



# Approaches to stereotactic body radiation therapy for large ( $\geq 5$ centimeter) non-small cell lung cancer

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**Abstract:** Although larger ( $\geq 5$  cm) node-negative non-small cell lung cancer (NSCLC) lesions are altogether uncommon, their incidence may increase following the implementation of lung cancer screening. A rigorous assessment of stereotactic body radiation therapy (SBRT) for these challenging cases is imperative not only owing to concerns of increased risks when delivering ablative doses to large volumes, but also due to lack of prospective data, as these patients were excluded from seminal phase II SBRT trials. In addition to appraising the available institutional or multi-institutional experiences, multiple strategies to reduce toxicities are discussed. These include exploration of several different dose/fractionation schemes and regimens, as well as specialized techniques for SBRT treatment planning and delivery. Because these lesions have a higher rate of occult lymphatic or distant spread, the role of systemic therapies (including chemotherapy and immunotherapy) are also discussed. Altogether, the publication of several key reports, entirely over the last few years, has created a more solid foundation with which to utilize evidence-based management for this unique patient population.

**Keywords:** Non-small cell lung cancer (NSCLC); stereotactic body radiation therapy (SBRT); stereotactic ablative radiation therapy; toxicities; node negative

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## Introduction and importance

Although non-small cell lung cancer (NSCLC) is most commonly diagnosed by the time it has become locally advanced or metastatic (1), early-stage disease is expected to be diagnosed substantially more frequently with the increasing use of low-dose computed tomography (CT) screening (2-4). In the National Lung Screening Trial, roughly two-thirds of cancer diagnoses were early-stage (5).

Management of early-stage NSCLC centers on surgical resection, with stereotactic body radiation therapy [SBRT, also known as stereotactic ablative radiation therapy (SABR)] as the primary treatment option for non-surgical candidates

(6-8). Results from the Radiation Therapy Oncology Group (RTOG) 0236 trial (9) demonstrated SBRT to be a safe and efficacious option with which to treat these patients, and ablative dosing has also been shown to provide markedly superior outcomes to conventionally-fractionated radiotherapy (RT) (9,10). Owing to the success of SBRT as a powerful oncologic tool for many neoplasms (11-19), the utility of SBRT (as compared to surgery) for medically operable early-stage NSCLC is now a major area of ongoing investigation (20,21); the highest level of available evidence points to equipoise at minimum (22).

Although the “general” early-stage, node-negative NSCLC patient population most commonly has tumors

**Table 1** Clinical studies of stereotactic body radiation therapy for large ( $\geq 5$  cm) non-small cell lung tumors

| Reference                   | Sample size | Dose (Gray)/ fractions (no.) | Median follow-up (months) | Local control                    | Crude grade $\geq 2$ toxicities (%) | Crude grade $\geq 3$ toxicities (%) | Instances of grade 5 events | Overall survival                 |
|-----------------------------|-------------|------------------------------|---------------------------|----------------------------------|-------------------------------------|-------------------------------------|-----------------------------|----------------------------------|
| Woody <i>et al.</i> (29)    | 40          | 50/5 (68%),<br>60/8 (20%)    | 11                        | 64% (locoregional) at 18 months  | 13                                  | 8                                   | 0                           | 20 months                        |
| Verma <i>et al.</i> (30)    | 92          | 50/5 (47%),<br>48/4 (23%)    | 12                        | 96% at 1 year,<br>73% at 2 years | 25                                  | 7                                   | 1                           | 21 months                        |
| Peterson <i>et al.</i> (31) | 41          | 50/5 (median)                | 15                        | 95% (crude) at 15 months         | 17                                  | 10                                  | 0                           | 65% at 1 year,<br>34% at 2 years |
| Tekattli <i>et al.</i> (32) | 63          | 50/5 or 60/8                 | 55                        | 96% at 2 years                   | –                                   | 30                                  | 12                          | 28 months                        |
| Verma <i>et al.</i> (33)    | 201         | 50/5 (30%),<br>48/4 (23%)    | 41                        | –                                | –                                   | –                                   | –                           | 25 months                        |

under 3 centimeters (9), larger node-negative tumors also occur, albeit less frequently. A threshold of 5 centimeters was considered an exclusion criterion for RTOG 0236 and other phase II trials (23) owing to the uncommonality and concerns of increased toxicities (24) when delivering ablative doses to large volumes. As a result, there are considerably fewer retrospective, and no prospective, experiences of SBRT for these patients. Therefore, it is important to ascertain whether SBRT is an appropriately safe and effective option for these cases. This is especially important because it is likely that the incidence of screen-detected, large, node-negative NSCLC lesions will increase as lung cancer screening increases in utilization.

Although for purposes of this review, the 5 cm cutoff is utilized to denote “larger” lesions, the findings herein may be considered when thinking through treatment approaches for somewhat smaller tumors as well. Not only does a single-dimension measurement not necessarily equate to the overall tumor volume, smaller tumors that display considerably higher respiratory-related excursion also result in larger treatment volumes. Nevertheless, this review aims to explore current evidence for SBRT in  $\geq 5$  cm NSCLC, and it additionally discusses strategies to reduce toxicities as well as the utility of systemic therapies for this unique and challenging patient population.

### Clinical evidence

Although several retrospective studies have utilized other definitions of “larger” NSCLC cases (25–28), a dedicated discussion for  $\geq 5$  cm node-negative disease will be presented hereafter, and the pertinent literature for this population is summarized in *Table 1*. These results must be critically

appraised in the context of their retrospective nature, pre-radiotherapy workup, disease extent, individualized treatment planning considerations, and follow-up details.

A series of 40 patients was reported by investigators from Cleveland Clinic, 27 of whom received 5-fraction SBRT (50 Gy), and the remainder of whom received 8 or 10 fractions (29). Nearly half underwent endobronchial ultrasound (EBUS), and 27 patients had tumors located within 2 cm of the proximal bronchial tree. Median follow-up was 11 months. The reported 18-month locoregional control was 64%; median disease-free survival (DFS) and overall survival (OS) were 14 and 20 months, respectively. Crude rates of grades  $\geq 2$  and  $\geq 3$  toxicities were 13% and 8%, respectively.

The largest experience to date is a multi-institutional investigation of 92 patients treated at 12 academic institutions in the United States (30). Of these patients, 28% had centrally located tumors, with mediastinal nodal staging performed in just 35%. All patients received  $\leq 5$  fractions, with nearly three-quarters of patients receiving 50 Gy in 5 fractions or 48 Gy in 4 fractions. At a median follow-up of 12 months, the 1- and 2-year actuarial local control were 96% and 73%, respectively; median OS was 21 months. Crude instances of grades  $\geq 2$  and  $\geq 3$  toxicities were 25% and 7%, respectively. Grade 4–5 toxicities were limited to a single patient with a 180 pack-year smoking history and a 7.5 cm tumor who had grade 5 radiation pneumonitis possibly attributed to SBRT.

A report of 41 patients was published from Cooper University Hospital (31). Sixty-three percent of lesions were central, with the median RT dose and fractionation of 50 Gy in 5 fractions. At a median 15-month follow-up, the crude rate of local control was 95%; 1- and 2-year OS were 65%

and 34%, respectively. Altogether, 17% and 10% of patients experienced adverse events of grades  $\geq 2$  and  $\geq 3$ , respectively.

The only report to date with long-term follow-up (median 55 months) is a 63-patient series from the Netherlands (32). All patients were treated with 50 Gy in 5 fractions or 60 Gy in 8 fractions. Although the two-year local control was 96% and median OS was 28 months, the grade  $\geq 3$  toxicity rate was 30%. Twelve patients experienced potential SBRT-related grade 5 toxicities, eight of whom had been previously diagnosed with interstitial lung disease.

These studies may be summatively analyzed. With the exception of the final investigation, which consisted of high-risk circumstances (for several reasons, not limited to the high proportion of patients with high-risk pre-existing lung disease), SBRT affords few higher-grade toxicities, estimated at 10% or less in the remaining series reported to date. However, a caveat to this statement is that the short follow-up in those series was insufficient to make definitive conclusions. Additionally, outcomes were certainly encouraging in all studies given that the vast majority of patients were medically inoperable, and not more than half received pathologic mediastinal assessment (34) (implying that a certain proportion were regionally and/or distantly metastatic at presentation).

Additionally, clinicians must continue to weigh balances of tumor control and toxicities; the local control figures from available evidence were, for the most part, inferior to those of the “general” SBRT population (9,23). As a result, there is a theoretical merit to (safe) dose-escalation in these settings, especially since these patients suffering local/locoregional recurrences (most of whom remain medically inoperable) are difficult to salvage. Nevertheless, these decisions must be judiciously assessed based on tumor location and individual patient anatomy, together with risk factors for developing toxicities, which is further elaborated upon in the subsequent section.

### Toxicity reduction strategies

The aforementioned studies, firstly, indicate that careful patient selection of SBRT for these circumstances is critical. Patients with interstitial lung disease and/or potentially even very poor pre-treatment lung function may not be optimal candidates for routine SBRT management, along with patients in the cited series with tumors 7–12 cm in size (recognizing that there is no established consensus “upper limit” regarding lesion size-based candidacy of SBRT). Nevertheless, strategies to deliver ablative dosing in these

high-risk patients will be discussed subsequently.

Although delivery of pre-SBRT chemotherapy and treating post-chemotherapy tumor volumes or performing re-simulation after initial RT delivery is possible for small cell lung cancer in efforts to decrease treatment volumes, such approaches are less likely to achieve meaningful treatment volume changes for large node-negative NSCLC lesions owing to the generally less rapid response of NSCLC to chemotherapy or RT. This may also risk delaying delivery of potentially curative SBRT, which may have detrimental impacts on survival.

Modifying dose/fractionation schemes is a logical step that is often employed when treating central NSCLC lesions. These include delivering 60 Gy in 8 fractions (biologically effective dose (BED) of 105 Gy, assuming an  $\alpha/\beta$  of 10) based on data from VU Medical Center (35), and 70 Gy in 10 fractions (BED of 119 Gy) per MD Anderson Cancer Center (36). Delivery of 60 Gy in 10 fractions (BED of 96 Gy) may also be quite safe but delivers a BED  $<100$  Gy that may be associated with inferior local control (10,37).

The only study to date comparing SBRT fractionation schemes specifically in  $\geq 5$  cm NSCLC lesions was a secondary analysis of a 92-patient multi-institutional study (38). Half of all patients received 3–5 SBRT fraction on consecutive days, and the other half received nondaily regimens [most commonly every other day (QOD)]. Baseline patient, tumor, and treatment characteristics were similar between both groups, and of note those receiving 5 fractions were more likely to receive daily treatment and those receiving 3–4 fractions were more likely to receive QOD treatment. Crude rates of grade  $\geq 2$  adverse events were 43% in the daily cohort and just 7% in the QOD group (encompassing one case each of grades 2 and 3 pneumonitis, and one instance of grade 3 dermatitis) ( $P < 0.001$ ); when plotted actuarially, freedom from grade  $\geq 2$  toxicities favored the QOD patients ( $P = 0.007$ ).

Another strategy can be to utilize an element of inverse-planned RT. Simultaneous integrated boosting is a technique that allows administration of different doses to separately defined volumes. This may carry utility in the lung SBRT setting by delivering a higher dose per fraction to gross disease, allowing the planning target volume (PTV) to receive a lower fractional dose (e.g., in 10 fractions, delivering 60–70 Gy to gross disease and 50–60 Gy to the PTV) (39).

Additionally, given that treatment volumes receiving prescription doses are reliant on respiratory excursion, creation of an integrated gross tumor volume (iGTV)

across all (generally 8–10) breathing phases may increase the overall volume treated. In efforts to decrease this, using breath-holding or gated techniques may be considered, in which the RT beam is not on continuously, but rather only when the tumor becomes “in-phase” with a predefined standard. Use of abdominal compression and/or voice coaching may also be used as adjunctive tools to limit excessive tumor movement with respiration (40). Although manipulation of margin length is uncommonly performed for lung SBRT (i.e., a 5 mm isotropic margin from the iGTV to PTV), it is also theoretically possible to decrease this (e.g., 3 mm) if precise image guidance is employed, especially with favorable tumor locations with little tumor excursion on respiration. However, when considering tumor volume expansion reductions, volumetric imaging (and not KV-KV imaging) is recommended (41), and consideration of an interplay effect with volumetric modulated arc therapy (VMAT) based treatments (42) as well as a potential for increased risk of microscopic tumor extension with larger tumors should be considered.

Additionally, the risk of radiation pneumonitis based on dose-volume constraints should continue to be re-evaluated. Although specific dose constraints are dependent on the number of fractions (6), contemporary RTOG protocols (0618, 0813, and 0915) suggest that the  $V_{20}$  of the total lung should be kept below 10% (with <15% acceptable). However, this constraint remains the same for a wide variety of PTV sizes, which is not intuitive since lung dose-volume parameters such as  $V_{20}$  are indirectly related to lesion size. Given the current lack of data, it is important to perform dosimetric analyses with novel methodologies such as machine learning algorithms (43) to better address these issues. Until further data are reported, however, stricter dose-volume constraints for patients with larger lesions should be considered in efforts to minimize the risk of radiation pneumonitis.

Lastly, there have been multiple reports of stereotactic body proton therapy (SBPT) for larger lung lesions, taking advantage of the characteristic Bragg peak of the heavy proton (44–47). These have encompassed a larger proportion of T2 tumors (including those 5 cm and greater), with 2-year local control 90% or higher and grade  $\geq 3$  pneumonitis rates 10% or less. However, due to concerns of the interplay effect (48), most reports have delivered treatment with hypofractionated (non-ablative) doses, generally in 10 or more fractions. Although in a meta-analysis proton therapy was associated with better survival and local control compared with photon-based SBRT in

early stage NSCLC (49), it is likely that proton therapy may not have as large of a magnitude of benefit for early-stage NSCLC compared with locally advanced NSCLC (50–52). That being said, protons may provide proportionally greater benefits for larger early stage tumors that are at higher risk of toxicities, while maintaining administration of ablative or escalated doses, or even allowing for dose escalation for these larger tumors that have suboptimal local control with current photon dose-fractionation regimens.

Taken together, even in high-risk SBRT populations, there are many strategies to attempt to mitigate potential toxicities. Although these options are presented in parallel, performing multiple of the aforementioned maneuvers in the same patient may prove to be the safest approach while still allowing for ablative dosing, thus enhancing the therapeutic ratio.

### Systemic therapy

From surgical series, node-negative NSCLC lesion size correlates with the rate of occult nodal positivity. Tumors <1, 1–2, 2–3, and >3 cm in size have pathologic node-positive disease in 0–2%, 10–16%, 30–47%, and >57% of specimens, respectively (53,54). Although from the aforementioned studies of larger tumors, the rate of isolated nodal failure remains low (<10%), nodal involvement may provide a nidus for distant metastases, the dominant mode of relapse in these patients. Although prophylactic mediastinal RT in these circumstances is wholly unproven, systemic therapy represents an option to safeguard against the risk of nodal and metastatic disease.

Outcomes of larger NSCLC lesions in the postoperative setting will be briefly described, although caveats must be exercised when directly extrapolating these data to the SBRT setting. The LACE meta-analysis estimated the influence of postoperative chemotherapy by tumor stage; this revealed a statistically significant effect only for stages IIA and above (55). However, although IIA disease encompasses both node-negative and node-positive disease, the study did not separate outcomes by these factors (potentially related to the loss of statistical power by doing so). Furthermore, an unplanned subset analysis of the CALGB 9633 trial showed an OS benefit to postoperative chemotherapy in lesions  $\geq 4$  cm in size (56). Based on these two studies, national guidelines endorse considering post-SBRT chemotherapy in tumors with high-risk features, including lymphovascular invasion, size  $\geq 4$  cm, visceral pleural invasion, and several other factors (6).

However, direct evidence in the SBRT setting is lacking. There are two known reports evaluating this issue. An investigation from China showed an OS benefit with the addition of chemotherapy to T1–3 disease, but it did not show a difference in cancer-specific survival (57). Given the absence of a multivariable analysis in that retrospective study, both of those findings may be explained by “healthier” patients having received chemotherapy, especially recognizing that T1 disease is unlikely to reap significant benefits from chemotherapy.

A 201-patient analysis of the National Cancer Data Base partially rectified some of the aforementioned concerns, although that dataset records no information on cancer-specific survival (33). That study specifically evaluated tumors  $\geq 5$  cm treated with SBRT; an increase in OS was demonstrated, along with an independent association on multivariable assessment. Although selection biases and availability of only OS are shortcomings to that publication, it may also be posited that patients receiving chemotherapy were likely of “higher-risk” to have justified the use of non-standard treatment. These patients may have had higher-risk surgery, lymphovascular invasion, or other factors that national recommendations deem as “high-risk” factors (6). Although these may predispose to worse outcomes with SBRT alone, the addition of chemotherapy did not equalize the survival curves but rather showed statistically significant improvement despite the potential presence of such poorer-risk features.

A rapidly expanding form of systemic therapy that may be efficacious for these circumstances is immunotherapy. These compounds, which galvanize the *de novo* immune system to adopt more enhanced anti-tumoral phenotypes, have shown high efficacy in NSCLC and may allow for synergy with radiotherapy (58–60). Immunotherapy is attractive as an adjunct to SBRT because the primary mode of post-SBRT failure is distant, and since immunotherapy is often better tolerated compared with conventional cytotoxic chemotherapy for NSCLC (61). The specificity and increased tolerance of immunotherapy may thus benefit a highly comorbid, medically inoperable SBRT population. Clinical trials of immunotherapy with RT for NSCLC are expanding, and an ongoing trial from MD Anderson Cancer Center is evaluating combined nivolumab and SBRT for not only stage I NSCLC, but tumors  $\geq 5$  cm as well (62).

### Concluding remarks

Amid the apprehension of delivering ablative RT doses

to large volumes with SBRT, there are now multiple corroborative studies that demonstrate the safety and efficacy of doing so. Several strategies can be considered in an attempt to reduce the risk of high-grade toxicities following SBRT to these large tumor volumes. The role of post-SBRT systemic therapy is also continuing to evolve, with increasing interest in immunotherapy. Although surgery currently remains the standard of care for early-stage NSCLC, and it is likely of proportionally greater benefit for  $\geq 5$  cm tumors (owing to the higher propensity for these tumors to have microscopic parenchymal spread that would be resected with surgery, the higher propensity for these tumors to have lymphatic spread that would be dissected with surgery, and the more limited long-term local control for these larger lesions following SBRT compared with smaller lesions), there is now a considerably higher evidence base for utilizing ablative RT in medically inoperable patients than existed even just a few years ago.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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