



Stereotactic body radiation therapy in early-stage NSCLC: historical review, contemporary evidence and future implications

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Practice points

- Current standard-of-care for early-stage, nonoperative NSCLC is stereotactic body radiation therapy (SBRT).
- SBRT is a noninvasive treatment involving the precise delivery of ablative dose radiation.
- Compared with fractionated radiation, SBRT achieves superior local control and survival.
- Prospective trials comparing surgical resection versus SBRT are currently accruing.
- Lung cancer screening and the obesity epidemic may increase the incidence of inoperable cases.

Clinical use of stereotactic body radiation therapy (SBRT) has increased dramatically over the last 2 decades and is the current standard-of-care in cases of inoperable early stage non-small-cell lung cancer. While surgical resection remains the standard-of-care for operable patients, several ongoing clinical trials are investigating the role of SBRT in these operative candidates as well. Taking into consideration the expanding role and utility of SBRT, this paper will: review the historical basis of SBRT; examine landmark trials establishing the framework for the current body of evidence; discuss areas of active and future research; and identify epidemiological trends that are likely to further increase the use of SBRT.

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Lung cancer is a commonly diagnosed malignancy and a major cause of oncologic morbidity and mortality. In 2018, lung cancer was estimated to account for 13% of newly diagnosed malignancies, as well as 25% of cancer-related deaths in the USA [1]. Of the approximately 234,000 annual cases of lung cancer diagnosed in the USA, the vast majority (80–85%) are of the non-small-cell lung cancer (NSCLC) variant. NSCLC is a discrete entity from small-cell lung carcinoma (SCLC) and includes the histological subtypes of adenocarcinoma, adenosquamous carcinoma, squamous cell carcinoma, large cell carcinoma and sarcomatoid carcinoma [2]. Although lung cancer historically has a poor prognosis, early-stage NSCLC (ES-NSCLC) generally has more favorable outcomes, particularly in patients amenable to surgical resection [3].

Current standard of care in ES-NSCLC: surgical resection

Surgical resection (segmentectomy or lobectomy/pneumonectomy depending on location, clinical factors and extent of disease) with mediastinal lymph node dissection represents a potentially curative treatment that is the current standard of care for patients with operable ES-NSCLC [3–5]. Survival is particularly favorable in patients with small or less invasive tumors (T1a–c), in which 5-year survival typically ranges from 80 to 90% [6]. The success of surgical resection in ES-NSCLC highlights the importance of early detection of disease in improving survival and the critical nature of identifying which patients are eligible for surgery. An adequate pretreatment workup is essential and begins with global assessment of functional status with history and physical examination, basic laboratory

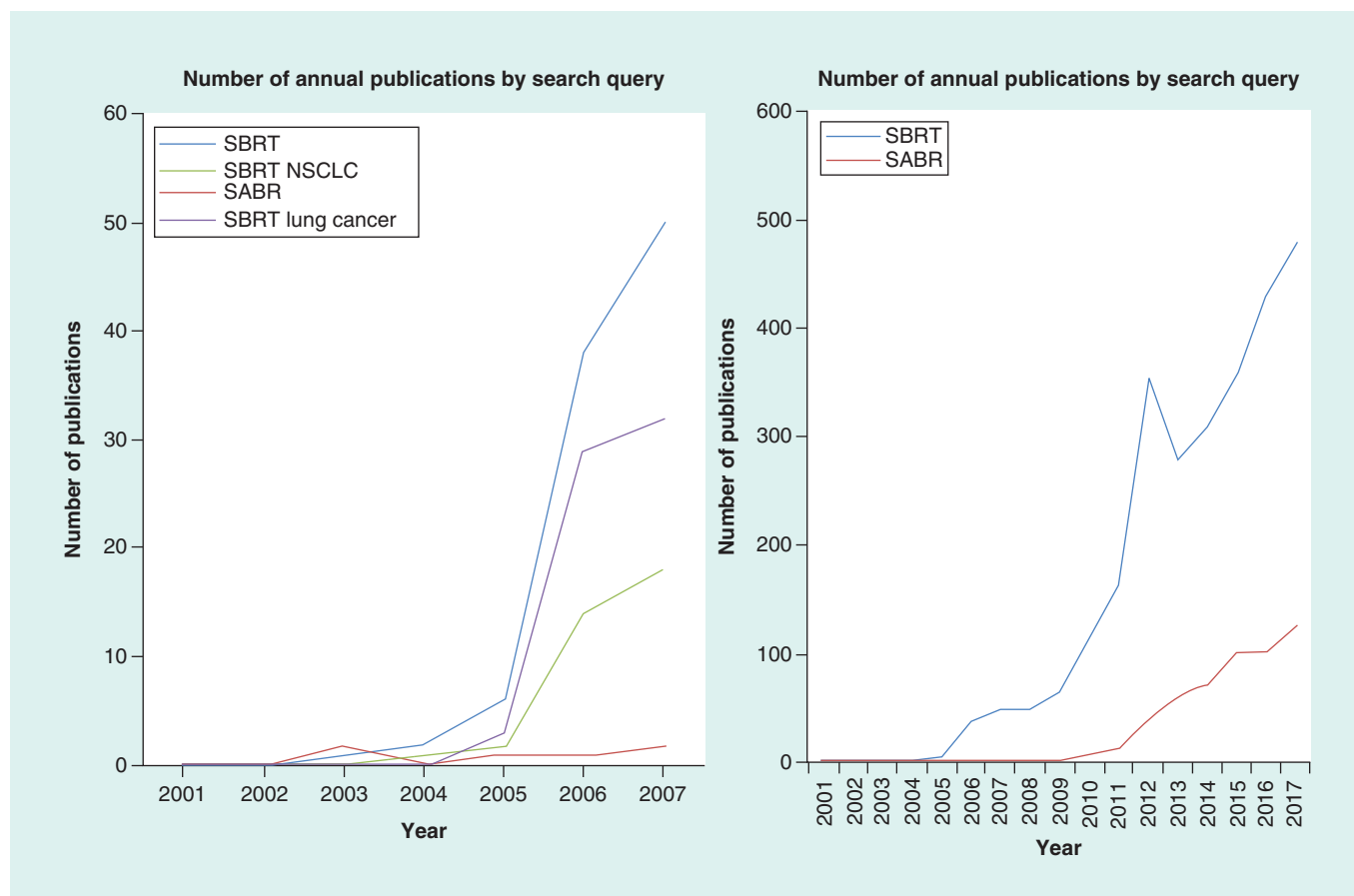


Figure 1. National Library of Medicine's PubMed publications by year based upon search query.
 NSCLC: Non-small-cell lung cancer; SABR: Stereotactic ablative radiotherapy; SBRT: Stereotactic body radiation therapy.

studies and recent pulmonary function tests. In addition, noninvasive staging modalities such as the appropriate structural and functional imaging studies are obtained and, if tolerated by the patient, invasive diagnostic strategies such as endobronchial and/or mediastinal evaluation [2]. Unfortunately, many patients diagnosed with lung cancer are either frail or have comorbid cardiopulmonary disease as a result of aging and/or tobacco abuse. In a subset of these patients, the degree of frailty or severity of cardiopulmonary comorbidities precludes surgery, theoretically reducing the patient's chance of curative therapy.

Historical approach to medically inoperable ES-NSCLC

Historically, the majority of the patients, who elected observation, died from cancer despite having severe cardiopulmonary comorbidities, thus emphasizing the need for oncologic treatment [7,8]. These nonsurgical patients, either deemed 'medically inoperable' or refusing surgical resection, were treated with conventionally fractionated radiation therapy (CFRT) with or without concurrent chemotherapy [9–11]. Alone, CFRT was usually delivered to a total dose of 60–70 Gy in 1.8–2.0 Gy fractions. With the aid of modern 3D conformal techniques, radiation dose escalation was investigated and found to improve survival when not used concurrently with chemotherapy [11–13]. A review by Sibley *et al.* [12], as well as, a meta-analysis by Ramroth *et al.* [11], corroborated the suggestion of improved outcomes with escalation of biologically effective dose (BED). Yet, survival and local control remained far inferior to that of surgery, and general consensus was the nominal benefit of CFRT did not adequately address the therapeutic need in these nonsurgical patients [14]. In search of alternative treatment approaches and drawing on the principles of BED escalation, clinicians in Sweden and Japan began to explore hypofractionated treatment schedules [15,16]. Described as stereotactic body radiation therapy (SBRT) and/or stereotactic ablative therapy (SABR), these hypofractionated regimens showed promising results, leading to increased use globally (Figure 1) [17–24].

Origins of SBRT

The origins of SBRT can be traced to the successes of intracranial stereotactic radiosurgery (SRS) first conceptualized in the 1950s by Swedish neurosurgeon, Lars Leksell [25]. Leksell's first prototype design was introduced clinically in 1967, a construct with multiple, nonopposed cobalt-60 sources arranged in a hemisphere with a surrounding collimator. Through manipulation of the collimator, output γ rays were converged on the target with a high degree of conformality. By the 1980s, linear accelerator-based SRS platforms were developed and employed [26]. The first reports demonstrating the feasibility and safety of high-dose-per-fraction treatments in the extracranial setting were the early efforts of the Swedish and Japanese [15,16]. Building on the efforts of the Swedish and Japanese, a German group began to investigate the role of stereotactic radiation therapy in the setting of inoperable lung and liver tumors [27]. In light of these encouraging international results, Phase I studies were soon to follow in North America [28].

Principles & technical challenges of extracranial stereotactic radiotherapy

SBRT is a noninvasive treatment involving the precise delivery of ablative doses of ionizing radiation in one or a 'few' fractions to extracranial sites of disease [29,30]. Regarding fractionation, the American Society of Therapeutic Radiation Oncology has a slightly more restrictive definition for SBRT (i.e., 1–5 fractions), whereas in Europe, SBRT encompasses 1–8 fractions [29,30]. As opposed to intracranial targets, the treatment of extracranial disease presents the challenge of target motion. This challenge is made more difficult since immobilization with a rigid frame as often utilized with intracranial SRS is not feasible given the necessary physiologic movement of the thorax. Devices such as body contour molds are utilized; however, these do not achieve the same degree of immobilization as seen with intracranial SRS. To account for limitations with immobilization, sophisticated image guidance is employed for daily target visualization and tracking during breathing-related motion. Techniques such as respiratory gating and 4D computed tomography have been developed to manage the issue of respiratory-related tumor motion. With appropriate image guidance, advantages of SBRT over CFRT include: higher dose-per-fraction treatments with a resultant increase in the BED, tight target margins with sharper dose gradient leading to reduced dose to normal tissue, and shorter treatment duration minimizing patient inconvenience and allowing for initiation/resumption of systemic therapy more quickly. Since the entire treatment dose is delivered over the course of 1–5 fractions, accuracy is of utmost importance. Errors can easily be magnified in comparison with CFRT, as an inaccuracy is more likely to allow tumor progression and/or contribute excessive toxicity to normal adjacent tissue.

Early clinical evidence in medically inoperable ES-NSCLC

In 2003, Timmerman *et al.*, from Indiana University, was the first North American group to report results on the safety of extracranial stereotactic radiation treatment in 37 patients [28]. Treatment was delivered to a cumulative dose of 60 Gy in three fractions (without accounting for tissue heterogeneity) and found to have acceptable tolerance with only two patients developing Grade 3 acute toxicity. Phase II trials were soon to follow in North America as the Radiation Therapy Oncology Group (RTOG) enrolled patients from 2004 to 2006 [31]. Patients diagnosed with medically inoperable ES-NSCLC having peripheral tumors <5 cm were included and treated to a prescription dose of 54 Gy in three fractions (with tissue heterogeneity correction). The results of this RTOG study (RTOG 0236) were reported in 2010 and showed excellent local control (97%) with 3-year survival of 56%. With local control exceeding 90–95%, the results of this prospective study corroborated findings of several retrospective series and previous Phase I trials, suggesting a significant local control benefit with SBRT compared with that of CFRT [20–24,32]. [Table 1](#) provides a summary of selected prospective studies.

Toxicity & adverse effects (clinically & radiographically)

With BED in the realm of 100–150 Gy₁₀, significant toxicity may occur if appropriate quality assurance measures are not followed. Toxicities can present acutely (<1 month from treatment) or as a late complication. Respecting normal tissue dose constraints and accurate target delineation during treatment planning and delivery is essential, particularly in patients with minimal lung reserve. Overall, treatment is well tolerated, with the majority of patients experiencing minimal to no adverse effects or decline in pulmonary function. Patients may experience treatment-related fatigue; however, this is usually mild and self-limiting [34]. With the exception of fatigue, adverse treatment effects and toxicity are typically related to the location of the tumor (peripheral vs central) and its proximity to adjacent organs at risk.

Table 1. Summary of selected prospective studies assessing stereotactic body radiation therapy in NSCLC.

Study/ Investigator(s) [Ref.]	Publication year	Number of patients	Radiation dose/fractionation (Gy)	BED ₁₀ (Gy)	Local control (%)	Overall survival (%)	Toxicity (≥ Grade 3)
Kyoto University, Japan/Nagata [17]	2005	45	48/4	105.6	98%	Stage IA at: 1 year: 92% 3 year: 83% Stage IB at: 1 year: 82% 3 year: 72%	None
Air Force General Hospital, China/Xia [19]	2006	43	50/5	100	95%	1 year: 100% 3 year: 91%	2% (n = 1); pneumonitis
Nordic Group/Baumann & Nyman [29]	2009	57	66/3	211.2	92%	3 year: 60%	30% (n = 17)
RTOG 0236/Timmerman [31]	2010	55	54/3	151.2	93%	5 year: 40 %	27% (n = 15)
Princess Margaret/Taremi [33]	2012	108	60/3 (n = 31) 54/3 (n = 20) 48/4 (n = 43) 60/8 (n = 9) 50/10 (n = 11)	180 151.2 105.6 105 75	100% 95% 95% 78% 82%	1 year: 84% 4 year: 30%	15% (n = 16)
RTOG 0915/Videtic [34]	2013	84	34/1 (n = 39) 48/4 (n = 45)	149.6 105.6	97% 98%	2 year: 61.3% 2 year: 77.7%	10% (n = 4) 13% (n = 6)
EORTC- LungTech/Adebahr [35]	2015	39	60/8	105	Not yet reported	Not yet reported	Not yet reported
SPACE/Nyman & Hallqvist [36]	2016	49	66/3	211.2	86%	1 year: 81% 3 year: 54%	14% (n = 7)

BED: Biologically effective dose; RTOG: Radiation Therapy Oncology Group.

Peripheral lesions

By definition, peripheral lesions are located > 2 cm from the primary bronchi or trachea. Previous prospective studies have reported Grade 3+ toxicities of 10–20% in patients receiving SBRT to peripheral lung lesions [37,38]. However, a number of retrospective and prospective studies have suggested that the rate of toxicity is much lower, with most reporting Grade 3+ toxicities of <5% [39–42]. Peripheral tumors are often located further from the proximal airways and closer to the chest wall. As a result, a larger volume of chest wall receives a greater dose, thus raising the probability of local toxicity including chest wall pain, rib fractures and occasionally radiodermatitis. Retrospective analyses suggest that the risk of ≥ Grade 2 chest wall, skin and rib toxicity are low, but not insignificant (2–3%) [43–46]. Both the max skin dose and volume of chest wall receiving 30 Gy have shown value in predicting toxicity [45,47]. Similarly, apical lung tumors have been associated with increased incidence of radiation induced brachial plexopathy. However, brachial plexopathy is more commonly due to tumor progression as opposed to radiation induced [48,49]. In addition to tumor related factors, patient related factors such as obesity and osteoporosis have also been associated with increased skin/chest wall toxicity and rib toxicity [46,50].

Radiation-induced pneumonitis is the most frequent acute pulmonary toxicity [30]. Clinically symptomatic pneumonitis develops in less than 10% of patients with most patients having asymptomatic Grade 1 pneumonitis [51–53]. Predictors of ≥ Grade 2 pneumonitis include mean lung dose of greater than 4 Gy and the volume of lung receiving ≥20 Gy (lung V20) exceeding 4% [54]. Pretreatment pulmonary function tests have not been shown to predict for pneumonitis [55]. The vast majority of patients develop late pulmonary toxicity characterized by asymptomatic localized pulmonary fibrosis in the high-dose treatment field [56]. Radiographic changes secondary to localized radiation induced fibrosis can lead to inaccurate radiologic interpretation. Incorrectly interpreting post-treatment changes as pneumonia can have downstream consequences including unnecessary exposure to antibiotics, needless hospitalizations and patient inconvenience. As a result, clinicians should inform patients of these effects in an effort to circumvent potential future incorrect diagnoses.

Central lesions

Located in close proximity to the mediastinal and primary tracheobronchial structures, central tumors have a degree of risk and toxicity profile that differs from peripheral lesions. In a prospective Phase II study conducted at

Indiana University, patients with ES-NSCLC were treated to 60 Gy in three fractions (without dose heterogeneity correction) using SBRT [38]. Treatment of the central tumors were shown to increase patient's risk of Grade 3+ toxicity by 11-fold when compared with peripheral tumors and was a predictive factor associated with severe toxicity. These findings brought to light the challenges of safely treating centrally located tumors and established a proverbial 'no fly zone' [38]. Historically, the 'no fly zone' was defined as presence of tumor within 2 cm of the proximal bronchial tree, which encompassed the distal 2 cm of the trachea, carina, main bronchi and named major lobar bronchi [38]. As a result of safety concerns, patients with tumors present in this region were excluded from the seminal North American cooperative group trial, RTOG 0236 [31]. Since that time, multiple institutions have demonstrated the safety of SBRT in treating centrally located tumors through a combination of improved image guidance, better immobilization techniques and adjustment of dose-fractionation parameters [57,58]. Improved safety was observed with dose per fraction reductions in the range of BED₁₀ 80–120 Gy; however, this was at the expense of increasing local failure rates when de-escalated below a BED₁₀ of 100 Gy [35,59]. While the optimal dose-fractionation scheme in centrally located tumors has yet to be definitively established, a safe but efficacious (i.e., BED₁₀ ≥ 100 Gy) 'risk-adapted' regimen, in which 60 Gy delivered over eight fractions was first described by Dutch investigators in 2011 [23]. This regimen demonstrated both excellent 3-year local control rates (>90%) and safety, as only 3% of patient experienced toxicity of Grade 3 or greater. These findings have led to the initiation of Phase I/II studies conducted by the RTOG (RTOG 0813) and EORTC (LungTech), which will attempt to clarify the interrelationships of dose-fractionation with safety and efficacy [33]. Recently, further characterization of central tumors has been suggested, in which tumors with direct abutment or invasion of the proximal bronchial tree, are subclassified as ultracentral [35]. Given the degree of anatomic centrality, these tumors are felt to increase the risk of treatment-related toxicity and merit further subclassification. With improvements in imaging techniques and refinement of motion management strategies, the definition of centrally located tumors will likely continue to be restricted.

Comparison of SBRT versus CFRT

As evidence supporting the role of SBRT continued to accumulate, three prospective studies were initiated to directly compare outcomes in patients treated with SBRT with CFRT. The first randomized Phase II trial was undertaken in Scandinavia from 2007 to 2011 [59]. A total of 102 patients with medically inoperable ES-NSCLC were randomly assigned to receive either SBRT (n = 49; 66 Gy in three fractions) or CFRT (n = 52; 70 Gy in 35 fractions). The SBRT arm included more patients with T2 tumors compared with the CFRT arm. Although no difference in progression free or overall survival (OS) was observed, a trend toward improved disease control was observed in the SBRT group. Furthermore, quality of life and toxicity were improved with SBRT as lower rates of patient-reported dyspnea, chest pain, cough and esophagitis were observed in the SBRT arm. The results of a second prospective investigation were reported in 2017 by the Trans-Tasman Radiation Oncology Group and Australasian Lung Cancer Trials Group (NCT01014130). Patients with peripheral medically inoperable ES-NSCLC were randomly assigned to receive SBRT (n = 66; 54 Gy/3 fractions or 48 Gy/4 fractions) or CFRT (n = 35; 66 Gy/33 fractions or 50 Gy/20 fractions) with the primary objective of time to local failure. Patients in the SBRT arm were reported to have superior freedom from local failure (HR: 0.29; p = 0.002) and improved OS (HR: 0.51; p = 0.020) compared with patients receiving CFRT. A third prospective investigation was initiated in Canada in 2014 [36]. Sponsored by the Ontario Clinical Oncology Group (OCOG), this multicenter Phase III investigation is ongoing and intends to enroll 320 patients with medically inoperable ES-NSCLC to SBRT versus CFRT in a 2:1 ratio. The estimated date of study completion is 2021, with a primary objective of local control at 5 years.

Comparison of SBRT versus surgery

The excellent local control rates (>90%) consistently observed in both retrospective and prospective series in patients with medically inoperable ES-NSCLC treated with SBRT, in conjunction with population-based studies and propensity-matched analyses suggesting comparable OS with that of surgery, led to the initiation of several prospective Phase III investigations that attempted to directly compare outcomes of SBRT with surgery in medically operable patient's with ES-NSCLC (ROSEL, STARS, ACOSOG Z4099). Of note, many physicians were reluctant to enroll patients within the SBRT arm, as treatment with SBRT leaves patients subject to both in-lobe recurrences, as well as, in-lobe secondary primary lung cancers; complications that would otherwise not occur with lobectomy. As a result of physician and/or patient hesitancy to enroll, all three randomized trials comparing surgery with SBRT

for ES-NSCLC (STARS [NCT00840749], ROSEL [NCT00687986] and ACOSOG Z4099 [NCT01336894]) were forced to close early due to poor accrual numbers. However, a pooled analysis by Chang *et al.* combining patients enrolled in the STARS and ROSEL studies was completed [42]. A total of 58 patients were included (SBRT: $n = 31$ and surgery $n = 27$) with a median follow-up of 35 months. Pooled estimated OS at 1 and 3 years was 100 and 95% in the SBRT group and 88 and 79% in the surgical group; a statistically significant difference ($p = 0.037$; HR: 0.14; 95% CI: 0.017–1.190). No difference in local, regional or distant metastasis was observed. With regards to toxicity, 10% of patients in the SBRT arm experienced Grade 3 toxicity with no Grade 4/5 toxicities; while 44% of patients in the surgical arm experienced Grade 3/4 toxicity with one patient experiencing Grade 5 toxicity.

A meta-analysis published in 2016 by Deng *et al.*, reviewed the results of 12 cohorts and compared outcomes of SBRT, sublobar resection and lobectomy [60]. No difference in 3-year locoregional control was observed between SBRT and resection; however, SBRT was associated with worse 3-year OS when compared with lobectomy. Interestingly, this difference in OS was not evident when comparing SBRT with sublobar resection. Considering that operative candidates generally carry less comorbidities and a higher degree of medical fitness, this perceived survival advantage may be confounded by patient selection. Patients with poorer overall health/more comorbidities (i.e., inoperable candidates) would be expected to have poorer OS compared with healthier patients (i.e., operable candidates) regardless of the local therapeutic modality employed. Additionally, more robust patients are more likely to be considered for systemic therapy in cases of disease progression, which may confound matters further. As such, the oncologic end point of OS should be interpreted with caution when comparing unbalanced populations. Although physicians may continue to be wary of in-lobe recurrences or the development of in-lobe secondary lung cancers following SBRT, retrospective data have demonstrated safe and effective use of SBRT as a salvage modality or in treatment of a new lung primary adjacent to a site previously treated with SBRT [61].

Future implications

Following a systemic literature review from 1995 to 2016, the American Society for Radiation Oncology issued a clinical guideline in 2017 regarding the use of SBRT in ES-NSCLC [62]. This guideline reinforced SBRT as the standard of care in medically inoperable patients, a viewpoint echoed by that of the American Society of Clinical Oncology in 2018 [63]. In addition, the American Society for Radiation Oncology guideline elaborated further regarding the customization of SBRT in medically inoperable patients, who have high-risk anatomic (i.e., management of centrally located tumors, tumors invading the chest wall, tumors > 5 cm in size) or complex clinical scenarios (i.e., salvage therapy after radiation or surgery, nonbiopsied patients, multiple primary lung cancers and patients who have undergone pneumonectomy) and the appropriateness of SBRT as an alternative to surgery for different subsets of medically operable patients (standard vs high risk of surgical-related morbidity and mortality). In regard to the latter, patients that are at greater risk of surgical morbidity/mortality or those who are unable to tolerate a lobectomy but are candidates for sublobar resection may be considered for SBRT after multidisciplinary review of the case and discussion with the patient. This subset of ‘high-risk’ patients often carries comorbidities that not only preclude lobectomy, but even needle biopsy. These patients have been increasingly treated with SBRT empirically (based upon PET/computed tomography [CT] findings), without establishment of a pathological diagnosis [64–66]. Overall, the results of retrospective series have been encouraging [64–66].

From an epidemiologic perspective, this subset of ‘high risk’ surgical candidates will conceivably increase considering the underlying healthcare landscape in the USA. First, the obesity epidemic continues to worsen, as approximately 40% of adult Americans are now considered obese [67]. Though obesity in its own right is generally not a contraindication to surgery, the multitude of comorbidities such as diabetes, cardiopulmonary disease and/or liver disease if present may preclude surgery. Second, increased screening efforts by primary care providers to detect lung cancer at an early stage will inevitably lead to an increasing number of early stage cases. Screening efforts are based upon the statement of the United States Preventative Services and Task Force in 2014 recommending annual screening for lung cancer with low-dose CT in adults age 55–80 years old who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years; a statement that has since been supported by numerous organizations including the National Comprehensive Cancer Network [2,68]. This recommendation carries a specifier which states that screening should be discontinued if a person develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. In an era of effective noninvasive treatment, this specifier will likely need to be modified if not eliminated.

International efforts are underway in an attempt to answer the valid question of whether SBRT and surgery are indeed at equipoise. Given the challenges of patient accrual, a Phase III feasibility study known as SABRTOOTH

(NCT02629458) is underway in the United Kingdom to assess the recruitment rate and determine whether or not the rate is sustainable to conduct a Phase III clinical trial comparing SBRT with resection. In China, the POSTLIV trial (NCT01753414) with a primary objective of locoregional control at 2 years is ongoing and will compare lobectomy with SBRT in peripheral-based tumors. Two Phase III trials are also ongoing in the USA. The first, known as STABLE-MATES, has enrolled 102 patients and will compare 2-year disease-free and OS in high risk surgical candidates, who undergo sublobar resection versus SBRT (NCT02468024). A second trial known as VALOR (NCT02984761), involves patients within the Veteran Affairs system. The trial opened in 2017 and will compare survival outcomes and quality of life between SBRT and surgical resection. As randomized, prospective data become available, we will hopefully come closer to clarifying the role of SBRT in ES-NSCLC. In the interim, treatment decisions will continue to be rooted in the available body of evidence and from discussions with both the multidisciplinary team and, most importantly, the patient.

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