Stereotactic Body Radiation Therapy (SBRT) for Primary Lung Cancer

Gregory M. M. Videtic

Abbreviations

BED	Biologically equivalent dose
CBCT	Cone beam computed tomography
CTV	Clinical target volume
EORTC	European Organisation for Research and Treatment of Cancer
GTV	Gross tumor volume
Gy	Gray
HRQOL	Health-related quality of life
IGRT	Image-guided radiotherapy
ITV	Internal target volume
kV	Kilovolt
LC	Local control
MTD	Maximum tolerable dose
Mv	Megavolt
NSCLC	Non-small cell lung cancer
OAR	Organ at risk
OS	Overall survival
PET; FDG-PET	Positron emission tomography; fluorodeoxyglucose-PET
PTV	Planning target volume
QOL	Quality of life
ROSEL	Radiosurgery Or Surgery for operable Early stage non-small cell Lung cancer
RTOG	Radiation Therapy Oncology Group
SABR	Stereotactic ablative body radiotherapy
SBRT	Stereotactic body radiotherapy
STARS	Stereotactic Ablative Radiotherapy in Stage I Non-small Cell Lung Cancer Patients Who Can Undergo Lobectomy
SUV	Standardized uptake value
SUVmax	Maximum standardized uptake value
VEGF	Vascular endothelial growth factor

Introduction

Lung cancer is the most common malignancy worldwide, with over one million cases being diagnosed yearly [1]. The most common histologic type seen is non-small cell lung cancer (NSCLC) [2]. It is the leading cause of cancer death in the United States, with more than 158,000 estimated deaths predicted for 2016 [3]. About 10–20% of lung cancer patients will present with early-stage ($T_{1–2}$ N_0) disease [4]. Early-stage NSCLC in medically fit patients is conventionally managed by surgical resection [5]. However, many lung cancer patients are considered medically inoperable due to their concurrent cardiovascular, pulmonary, or other comorbidities and these preclude surgical management [5]. Despite these substantial patient comorbidities, observation alone of inoperable patients results in unacceptable outcomes; in a study by McGarry and coauthors [6], lung cancer was shown to be cause of death in 53% of 75 stage I medically inoperable patients not receiving definitive therapy. Historically, any treatment offered this population aimed at limiting treatment-related injury. Options often then considered included limited surgical resection such as a wedge [7] or conventional radiotherapy (RT) given over 6–7 weeks [8]; however, cancer outcomes with either of these were found generally to be inferior to anatomic resection [5]. When conventional radiotherapy was used for these vulnerable patients, the practice was often to use simple beam arrangements and/or modest doses for safety. However, this approach resulted not only in high rates of local failure because of inability to deliver effective dose, but also often unwanted lung toxicity because

G. M. M. Videtic (✉)
Cleveland Clinic, Department of Radiation Oncology, Cleveland, OH, USA

Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA
e-mail: videtig@ccf.org

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of both the underlying functional impairments of the patients and the radiation oncologist's limitations in defining and constraining the cancer target volume [9].

This clinical challenge was eventually resolved in two ways. Technologic advances occurred in the diagnostic and radiologic disciplines that better defined early-stage disease, and clinicians adapted the high RT dose delivery techniques already in use for brain tumors (SRS) to extracranial sites [5]. The publication in 1995 by Blomgren and coauthors was the first to describe an experience of stereotactic high-dose fraction radiation therapy of extracranial tumors using a linear accelerator that delivered very high doses of radiation to tumors, including those in the lung, over a few fractions using highly conformal techniques [10]. The subsequent two decades following the publication of that landmark paper have seen the evolution and refinement of the technological developments in lung stereotactic body radiotherapy (SBRT; also known as stereotactic ablative body radiotherapy or SABR), so that its utilization in the medically inoperable early-stage lung cancer population has emerged as the standard of care for these patients.

Site-Specific Considerations

From its inception, SBRT has been considered primarily appropriate for organs whose functional structures can support focal ablation of physiologic units without compromising overall functionality. Because the lung has been considered such an organ based on the concept of its functional subunits being in "parallel," it was an early site for testing the feasibility and efficacy of SBRT [5]. Nonetheless, limiting the amount of normal thoracic tissues that are exposed to any amount of radiation that is prescribed to the target remains crucial. In that regard, the thorax includes a number of normal structures which historically have always elicited particular caution when planning radiotherapy. Based on a hierarchy of severe and/or irreversible injury potential, these structures always include the spinal cord, the esophagus, the major airways, the heart and the lungs. Accurate delineation of both the tumor and its adjacent organs at risk (OARs) is therefore essential for successful and safe planning and delivery of lung SBRT. In principle, to achieve both effective delivery of very high individual doses of radiation and minimal damage to normal tissues, SBRT dose to the primary tumor must be (1) tightly conformed to the shape of the tumor, (2) rapidly dropped off in the surrounding normal tissues, and (3) administered to discrete targets without regional micrometastatic spread (i.e., without nodal involvement) [5].

Gross tumor volume (GTV) is defined as all visible tumor on images acquired during simulation with assistance from fused diagnostic images as needed. Targets in lung will generally be drawn using CT pulmonary windows; however, soft tissue windows, ideally with contrast, may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. As indicated by clinical presentations where the GTV is ill-defined, fusion of planning studies with positron emission tomography (PET) studies may facilitate contouring. By convention, a clinical target volume (CTV) is not designated in routine lung SBRT planning based on the characteristics of dose deposition around the target, so that the GTV is equal to the CTV [11]. In accounting for any residual respiratory motion noted on imaging after implementation of the selected motion management technique (see below), the GTV is expanded to create an internal target volume (ITV). Lastly a planning target volume (PTV) is defined to account for setup error, deformation, and any additional uncertainty during the treatment process and is typically 5 mm based on the robustness of most SBRT systems (Fig. 1).

Accurate OAR delineation is as noted necessary for accurate treatment planning. Consistency in outlining structures as well as uniformity of OAR definitions between plans helps in minimizing inter- and intra-observer variability. For example, lung SBRT plans usually include several OARs not commonly delineated or considered in standard fractionated lung treatment, such as the ribs, the proximal bronchial tree and the brachial plexus. In that regard, clinicians can access original protocols wherein detailed instructions on standardized OAR definitions and contouring are readily available, e.g., NRG Oncology's Radiation Therapy Oncology Group (RTOG) 0236 [12].

By its nature, lung SBRT requires reproducible means to achieve highly accurate treatment setups and to account for, and mitigate the effects of, respiratory motion. To provide accuracy in treatment setup for lung SBRT, a robust immobilization system is necessary to keep the patient precisely in

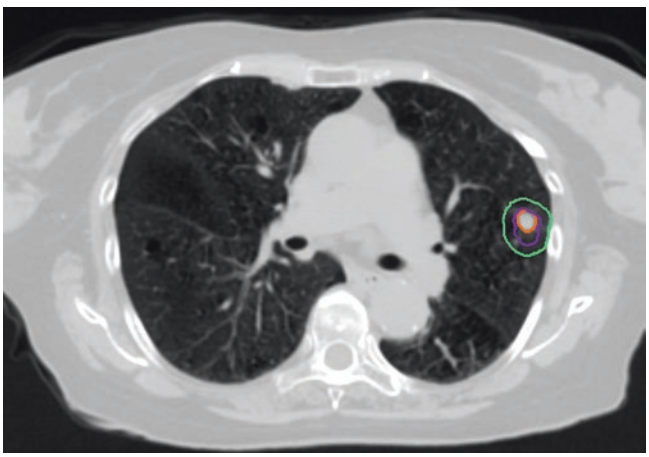

Fig. 1 Representative axial slice from the planning CT images of the chest for a $T_{1a}N_0M_0$ cancer of the left upper lobe of the lung, demonstrating the GTV (orange), ITV (purple), and PTV (green) contours used for lung SBRT planning

the same position throughout the whole treatment delivery. Devices such as body frames, vacuum pillows, and thermoplastic devices have been used for such immobilization. Regardless of the device used, by customizing it so that it is fitted snugly around the patient any potential movement of the torso is then limited. With proper usage, the type of device used will not have an impact on clinical outcomes. The next critical step in lung SBRT patient simulation is accounting for tumor and organ motion. Maneuvers to control the impact of breathing can be divided into restriction, gating, and tracking approaches, as summarized by Folkert and Timmerman [13]. Techniques used for limiting or minimizing motion include abdominal compression and breath-hold maneuvers to freeze the tumor in a specific stage of the respiratory cycle. Gating involves tracking the tumor's range of motion during respiratory cycles; the radiation beam is triggered only during a specific segment of each cycle. Tracking (or chasing) involves moving the radiation beam in real time so that the motion of the target is followed during respiration. This may require placement of radiographically identifiable markers (fiducials) in the vicinity of the tumor. Regardless of the system used to control for the effects of motion, the acquisition of planning data should incorporate the same considerations. Lastly, reproducible means of verification at the time of SBRT delivery (termed image guidance radiotherapy, or IGRT) complete the requirement for accuracy. Different treatment platforms will provide various IGRT capabilities to enable verification of the location of the tumor or target volume before treatment delivery. These methods include radiographic and tomographic imaging systems (cone beam CT, or CBCT) integrated into a linear accelerator, using photon energies in the kV range for target localization; automatic six-dimensional fusion of reference digitally reconstructed radiographs and stereoscopic X-rays taken prior to treatment which identify any setup errors or target shifts in any direction and compensate for the discrepancy for with robotic table movements; and frameless systems in which orthogonal radiographs allow for real-time tracking by imaging reliable bony landmarks or implanted fiducial markers are utilized for target tracking and treatment delivery.

Regarding dose/fractionation schedules in lung SBRT, there is no single standard regimen for all tumor presentations. Published data have generally reflected single institution experiences, and this explains to some degree variations among institutions with respect to total dose, fractionation schedules, overall treatment time, and techniques of dose delivery. These differences have made it challenging to standardize dose schedules and dosimetric specifications in the administration of SBRT. For example, in some of the earliest work in lung SBRT accomplished by investigators in Japan, Uematsu and coauthors [14] reported outcomes from 50 patients treated with SBRT to dose fractionation schedules ranging from 50 to 60 Gy in 5–10 fractions in 2001. The majority of patients (47 of 50) achieved long-term local control (LC), with 3-year overall survival (OS) of 66% and cause-specific survival of 88%. In this same era, clinicians at Indiana University were conducting prospective phase I/II trials of dose escalation starting at 8 Gy per fraction for a total of 3 fractions delivered over 2 weeks. The maximum tolerated dose (MTD) was not reached for T1 tumors and the MTD for T2 tumors greater than 5 cm was met at 24 Gy per fraction. LC was excellent with only 1 failure seen when dose per fraction was higher than 16 Gy compared to 9 failures at doses less than 16 Gy, and this was achieved without significant toxicity [15, 16]. With that Indiana experience, the phenomenon of toxicity dependency on dose delivered and tumor location in the lung was also revealed, something not previously described. It showed that treatment of "central" and perihilar tumors with greater than 60 Gy in 3 fractions, where "central" was defined as a tumor within 2 cm of the proximal tracheobronchial tree, posed a higher risk of severe toxicity than treatment of "peripheral" tumors [17]. When the RTOG initiated a prospective phase I/II trial (RTOG 0236) in medically inoperable peripheral early-stage NSCLC, they consequently assessed 60 Gy (without heterogeneity corrections) in 3 fractions over 8–14 days, with minimal interfraction intervals of 40 hours. This pioneering study showed a survival rate of 55.8% at 3 years, high rates of local tumor control with an estimated 3-year primary tumor control rate of 97.6%, and moderate treatment-related morbidity with protocol-specified treatment-related grade 3 or higher adverse events of 16.3% and with no grade 5 events [18]. Investigation of dose schedules for central tumors has included RTOG 0813, dose escalation study starting at 50 Gy in 5 fractions given every other day and achieving the MTD of 60 Gy in 5 fractions. The LungTech trial (European Organisation for Research and Treatment of Cancer (EORTC) 22113-08113) is studying 60 Gy in 8 fractions for central tumors. In the United States, Chang and coauthors at MD Anderson Cancer Center have published their experience with a regimen of 50 Gy in 4 fractions [19]. Recent studies have looked at single-fraction lung SBRT in peripheral tumors. For example, RTOG 0915 was a prospective, randomized phase II trial that compared 34 Gy in 1 fraction with 48 Gy in 4 fractions and based on a co-primary endpoint of toxicity and local control showed that the single-fraction arm had the least toxicity for equal efficacy of the two regimens [20]. As presented in abstract form, results from a randomized phase II trial that compared 30 Gy in one fraction to 60 Gy in 3 fractions showed the arms with equal efficacy and modest toxicity [21].

Clinical Evidence

Published results for lung SBRT over the past two decades consistently report on its outstanding LC in inoperable stage I NSCLC patients, with nearly all series reporting 85–95%

control rates [11, 15, 18, 22, 23]. Clinicians must be mindful, however, that the definition of local control after this form of therapy can be difficult because distinguishing true tumor failure from radiation-induced lung damage is often challenging. Many treated patients develop radiographic changes of fibrosis that may be mistaken for recurrence, and interpretation of images may require an experienced reader [24]. Positron emission tomography (PET)-based imaging may help in the interpretation of ambiguous cases on CT imaging [25] (Fig. 2a–d), though biopsy may occasionally be required. That said, lung SBRT LC rates are in keeping with those from prospective surgical series showing a locoregional failure rate of 5–7% for lobectomy and 8–17% for sublobar resection [26, 27]. A pooled meta-analysis of 40 SBRT studies totaling 4850 patients and 23 surgical studies (lobar or sublobar resection, 7071 patients in total) likewise suggested LC by this definition is similar [28]. It remains that identifying local failure after SBRT is more challenging than after lobectomy (where there is no longer any physical tumor), so that postradiation fibrosis may lead to overestimation of local failure or, on the other hand, the comparatively shorter follow-up of most published SBRT series might result in underestimation of local failure [29]. Another issue in making comparisons between surgical and radiation treatment modalities is that LC in surgical series is more often reported as locoregional control. Concerning LC after SBRT, radiation oncologists have typically defined LC as the absence of tumor progression within 1 cm of the primary tumor site. If using surgical definitions when accounting for lobar failure, LC in SBRT series drops slightly. RTOG 0236, a landmark prospective trial of SBRT utilizing 60 Gy in 3 fractions (estimated 54 Gy in 3 fractions with heterogeneity corrections) for peripheral stage I NSCLC, demonstrated 3-year LC of 97.6%, lobar control of 90.6%, locoregional control of 87.2%, and a 22.1% rate of distant recurrence [11].

When it comes to regional nodal failure after lung SBRT, its reported incidence ranging from 6% to 22% is surprisingly lower than might be expected for non-resected patients given the known rate of nodal upstaging after surgical nodal dissection for clinical stage I lung cancer [30, 31]. Increasing quality of pretreatment imaging as well as availability of nonsurgical nodal staging techniques, only modestly used in most SBRT series, may also impact the incidence of nodal failure going forward. Another theory for the low nodal recurrence rate after SBRT is that ablative doses of radiation may initiate a T-cell, immune-mediated tumor cell killing response [32]. Others suggest that radiation may scatter effective dose to the regional lymph nodes that may be harboring microscopic metastases [33].

In keeping with what is seen in surgical series of resected operable early-stage lung cancer patients, distant failure remains the predominant pattern of failure in medically inop-

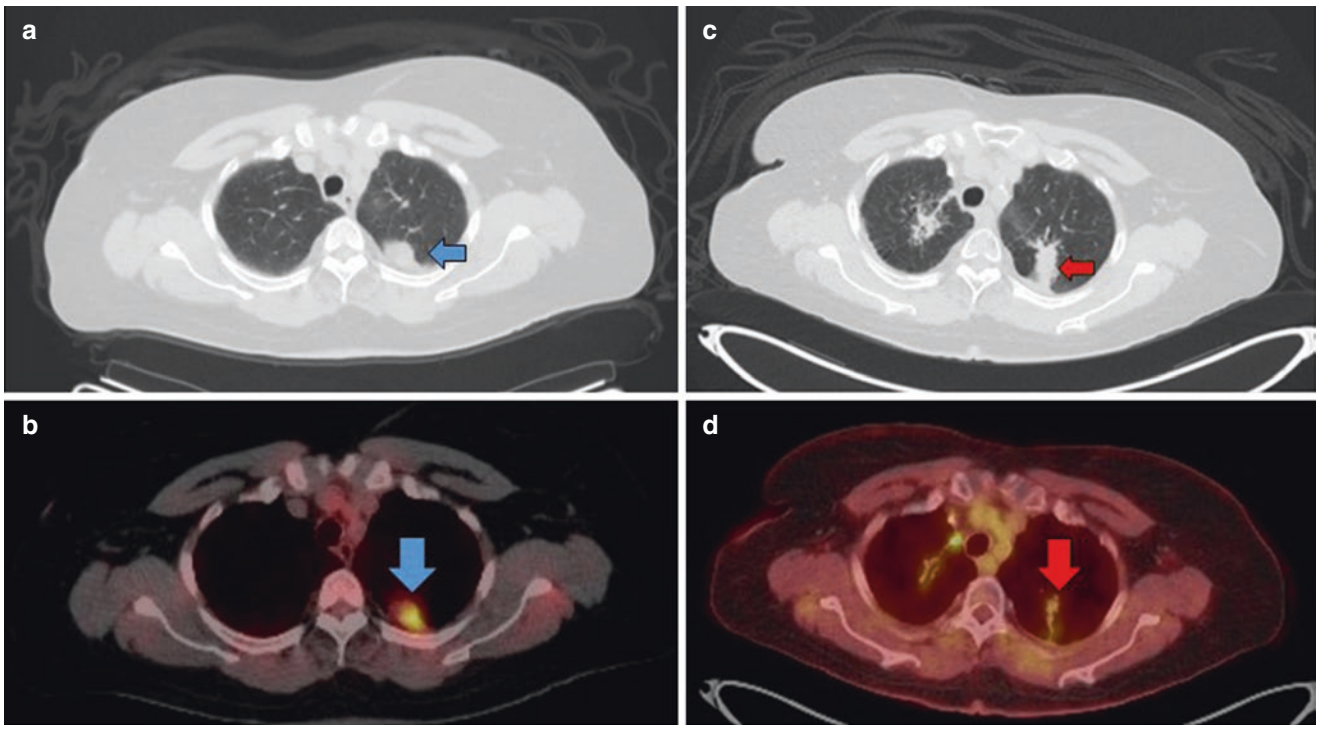

Fig. 2 (**a**–**d**) Representative axial FDG-PET CT images from a 68-year-old female with medically inoperable, early-stage squamous cell carcinoma of the left upper lobe of the lung, following lung SBRT (34 Gy/1 fraction): **a**, **b** lesion (blue arrow) pre-treatment, dated Nov 2007, 1.6 cm, SUVmax 15.3, and **c**, **d** lesion (red arrow) posttreatment dated Aug 2017, 3.4 cm, SUVmax 3.6

erable patients treated with SBRT, even though early stage. Distant metastasis is reported to occur in 15% to 30% of stage I patients treated with SBRT, mimicking the rates seen in resected patients [34–36].

In comparison to surgical series, SBRT for stage I NSCLC is typically associated with lower reported OS. This is likely in large part due to patient selection given the predominance of medically inoperable patients and high rates of death due to comorbid conditions in SBRT series [28, 31, 37]. It is supported by the observation that after performing multivariate adjustment or propensity score–based analysis SBRT OS is typical similar to surgical cohorts [28, 31, 37]. Notably small series of SBRT in medically operable patients have yielded excellent OS [34, 35]. The previously noted pooled analysis also demonstrated a relationship between OS and the percent of operable patients within individual SBRT series, which when curve-fit to surgical series also suggested the potential for similar OS in equally operable patients [28]. Ultimately, however, modeling data cannot replace clinical data, and with no long-term series of sufficient volume for SBRT in operable patients in the US population, surgery should be the standard of care for operable patients in this country.

Patient-related outcomes for lung SBRT have also been validated by prospective measurements using quality-of-life (QoL) instruments. A recent systematic review addressing QoL after SBRT for early-stage lung cancer found 9 prospective studies published between 2010 and 2015 [38]. The overall results of this review suggested few clinically significant changes in health-related quality-of-life (HRQoL) scores after lung SBRT, further indicating the appropriateness of SBRT in the medically inoperable population.

Toxicity

Considering the remarkably high radiation doses used in lung SBRT, the consistent finding from numerous clinical reports over the last decades has been the paucity of severe lung toxicity seen after treatment. For patients already with baseline pulmonary dysfunction, the rates of grade 3 or higher radiation pneumonitis have been typically less than 5% [39]. These low rates of toxicity are presumably due to both the precision of treatment delivery and the structural physiology of lung tissue. While SBRT causes inevitable focal lung parenchymal changes (as seen on CT imaging of the chest over years) in most patients [24], its functional impact (as evidenced by symptom development) is typically minimal, likely because adequate remaining functional lung tissue is preserved. In addition, it is hypothesized that the high doses may obliterate blood vessels in the treated area, thereby mitigating ventilation-perfusion mismatch felt to play a role in the symptomatic toxicity of standard RT [5]. On average there is little to no decrease in the pulmonary function of treated patients, with a report showing that post-SBRT, fluctuations in pulmonary function tests from baseline occur in both positive and negative direction, and with these results ultimately falling into a normal distribution so that no association between treatment and PFT changes can be made [40]. In a secondary analysis of RTOG 0236, Stanic and coauthors also showed no clinically significant changes in pulmonary function following lung SBRT [41]. Even patients with extremely compromised pulmonary function (e.g., diffusion capacity <20% predicted) show overall survival outcomes comparable to less compromised patients [40, 42], suggesting no lower limit to pulmonary function when selecting patients as appropriate for lung SBRT, along as they are medically stable. In noting that lung toxicity is generally low, it has become clear that tumor location does play a critical role in the risk and development of treatment-related lung morbidity. Thus, the exception to the low rates of SBRT toxicity was first reported by Timmerman and colleagues following their experience of treating "central" lung tumors in the setting of their phase I/II at Indiana University, where "central" was defined as lesions lying within 2 cm of the tracheobronchial tree [17, 43]. In that phase II experience, patients with tumors treated in the central lung had 2-year freedom from severe toxicity of only 54%. That the particular interaction between tumor location and toxicity is SBRT dose/fractionation-specific since "central" lesions have otherwise been safely treated with slightly lower total doses and doses per fraction (such as 50 Gy in five fractions) with similar local control and toxicity as seen in treatment of peripheral lesions to higher doses [23, 34].

As clinical experience with lung SBRT evolved over years and with routine follow-up of patients following treatment, non-lung toxicities began to declare themselves. Thus, chest wall pain or rib fracture developing many months to years after treatment became an increasingly reported delayed side effect. Though symptoms are typically mild to moderate, chest wall symptoms are reported in 5–15% of patients with peripheral lesions, and appear to be related to treatment dose, fractionation, and beam arrangement [23, 44, 45]. With advances in understanding of the causative factors, and improved treatment planning, rates of toxicity may be lowered for future patients. Overall the prospect of chest wall toxicity remains mild in comparison with surgical alternatives [46], is typically self-limited and can be managed medically [47]. Other less common late side-effects such as soft-tissue fibrosis [48], skin reaction [49], and brachial plexopathy [50] have been described; however, these occur in less than 1% of treatments and are likewise preventable with changes in treatment planning. Grade 5 toxicities are very rare and not predictable. For example, esophageal fistula development followed by death was seen in 2 patients as a rare complication of SBRT and only in those patients who also received adjuvant vascular endothelial growth factor

(VEGF)-modulating agents after treatment, suggesting that clinicians need to be mindful of the potential interaction of SBRT and adjuvant therapy [51]. Fatal central-airway necrosis was reported in a patient with a very centrally located lung tumor and who had received SBRT, with 50 Gy administered in 5 fractions, 8 months earlier [52].

Plan Quality

Early reports in lung SBRT often provided institution-specific approaches to planning development and review. With time, prospective trials, such as RTOG 0236, provided structured and rigorous parameters to ensure uniform approaches to planning across a range of institutions. This allowed for consistent development of high quality plans for the delivery of lung SBRT and thus provided a model for structured planning review. In addressing the treatment requirements for an early-stage lung cancer, lung SBRT has to provide an extremely conformal radiation dose distribution around the PTV generated off of the tumor, while simultaneously allowing for a very rapid falloff of the radiation dose beyond the prescribed isodose line (Fig. 3). One of the most important parameters in the evaluation of a computerized treatment plan for SBRT, therefore, has been the conformality index (i.e., dosing to tumor) and zones of high-dose and low-dose spillage (i.e., dosing to OARs). As outlined in RTOG 0236 [12] and applied to subsequent lung SBRT protocols from NRG, the conformality index is the ratio of the prescription isodose volume to the planning target volume (PTV). High-dose spillage refers to the amount of normal tissue included in the prescription isodose shell, which can be quantified using the conformality index. Low-dose spillage is defined as the maximum dose at a defined distance away from the PTV or the ratio of 50% of the prescription isodose volume to the PTV. RTOG protocol tables in that regard provide tumor size-specific reference tables to ensure compliance with these treatment requirements for safety. Likewise, organ-specific point and/or volumetric dosing limits are provided per protocol to ensure plan appropriateness so that in situations in which the PTV is particularly in close proximity to critical organs or structures, the maximum point doses as well as the dose volume histograms of those organs or structures can be evaluated to provide a hierarchy of planning constraints based on OAR-specific injury implications.

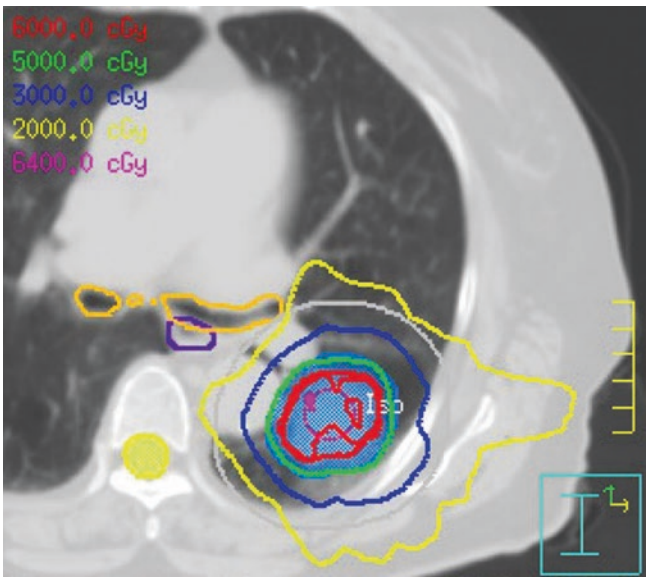

Fig. 3 Representative axial slice from the CT images of the SBRT plan for a stage I left lower lobe cancer treated with 50 Gy in 5 fractions: PTV (blue cloud), 60 Gy isodose line (red), 50 Gy isodose line (green), 30 Gy isodose line (blue), 20 Gy isodose line (yellow), 2 cm ring expansion from the PTV for planning (gray line), esophagus (purple line), and proximal bronchial tree (orange line)

Typically, to achieve the above planning goals at delivery, three-dimensional conformal radiotherapy planning with a large number of highly conformal beams, or intensity modulated radiation therapy planning is used, depending on the site of the tumor and the preference of the treating clinician and physicist. Coplanar or non-coplanar, non-overlapping, non-opposing beams or arc therapy are all valid approaches to beam arrangement, with some authors encouraging non-coplanar arcs to improve conformality and OAR sparing in complex anatomical geometries. Combination of static and arc beams can also be employed. Gantry clearance verification prior to treatment is generally recommended to ensure technical deliverability. As with the general principles regarding use of photons in the thorax, lower energies $\leq$10MV are preferred for lung, although specific clinical scenarios may require other approaches.

Future Directions

Establishing a standard SBRT schedule with uniform planning approaches for medically inoperable tumors has been considered a desirable goal by many clinicians. Thus, within the RTOG, in the formulation of RTOG 0915 there were stated plans in the protocol to utilize the optimal regimen determined by that randomized phase II trial for a randomized phase III trial comparing it to the current standard of 60 Gy in three fractions set by RTOG 0236, with a primary endpoint of overall survival. Such a proposal, however, has not been able to move forward and currently there is no single "optimal" regimen. Thus, selection of dose regimens will have to continue to, first, reflect tumor location. Second, Onishi and coauthors [34] observed that in order to achieve equivalence in local control, differing SBRT schedules require a biologically equivalent dose (BED) of at least equivalent 100 Gy_{10}, where the Gy_{10} value represents a con-

version factor for making comparison between dose and fractionation schedules using a mathematical model based on tissue responses [53].

Since distant failure remains the predominant pattern of failure for medically inoperable early-stage lung cancer patients treated with SBRT, the appropriate use of adjuvant systemic or biologic therapies has also become a question of great interest. It is nonetheless controversial since that practice is currently ill-defined in the standard surgical population and is relatively contraindicated in the medically compromised with more advanced disease. In that regard, it is important to note that the treatment of advanced NSCLC has undergone a major theory shift in the past decade, from the primary use of cytotoxic chemotherapy to the discovery of driver mutations and the subsequent discovery and use of genotype-directed targeted therapies [54]. Such agents are not only favored due to their selectivity but also due to their potentially more favorable side effect profile. Hence, many such agents are now being considered in the non-metastatic setting. In that regard, recently discovered strategies using monoclonal antibodies targeting the immune-checkpoint pathways have recently shown impressive activity in several solid tumors including NSCLC [55]. These drug features explain the rationale in developing research proposals involving immunotherapy for early-stage lung cancer patients being treated with lung SBRT.

Lastly, among the most provocative findings published in the early lung cancer SBRT literature were the results of Onishi and colleagues [34] in which the survival of a subgroup of medically operable patients treated with SBRT was equivalent to similar-stage patients treated with video-assisted thoracoscopic surgery or lobectomy. This evidence combined with the favorable treatment profile for lung SBRT eventually prompted 3 randomized trials in the medically operable population (American College of Surgeons Oncology Group Z4099/RTOG 1021; ROSEL [Radiosurgery Or Surgery for operable Early stage non-small cell Lung cancer]; and Stereotactic Ablative Radiotherapy in Stage I Non-small Cell Lung Cancer Patients Who Can Undergo Lobectomy (STARS)). Unfortunately, all were terminated early because of poor accrual, but a pooled analysis of 2 of the trials (ROSEL and STARS) was published recently and involved 58 patients. The results, which have been controversial not the least because of the small sample size, suggested a potential survival benefit to SBRT over surgery, if not equivalence with respect to local control [56]. The role of lung SBRT for operable patients therefore remains a contentious question. Currently, there are two ongoing multi-institutional trials in the United States for high-risk operable patients comparing limited surgical resection versus SBRT with a primary endpoint of overall survival [57].

Practical Considerations

(a) Patient Selection:
  (i) Patient evaluation by experienced multidisciplinary thoracic oncology team, including, at a minimum, a thoracic surgeon, a pulmonologist, and a radiation oncologist, is recommended.
  (ii) Active medical conditions likely to influence short-term patient survival need to be addressed and may preclude appropriateness of lung SBRT for early-stage inoperable cancer.
  (iii) There is no lower limit to the degree of impaired pulmonary function which acts as a contra-indication to lung SBRT.
  (iv) Pathologic confirmation of malignancy by biopsy is desirable but may not be readily achievable in many inoperable patients due to medical contraindications. For non-biopsied patients, one may consider a clinical diagnosis of malignancy based on radiographic criteria such as serial CT chest scans showing growth and/or FDG-PET scan either demonstrating high (SUV >5) metabolic activity on a single scan or progression of intermediate activity over serial scans.
  (v) Invasive mediastinal staging is not absolutely required prior to lung SBRT. On a case by case basis, clinicians can consider the appropriateness of endobronchial ultrasound-, or PET-only-, based staging to characterize and clinically define mediastinal lymph nodes.

(b) Dose Selection:
  (i) To be deemed "SBRT," any schedule requires BED of at least equivalent 100 Gy_{10}.
  (ii) Dose schedule will be selected as a function of location with reference to the airways and/or mediastinum.
  (iii) For lesions deemed "peripheral," SBRT lung schedules may include 60 Gy in 3 fractions, 50 Gy in 5 fractions, 48 Gy in 4 fractions, and 30 Gy or 34 Gy in 1 fraction.
  (iv) "Central" lesions are preferentially treated with 50 Gy in 4/5 fractions or 60 Gy in 8 fractions.
  (v) See Table 1.

(c) Treatment Delivery:
  (i) Ensure usage of a robust immobilization device integrated with a reliable system to account for motion.
  (ii) Ensure proficiency in the use of any of the range of SBRT treatment platforms available, with fiducial usage as indicated by the technical characteristics of the given platform and per clinician preference.

Table 1 Representative dose constraints for organs at risk (OARs) when planning lung SBRT based on selected common fractionation schedules

		One-fraction treatment		Three-fraction treatment		Five-fraction treatment		
Critical structure	Max critical volume above threshold (cc)	Threshold dose (Gy)	Max point dose (Gy)[a]	Threshold dose (Gy)	Max point dose (Gy)[a]	Threshold dose (Gy)	Max point dose (Gy)[a]	Toxicity endpoint
Spinal cord	Point	14 (14 Gy/fx)	(Gy/fx)	21.9 (7.3 Gy/fx)	21.9 (7.3 Gy/fx)	30 (6 Gy/fx)	30 (6 Gy/fx)	Myelitis
	<0.35	10 (10 Gy/fx)	(Gy/fx)	18 (6 Gy/fx)	(Gy/fx)	23 (4.6 Gy/fx)	(Gy/fx)	
	<0.12	7 (7 Gy/fx)	(Gy/fx)	12.3 (4.1 Gy/fx)	(Gy/fx)	14.5 (2.9 Gy/fx)	(Gy/fx)	
Esophagus[b]	<5	11.9 (11.9 Gy/fx)	15.4 (15.4 Gy/fx)	17.7 (5.9 Gy/fx)	25.2 (8.4 Gy/fx)	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	Stenosis or fistula
Brachial plexus	<3	14 (14 Gy/fx)	17.5 (17.5 Gy/fx)	20.4 (6.8 Gy/fx)	24.0 (8.0 Gy/fx)	27.0 (5.4 Gy/fx)	30.5 (6.1 Gy/fx)	Neuropathy
Heart/pericardium	<15	16 (16 Gy/fx)	22 (22 Gy/fx)	24.0 (8.0 Gy/fx)	30.0 (10.0 Gy/fx)	32.0 (6.4 Gy/fx)	38 (7.6 Gy/fx)	Pericarditis
Great vessels	<10	31 (31 Gy/fx)	37 (37 Gy/fx)	39.0 (13.0 Gy/fx)	45.0 (15.0 Gy/fx)	47.0 (9.4 Gy/fx)	53 (10.6 Gy/fx)	Aneurysm
Trachea and large bronchus[b]	<4	10.5 (10.5 Gy/fx)	20.2 (20.2 Gy/fx)	15.0 (5.0 Gy/fx)	30.0 (10.0 Gy/fx)	16.5 (3.3 Gy/fx)	40 (8 Gy/fx)	Stenosis or fistula
Rib/chest wall[c]	<1	22 (22 Gy/fx)	30 (30 Gy/fx)	28.8 (9.6 Gy/fx)	36.9 (12.3 Gy/fx)	35.0 (7.0 Gy/fx)	43 (8.6 Gy/fx)	Pain or fracture
Skin	<10	23 (23 Gy/fx)	26 (26 Gy/fx)	30.0 (10.0 Gy/fx)	33.0 (11.0 Gy/fx)	36.5 (7.3 Gy/fx)	39.5 (7.9 Gy/fx)	Ulceration
Lung (right and left)	1500	7 (7 Gy/fx)	(Gy/fx)	11.6 (2.9 Gy/fx)	–	12.5 (2.5 Gy/fx)	–	Basic lung function
	1000	7.4 (7.4 Gy/fx)	(Gy/fx)	12.4 (3.1 Gy/fx)	–	13.5 (2.7 Gy/fx)	–	Pneumonitis

Data from Refs. [58, 59]
Gy gray, *fx* fraction
[a]Max point dose corresponds to 0.035 cc of tissue or less
[b]Avoid circumferential radiation
[c]In attempting to optimize target treatment parameters, being mindful of rib dosing (as low as reasonably achievable [ALARA]) should in no way compromise target coverage or restrict potential delivery parameters for the sake of rib dosing. Rib "limits" provided in the table above may in that respect be exceeded for an otherwise excellent plan

(iii) Observe rules for overall treatment time as published; e.g., for 60 Gy in 3 fractions, overall treatment time is 8–14 days, and interfraction interval is minimum of 40 hours/maximum of 7 days.

(d) Follow-Up:
  (i) Optimal follow-up schedules and testing requirements after lung SBRT are not formalized.
  (ii) Clinicians should employ thoracic CT scans for follow-up imaging since there is limited evidence to support routine use of FDG-PET/CT.
  (iii) Consider patient visits at months 3, 6, and 12 in year 1, every 6 months in year 2, and annually in years 3–5, after completion of SBRT.
  (iv) Consider FDG-PET/CT imaging only if CT findings are suspicious for local recurrence.
  (v) Consider pathologic confirmation if suspicion of recurrence, but consider imaging findings alone if biopsy is not safe or feasible.
  (vi) Consider yearly survivorship monitoring after 5 years, using CT imaging for assessment.

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