Stereotactic body radiation therapy (SBRT) has evolved over the past 15 years and revolutionized the management of early stage non-small cell lung cancer (NSCLC). Compared to conventional radiation therapy, SBRT offers superior outcomes, lower costs and greater patient convenience. SBRT likewise offers local control and cancer outcomes approaching surgical resection with lower risk of treatment-related morbidity, making SBRT the treatment of choice for medically inoperable and many high-risk surgical candidates. Encouraging results in this population have led to the investigation of SBRT’s role in operable stage I NSCLC, lung oligometastasis, stage I small cell lung cancer, and potentially as a boost to conventional radiation therapy for locally advanced NSCLC. The lessons learned in the lung SBRT experience also serve as a model for developing SBRT in other mobile soft-tissue sites, including the liver, pancreas, adrenal gland and prostate.

Technique

SBRT treatment planning begins with careful immobilization of the target with motion limited to <5-10 mm. This may be accomplished by abdominal compression (Figure 1), respiratory gating using either controlled breath-hold or external surrogates, or tumor tracking/respiratory modeling. Immobilization should be assessed by either fluoroscopy or 4DCT imaging at simulation, and verified by cone-beam CT (CBCT) or other imaging during treatment.

Historically, the planning target volume (PTV) was created from a fixed expansion (1 cm superior-inferior, 5 mm axially) of the contoured gross tumor volume (GTV), although this can alternatively be derived from the union of multi-phasic CT GTV’s (free-breathing, inhale, exhale) or 4DCT images into an internal target volume (ITV), which is then expanded uniformly by 5 mm yielding the PTV. Expanding the 4DCT ITV typically results in a smaller PTV, and likely more consistently represents the actual tumor motion, as well as center of mass.

Beam arrangement may consist of 6 or more non-coplanar open beams, intensity-modulated radiation therapy (IMRT) beams, non-coplanar volumetric arcs (typically at least 3 arcs, each offset by 30-40 degrees), intensity-modulated arc therapy, or alternatively,
particle-based therapy.\textsuperscript{10,11} The use of IMRT in treating small moving lung targets is controversial due to concerns of potential underdosing, although IMRT is allowed by recent protocols such as RTOG 0813,\textsuperscript{10} and reported outcomes with IMRT have been on par with other techniques.\textsuperscript{12} Planning should utilize collapsed cone convolution or Monte Carlo algorithms, as there is a suggestion that pencil-beam algorithms may compromise tumor control due to more variable under-dosing.\textsuperscript{13} Our institution uses the 4D-derived average CT as the planning image for the best estimate of density and tumor center-of-mass. Planning should focus on maximizing conformity and rapid dose fall-off. Heterogeneity is acceptable and may be desirable for purposes of faster fall-off, provided critical serial structures are not overexposed (Figures 2 and 3). Constraints should be based on appropriate protocols for the target being treated, such as RTOG 0236, 0813, 0915, or large institutional experiences.

Image guidance during treatment initially consisted of bony registration followed by port films, although modern approaches typically rely on CBCT (Figure 4). Free-breathing CT may not represent the true tumor center-of-mass due to respiratory motion, and a pitfall can be created by matching free-breathing CT to a CBCT tumor at the time of treatment, potentially introducing a systematic error that occasionally exceeds the PTV expansion.\textsuperscript{9} One should either use the average CT as the reference for matching, or otherwise localize only to bony anatomy if using a free-breathing image while verifying that the CBCT tumor falls within the ITV.

Patients should be routinely reimaged with CT after treatment for response assessment realizing that significant fibrotic reactions may occur (Figure 5).\textsuperscript{14} Concerning features on CT include an enlarging mass-like density,
as well as enlargement in the superior-inferior axis. We typically reserve positron emission tomography (PET) scans for evaluating whether a lesion which appears suspicious on CT is recurrence vs. fibrosis. While no absolute standardized uptake value (SUV) cut-off exists, recurrence has been associated with SUV increases as well as residual SUV > 5 after SBRT. Enlarging hypermetabolic lesions should undergo biopsy as there are occasional cases where high residual metabolism may be due to inflammation rather than recurrence.

Cancer outcomes after SBRT for stage I NSCLC

Tumor control

Local control (LC) of the index lesion after lung SBRT is typically defined as the absence of tumor progression within 1 cm of the primary tumor site, and has historically ranged from 90-98%, consistent with a prospective surgical series showing an LRF rate of 5-7% for lobectomy, and 8-17% for sublobar resection. Of note when comparing to surgical series, the terms lobar control (absence of failure within the treated lobe), and loco-regional control (LRC, absence of local, lobar, or nodal recurrence) become relevant. RT0G 0236, a landmark prospective trial of SBRT using 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%, LRC of 87.2%, and a 22.1% rate of distant recurrence, consistent with other series. Due in large part to the comorbidities of medically inoperable patients receiving SBRT, overall survival (OS) is typically lower in surgical series (48.3% at 3 years on RT0G 0236 for instance), while cancer-specific survival is comparable.

There are no reported randomized trials comparing the outcomes of SBRT to surgical resection, and initial attempts have closed due to poor accrual, potentially reflecting differences between perceptions of the 2 treatments. Comparing outcomes in non-randomized series suffers from selection bias, and attempts at matched-pair or propensity-adjusted analysis are still likely influenced by SBRT series including older patients with more significant comorbidities, lower performance status, and lower pulmonary function than surgical series. A matched-pair analysis between SBRT and wedge resection suggested improved LC with SBRT (96% vs. 80%), equivalent cause-specific survival, but better OS with surgery, attributed to differences in comorbidity. Comparing lobectomy to SBRT, Robinson et al. found similar LC (98.7% vs. 95.3%, p=0.088), regional control, and distant control with improved lobar control and survival in surgical patients.
with survival again perhaps related to selection. An earlier series from the same institution suggested improved local control and survival with surgical resection; however, after propensity matching, patient outcomes—including OS—came together. Small series from Japan and the Netherlands reporting on SBRT for potentially operable patients within SBRT series on LC. The meta-analysis suggests better OS in a surgical series; however, within SBRT series, mean OS was correlated with reported percent operable patients, and a regression model using age and percent operability showed no significant OS differences between SBRT and surgery after correction.

**Toxicity**

SBRT is well-tolerated even in the medically inoperable population. Patients may experience fatigue for 4-6 weeks following treatment. Pulmonary function is well-conserved with generally <3% risk of radiation pneumonitis, and even patients with extremely compromised pulmonary function exhibiting OS outcomes at or above the mean. This suggests there is no lower limit to pulmonary function for SBRT, provided patients are medically stable. Neuropathic pain and rib fractures may occur with 10-15% of treatments of targets abutting the chest wall, although symptoms are generally modest and potentially less common than in surgical series. Skin ulcers, brachial plexopathy, and bronchial or esophageal fistulas have been reported, but are extremely uncommon, and risk is modifiable during the planning process when identified.

**Patient selection: Stage I NSCLC and the spectrum of operability**

While there is no uniform definition of “medically inoperable,” several surrogates and multiple predictive models of surgical morbidity are in use. In practice, lung cancer patients fall on a spectrum from frankly unsuitable for surgery, to those at risk for surgical complications and mortality, to those at risk for quality of life changes with surgery and, finally, to patients in good health with minimal surgical risk. The first step in patient selection is for the multidisciplinary lung cancer team to stratify operative risk by considering the following:
Medically inoperable stage I NSCLC patients should receive SBRT, and not conventional radiation.1  
Low-risk operable patients should proceed with surgical resection, which is the standard of care, and shown to be cost-effective relative to SBRT in modeling studies.35,36 While early data for SBRT in operable patients is encouraging,4,5 and OS between surgery and SBRT may be much closer after correction for age and comorbidities,8,19 further data is needed before accepting SBRT as a first-line option for most operable patients. 
As operative risk increases, SBRT rapidly becomes the treatment of choice. Modeling studies suggest a surgical risk threshold of between 3-4% above which the cost-effectiveness decisively swings in favor of SBRT,35 a threshold consistent with treatment stratification in our clinic as well. 
Some patients below this threshold may also choose SBRT due to better preservation of pulmonary function and to avoid oxygen requirements. In addition, a patient’s advancing age (despite good health) and evolving priorities may prompt the decision of a more convenient and less invasive procedure.

Peripheral tumors  
SBRT for peripheral tumors has demonstrated excellent long-term safety and efficacy as noted above. Areas of controversy include:

What degree of pre-treatment staging is required?  
Historically, this has been PET-based (with brain imaging for stage IB or neurological symptoms). The development of less invasive mediastinal staging such as endobronchial ultrasound-guided sampling, and migration of healthier patients toward SBRT, has raised the question of whether more aggressive staging might improve outcomes. While 15-30% of clinical stage I NSCLC is upstaged by the finding of positive hilar nodes at surgery,21,37 nodal failure rates appear paradoxically much lower after SBRT at 3-10%.2-7 Without clear predictors of a high-risk subgroup for nodal failure,38 the role of invasive staging remains controversial.

What is the ideal SBRT dose?  
Excellent local control is seen with 60 Gy in 3 fractions as per RTOG 0236, although other regimens (48 Gy/4, 50 Gy/5, and 60 Gy/5) have similar outcomes without requiring as high of a biologically equivalent dose (BED). While regimens with BED > 100 Gy/10 may saturate the dose response curve at low risk of toxicity,6 perhaps some safety margin is helpful.

Simplifying treatment to single fraction regimens is also under investigation with RTOG 0915 recently suggesting similar outcomes between 48 Gy in 4 fractions and 34 Gy in 1 fraction,11 while retrospective single fraction series continue to emerge.39 The ideal fractionation for peripheral tumors remains controversial with a wide range of accepted fractionation schedules. As a result, more prospective data is needed.

Central tumors  
While SBRT for peripheral stage I NSCLC has uniformly been associated with low risk, treatment of tumors within 2 cm of the trachea and proximal bronchial tree was associated with only a 50% freedom from grade 3 or higher toxicity after 60 Gy in 3 fractions in an Indiana University phase II report,40 temporarily calling into question the safety of SBRT for central lung tumors. Of note, the early Japanese experiences using more moderate regimens such as 50 Gy in 5 fractions never discriminated between central or peripheral lesions without note of excessive toxicity in any subgroup.8 Since then, additional reports of SBRT safety for central tumors have emerged using moderate dose regimens from 50-70 Gy in 4-10 fractions.41-43 RTOG 0813, a multi-institutional dose escalation study for centrally located stage I NSCLC, also recently completed accrual escalating SBRT dose from 50 to 60 Gy in 5 fractions without protocol interruption due to dose-limiting toxicity.10 The early SBRT experiences employed few constraints focusing primarily on the maximization of conformity. Modern reports include a far more extensive set of normal tissue constraints, albeit still preliminary and only modestly validated. For patients presenting with larger central tumors, these constraints may not always be achievable. In this case, there is controversy over defaulting to conventionally fractionated radiation, although in my opinion, risk-adapted SBRT techniques such as the Dutch regimen of 60 Gy in 8 fractions maintain a BED > 100 Gy and are associated with excellent local control and safety.42 While there is some inherent risk with SBRT for such large targets, failure to control these lesions often also leads to local morbidity.

Additional lung SBRT applications  
Stage I small cell lung cancer (SCLC)  
While SCLC is typically treated with concurrent chemoradiation, rare stage I presentations have been managed with success by surgery and adjuvant chemotherapy. By extension, 2 recent small series have explored SBRT followed by adjuvant chemotherapy in medically inoperable and poor risk stage I SCLC.44,45 Prophylactic cranial irradiation in this setting is controversial.

Oligometastasis  
SBRT may serve a role in managing lung oligometastasis with published series frequently treating up to 5 lung metastasis during SBRT, although in our practice it’s typically limited to 1-2 oligometastatic sites. When treating oligometastasis, the intent of treatment must be clearly defined and balanced against the risks and cost of therapy.46
SBRT is most likely to add value in this setting with careful patient selection and with potential indications, including:

Curative intent treatment of patients with single lesions from metastatic colon or breast primaries based on extrapolation from surgical literature.

Newly diagnosed limited metastasis—ideally solitary—with a long interval from previous therapy, in which case SBRT might offer a delay in the need for potentially more toxic systemic therapy.

Isolated progression after a long interval of control on systemic therapy, possibly sterilizing isolated drug-resistant clones, best described in the anaplastic lymphoma kinase (ALK)- or epidermal growth factor receptor (EGFR)-mutated NSCLC setting.\(^47\)

Limited residual disease after a long interval of control on systemic therapy with the intent of a break from systemic therapy.

**SBRT as a boost for stage III NSCLC**

While OS is not compromised, local control after chemoradiation for locally advanced NSCLC has been modest compared to surgical series with further dose escalation failing to improve outcomes.\(^48,49,53\) SBRT is an alternative method of dose-intensification recently explored in 2 prospective series.\(^50,51\) Feddock et al. reported the use of an SBRT boost of either 10 Gy x 2 for peripheral targets, or 6.5 Gy x 3 for central targets (per the RTOG 0813 definition) after 60 Gy conventional chemoradiation.\(^50\) Treatment was well-tolerated (after modifications to the initial dose regimen for central tumors), and LC was a promising 83% at median 13 months. SBRT boost is a novel treatment approach with further investigation needed before widespread adoption.

**Re-irradiation**

Several series describe the use of SBRT for salvage of either isolated failure after conventional radiation for locally advanced disease.\(^52-56\) or SBRT for early stage disease.\(^57-59\) In both cases, patient selection is critical given modest progression-free survival and risk of toxicity. For local recurrences after prior EBRT, SBRT doses with BED > 100 Gy\(_{10}\) are associated with short-term LC ranging from 65-98%, although dyspnea and pneumonitis are common. Treatment of central or nodal recurrences is associated with a very high risk of toxicity.\(^56\) SBRT for local recurrence after previous SBRT of peripheral recurrences <5 cm is associated with short-term LC of 33-60% after re-irradiation, while repeat SBRT for central tumors has been associated with significant toxicity and should be approached with extreme caution.

**Conclusion**

SBRT is an innovative treatment approach and represents the standard of care for medically inoperable stage I NSCLC. As results mature and techniques evolve, SBRT may be expanded to progressively healthier populations, while its role in locally advanced disease, recurrent disease, SCLC and oligometatasis continues to be explored.

**References**


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