis of the 22 enrolled patients on the ROSEL trial suggested a possible advantage to SBRT, particularly in health-related QOL (94). All analyses of these trials, however, are extremely limited due to being underpowered, as all the trials closed early due to poor accrual.

To mitigate this statistical limitation, a pooled analysis of the STARS and ROSEL trials was performed with a combined total of 58 T1–T2 (<4 cm) operable patients (95). Patients were randomized in a 1:1 fashion to surgery or SBRT (54 Gy/3 fractions for peripheral lesions given over 5–8 days *vs.* 50 Gy/4 fractions or 60 Gy/5 fractions for central lesions). Surprisingly, OS for the SBRT cohort was superior to the surgical cohort, with 3-year OS of 95% in the SBRT cohort *vs.* 79% with surgery ($P < 0.05$). Toxicity rates were also lower in the SBRT arm than the surgery arm (10% and 44%, respectively, grade 3 or greater toxicities). The surgical arm also had one grade 5 toxicity. These randomized trials, although underpowered, suggest that SBRT may be better tolerated than surgery, with the possibility of improved survival.

Future work

Technological improvements will continue to drive significant innovation in the field of SBRT. To address the above technical challenges in 3DCRT/IMRT/VMAT planning and delivery for SBRT, such as reliable setup, motion management, and accurate target and normal structure delineation, new tools will be needed to improve the therapeutic ratio. Reliable and consistent patient immobilization systems, tumor motion management strategies (such as abdominal compression, breath-hold, respiratory gating, coaching with audiovisual feedback, and intra-fraction tumor-tracking real-time imaging techniques with dynamic beam and/or couch compensation), and improved imaging modalities (such as ^{18}F -FDG PET for

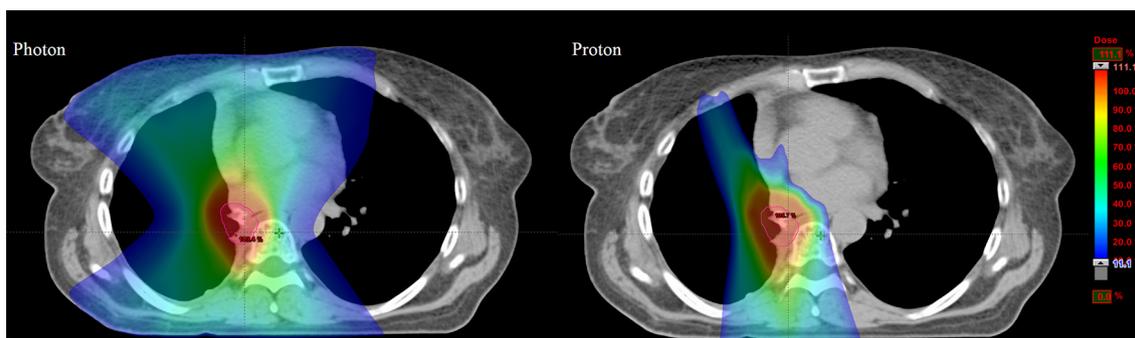


Figure 3 Proton therapy has improved the low-dose bath to the heart and lungs with relatively unchanged high-dose conformity compared with photon therapy. The relative isodose is depicted in colorwash as per the color scale in the picture.

better identification of GTV) all appear to be potential strategies to improve outcomes and decrease toxicity from SBRT. Further clinical research is needed to directly answer the question about equivalence with surgical management, and, to that end, multiple randomized trials, including STABLE-MATES, SABRTooth, VALOR (Veterans Affairs Lung Cancer Surgery Or Stereotactic Radiotherapy), and POSTILV (A Randomized Phase II Trial In Patients With Operable Stage I Non-Small Cell Lung Cancer: Radical Resection Versus Ablative Stereotactic Radiotherapy-RTOG3502), are planned or underway (96). Additionally, emerging data looking at expanding the cohort of patients eligible for SBRT [e.g., patients with central tumors (97) or tumors >5 cm (98)] are promising; and further clinical data are imminent.

Proton therapy

Introduction

Proton therapy offers a unique pattern of energy deposition, with the majority of dose delivered at the end of range, with virtually no exit dose. This property makes the modality particularly attractive for clinical use in the thorax, where numerous radiosensitive critical structures reside in close proximity to the target (i.e., uninvolved lung, heart, esophagus, spinal cord, major vessels, and chest wall) (Figure 3). Dose distributions associated with proton therapy allow the possibility of dose escalation while maintaining current levels of normal tissue exposure. As noted, recent clinical trials suggest that RT can achieve local disease control rates similar to surgical approaches with potentially less toxicity in early-stage NSCLC (90,95). Such results have correlated with significant dose escalation,

in the range of BED >100 Gy₁₀, over doses traditionally achieved with non-stereotactic techniques or in locally advanced disease (88). Results from RTOG 0617, however, have given clinicians pause in attempting to achieve higher doses with traditional 3DCRT or IMRT, considering the worsened outcomes with 74 vs. 60 Gy (63). These outcomes were attributed to, and correlated on multivariate analysis, with increased exposure of normal tissues, such as the heart and esophagus, to significant doses of radiation. These may be areas where, in well-selected patients, proton therapy could offer substantial dosimetric advantages.

Proton therapy technique

Modalities

Proton therapy can now be delivered through several methodologies. The most widely used, passive scattering (PS-PT), employs a single beam that is spread out in the depth dimension by a range-modulator wheel (spread-out Bragg peak) prior to widening in the other dimensions by a scatterer. The lateral edge of the beam is then shaped by an aperture and the distal edge by a compensator. Of note, it is not possible to conform the proximal edge of a PS-PT beam.

On the other hand, the rapidly expanding technique of PBS proton therapy, also known as “spot scanning”, employs scanning magnets to deliver discrete spots of proton beams across a 2D rectilinear grid in the vertical and lateral directions. The range is set for each layer by the energy selection system. This approach allows for both improved proximal dose conformity and intensity-modulated proton therapy (IMPT) within the target. By utilizing multifield optimization and a few (usually 2–4) highly heterogeneous fields that sum to the desired improved dose distribution,

IMPT has shown dosimetric improvements over IMRT and PS-PT in multiple *in silico* studies (99,100). However, these advantages do not come without some increase in uncertainties and diminution in robustness of plan delivery. These uncertainties are highlighted in lung cancers (101-104). In particular, several studies have demonstrated the heightened sensitivity of IMPT to changes in heterogeneity and motion interplay effects as compared with PS-PT (105-109).

Several methods are available to mitigate these uncertainties: robust beam angle selection utilizing water-equivalent thickness optimization, 4DCT-based robust optimization, layer or volumetric “repainting” delivery, spot-sequence delivery optimization, increased fractionation, spot-size modulation, mini-ridge filter utilization, and respiratory gating or breath-hold-based treatment, to name a few (105,110-114). Unfortunately, most of these methods require additional treatment planning software and devices or increase time and logistical burden on planning, quality assurance, and treatment delivery.

Dosimetric studies

Multiple dosimetric planning efforts have revealed the theoretical benefits of proton therapy and especially PBS-PT over 3DCRT and IMRT techniques. For example, planning comparisons in patients with stage I disease demonstrated reductions in mean dose to ipsilateral lung, total lung, heart, esophagus, and spinal cord for proton therapy over 3DCRT (115). Important dosimetric surrogates for pulmonary complications (V5 and V20) were also substantially reduced. Additional work from MDACC and the University of Florida has exhibited the potential for PT to reduce dose to other structures of concern, such as the chest wall in SBRT approaches (116,117).

Similar results were demonstrated in the locally advanced setting. In fact, proton therapy has shown the potential for targeting more comprehensive volumes, including prophylactic treatment of at-risk nodal volumes, with persistently reduced dosimetric markers for complication when compared with photon approaches (117,118). Another approach being evaluated is photon-SBRT with proton mediastinal nodal irradiation (119). These data also encouraged investigators to compare dose-escalated proton planning with 3DCRT and IMRT in both early- and late-stage disease (120,121). In stage I tumors, dose was escalated from 66 Gy to 87.5 CGE without increases in lung V5, V10, or V20 (121). Similarly, in stage III tumors,

74 CGE was achieved versus 63 Gy with 3DCRT, again without worsening of lung dosimetric constraints (121). Spinal cord, heart, esophageal, and integral doses were also all improved with proton therapy. IMPT has shown a particular ability to reduce projected complication rates in early-stage, late-stage, and postoperative patients with lung cancer. As a result, dosimetric studies for dose escalation with IMPT have shown great promise over comparative plans with 3DCRT, IMRT, and PS-PT (99,100,118,122).

When compared with photon techniques, proton therapy in general substantially reduces moderate-to-low-dose exposure of normal lung and nearby critical tissues when targeting lung cancers. Conformality of high-dose regions, however, is compromised due to the increased uncertainty that results from a combination of highly heterogeneous beam paths in the thorax and the finite range of the proton beams. Mitigation of these uncertainties necessitates motion-robust planning approaches that inherently degrade the high-dose conformality. However, the resulting improvements in dosimetric surrogates for complication from photon experiences would seem to allow for further target dose escalation without increasing toxicity.

Clinical outcomes

Numerous clinical trials have been initiated to investigate proton therapy in lung cancer patients; however, initial results have been mixed. A phase I trial performed at MDACC demonstrated in 25 patients the potential for a moderately hypofractionated course (15 fractions of 3–4 Gy/fraction) of proton therapy without concurrent chemotherapy (biologic agents allowed) (123). Two high-grade toxicities occurred, including a tracheoesophageal fistula in a patient who also received bevacizumab, as well as a case of radiation pneumonitis. A Japanese study escalated dose in stage IA and IB patients to 70–94 CGE (3.5–4.9 CGE/fraction) in 37 patients (124). The authors demonstrated excellent local control and low rates of toxicity. Specifically, they achieved 80% local control and 84% survival at 2 years, with only 6 patients experiencing grade 2 and 3 (3 patients each) pulmonary toxicities. Of these 6, 5 patients had stage IB disease, highlighting the significance of the dose-volume effect. Work at Loma Linda University utilizing PS-PT has shown the efficacy and safety of dose escalation from 50 to 70 CGE in 10 fractions in early-stage lung cancers (125,126). They demonstrated

a 4-year OS rate of 51%, and none of the 111 patients required steroid treatment for pneumonitis (125). Further evidence, primarily out of Japan, has strengthened the case for comparable efficacy of proton therapy and photon SBRT, although some high-grade toxicities have been encountered at relatively acceptable rates (125,127,128).

In locally advanced disease, a recent National Cancer Database analysis suggested a possible improvement in OS for stage II and III patients receiving proton therapy compared with photon therapies, however this difference was not significant on propensity-matched analysis (129). Early clinical trials have also been relatively positive. Following the previously cited study at MDACC, Chang *et al.* published the results of a phase II effort investigating concurrent chemoradiotherapy utilizing proton therapy in unresectable stage III NSCLC (130). This study employed a total dose of 74 CGE, similar to the high-dose arm in RTOG 0617 that demonstrated increased complications and worsened survival with photons. In contrast, Chang *et al.* encountered no grade 4 or 5 toxicities. Grade 3 toxicities were limited to 5 patients with dermatitis, 5 with esophagitis, and 1 with pneumonitis out of total 44 patients enrolled. OS and progression-free survival were 86% and 63%, respectively, at 1 year, with only 4 (9.1%) local-only recurrences. Median survival was 29.4 months. A similar study from the University of Florida closed early after enrolling 14 patients but employed 74 to 80 CGE in conventional fractionation in patients with stage III disease (131). Median OS and progression-free survival were 33 and 14 months, respectively, with no acute grade 3 toxicities and only two patients experiencing late grade 3 toxicities (one gastrointestinal, one pulmonary). Another 15-patient effort from the University of Tsukuba demonstrated similar results at the 74-CGE mark (132).

Multiple phase II and III clinical trials have been initiated to compare proton results to those with photons or to further test dose escalation, especially in the setting of concurrent chemotherapy. Recently, Chang *et al.* nicely summarized trials underway or recently completed (133). The only randomized data to date were presented at the 2016 meeting of the American Society for Clinical Oncology. Disappointingly, this MDACC/Massachusetts General Hospital trial failed to demonstrate a reduction in toxicity with PS-PT versus IMRT, despite relatively similar outcomes (134). It is notable that target volumes were larger in the proton therapy group ($P=0.071$) and that higher doses were generally prescribed in the proton cohort with higher resultant lung volumes receiving 30 and 80 Gy.

Future directions

Proton therapy, mainly through PS-PT experiences, has demonstrated largely acceptable toxicity rates with similar-to-improved outcomes in several small institutional trials. With rapidly expanding availability, the shift toward PBS-PT techniques, improvements in gating/breath-hold approaches, and the potential for daily volumetric image guidance, great promise remains for the application of proton therapy in early, locally advanced, and recurrent lung cancers. Further evidence and clinical investigation are anticipated.

Conclusions

Technological advances in RT, starting with volumetric imaging, have revolutionized the paradigm for lung cancer treatment. These improvements have allowed development of a variety of techniques that can enhance the therapeutic ratio. Application of these techniques has allowed physicians to reduce toxicity by sparing normal tissue in certain cases and to dose escalate the BED to improve tumor control in others. Clinical validation of these advantages has been demonstrated in the form of IMRT and SBRT, respectively. Emerging technologies, such as highly non-coplanar planning (4π) and PBS, continue to push the boundaries of the therapeutic ratio. And although they have raised new challenges regarding precision of delivery, dosimetric comparisons have been promising and clinical data are eagerly awaited. Finally, these technological advances in radiation therapy are paving the way to safely and effectively expand our multimodality treatment arsenal to integrate burgeoning systemic therapies, including immunotherapy.

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Footnote

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