Review Article

Stereotactic body radiation therapy (SBRT) for early stage non-small cell lung cancer (NSCLC): contemporary insights and advances

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Abstract: The standard-of-care treatment for early-stage non-small cell lung cancer (NSCLC) continues to be surgery in the form of lobectomy or pneumonectomy. Stereotactic body radiation therapy (SBRT) has evolved as a viable alternative to surgery for medically inoperable patients, achieving excellent local control (LC) with relatively minimal toxicity in standard-risk patients. Nevertheless, the maturation of SBRT has fostered debate regarding its use, technique, dose, and fractionation, particularly in the context of patient- and disease-specific characteristics such as tumor size and location. This review will cover the recent trends and future directions of SBRT as it becomes an increasingly individualized modality in the treatment of early-stage NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); early-stage lung cancer; stereotactic ablative radiotherapy (SABR)

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Introduction

Despite the decline of smoking in the past several years (1), lung cancer remains the second most common cancer in men and women, but remains the most common cause of cancer-related death, accounting for over one-quarter of cancer-related deaths in the United States. There are over 200,000 new cases of lung cancer each year (2), approximately 85% of which are non-small cell lung cancers (NSCLCs), the predominant histologic type. Roughly 15% of NSCLCs are at an early, localized stage at presentation (3). Surgery, in the form of lobectomy, bi-lobectomy, or pneumonectomy, remains the standard of care in early stage (T1T2N0) NSCLC and results in 5-year survival rates of 60–70% (4-6). These anatomic pulmonary resections are preferred over sublobar resections due to previous data suggesting inferior survival outcomes with lesser surgery (7), but sublobar resection (including wedge and segmentectomy) can be considered appropriate for patients at high-risk for lobectomy and who have a small peripheral nodule (ideally 2 cm or less).

Patients deemed medically inoperable, either due to comorbidity or refusal of surgery, have historically been treated with definitive conventionally-fractionated external beam radiotherapy over 6–7 weeks with generally inferior results to surgery (reported 5-year survival range from 6–32%). This is likely in part due to selection bias (since medically inoperable patients typically have more medical co-morbidities and are older), and the inferiority of clinical *vs.* pathologic staging (8-11). Given these inadequate outcomes, there have been multiple attempts at dose-

escalation, many of which demonstrate benefit (9,12-16) and few that do not (17,18).

Since its development in the 1990s at the Karolinska Institute in Stockholm, Sweden as an adaptation of intracranial stereotactic radiosurgery (19), SBRT [synonym stereotactic ablative radiotherapy (SABR)] has emerged as one of the most significant advances in modern radiotherapy. By utilizing accurate target delineation, motion management, conformal treatment planning, and daily image guidance, SBRT is able to deliver high doses in few fractions and provide a steep dose fall-off outside the target (20,21). As a natural extension of attempts at dose-escalation in the setting of lung cancer, SBRT has now become the standard of care in early stage medically inoperable NSCLC, with excellent local control (LC) rates (22-24). Despite this, the growing body of data available suggests continued progress will come from maximizing efficacy while minimizing toxicity, as well as tailoring treatment for high-risk clinical scenarios (24).

Dose optimization and outcomes for peripheral *vs.* central tumors

Peripheral tumors

The pioneering prospective dose-finding SBRT study was conducted at Indiana University and determined maximal tolerable doses in 47 medically inoperable patients to be 3×20 Gy and 3×22 Gy for T1 and T2 lesions, respectively. Crude LC rate was 79%, however only 1 of the 10 local failures occurred in patients receiving >16 Gy per fraction (25). In another prospective study, 57 patients in Nordic countries were treated with 45 Gy in 3 fractions to the 67% isodose line, achieving 3-year LC and overall survival (OS) of 92% and 60% respectively (26). Subsequently, in a landmark phase II multicenter study by Timmerman *et al.* (27), 70 patients with T1-2N0 inoperable tumors were treated with 60 and 66 Gy in 3 fractions, respectively, for T1 and T2 tumors. Despite excellent 2-year LC of 95%, toxicity was unacceptably high. Toxicity from SBRT correlated with tumor location, with freedom from grade 3+ toxicity 83% *vs.* 54% between peripheral *vs.* central lung tumors (27).

The aforementioned phase I and II studies were the foundation for Radiation Therapy Oncology Group (RTOG) 0236 (May 2004–Oct 2006), a phase II multicenter trial that treated patients with 60 Gy in 3 fractions, but excluded patients with tumors in the defined "central zone" of the lung within 2 cm of the proximal bronchial tree. The prescription dose of 60 Gy in 3 fractions was assuming all water density; with tissue inhomogeneity corrections, the effective dose was determined to be 54 Gy in 3 fractions (28). With 55 evaluable patients and a median follow up of 4 years, 5-year local failure, locoregional, and disseminated failure were 20%, 38%, and 31%, respectively. Disease-free and OS were 26% and 40%, respectively. Importantly, toxicity was acceptable, with 15 patients experiencing grade 3 toxicity and 2 patients experiencing grade 4 toxicity (29).

Central tumors

The notion that central tumors have a higher propensity for severe toxicity compared with peripheral tumors spurred a number of studies evaluating the appropriate dose and fractionation for higher-risk central tumors (*Table 1*). RTOG 0813 (Feb 2009–Sep 2013), a seamless phase I/II study, sought to evaluate the toxicity of centrally located tumors using escalated doses beginning with 50 Gy in 5 fractions escalated by 0.5 Gy per fraction to a maximum dose of 60 Gy in 5 fractions. The most recent data with median of 30–33 months shows 2-year LC of 89.4% (57.5 Gy cohort) and 87.7% (60 Gy cohort) and grade 3+ toxicity in 6/38 patients (16%) in the 57.5 Gy cohort and 7/33 patients (21%) in the 60 Gy cohort. A total of 3 grade 5 toxicities attributed to SBRT were reported, 2 in the 57.5 Gy cohort, 1 in the 60 Gy cohort. Two-year OS of 70–72% was comparable to patients treated with peripheral tumors. Of note, "central tumors" in this study were considered those within 2 cm of the proximal bronchial tree and immediately adjacent to mediastinal or pericardial pleura, to account for the complexity of treating tumors close to critical mediastinal organs at risk (30).

The Nordic HILUS trial (2011–2016) was a phase II nonrandomized multicenter trial of SBRT to central tumors, defined as ≤1 cm from the proximal bronchial tree, and included both primary NSCLC and progressive metastases from other primary sites. All patients received 7 Gy × 8 fractions. Of the 74 patients, 42 had tumors close to the main bronchus (arm A) and 31 had tumors close to a lobar bronchus (arm B). Twenty-eight percent of patients experienced grade 3+ toxicity and 7 patients (6 of these in arm A) experienced grade 5 side effects (lethal hemoptysis in 6 patients and pneumonitis in 1 patient). Grade 4+ side effects were more common in arm A *vs.* B (19% *vs.* 3%). Given the overall high rate of serious toxicity, particularly with tumors in close proximity to the main bronchus, the authors expressed the need for further study of clinical and

Table 1 Studies of SBRT to central/ultracentral tumors

Study	n	Follow up	Tumor location	Fractionation	LC (%)	OS (%)	G3+T (%)	G5T (%)
Bezjak *et al.* (30), 2016	71	2 y	Central (≤2 cm from PBT or adjacent to mediastinal/pericardial pleural)	57.5 Gy/5 fx	89.4	70.2	16	5.3
				60 Gy/5 fx	87.7	72.7	21	3.0
Lindberg *et al.* (31), 2017	74	2 y	Central (≤1 cm from PBT)	56 Gy/8 fx	–	–	28	9.5
Chang *et al.* (32), 2008	27	17 mo	Central*	50 Gy/4 fx	100	–	11.1†	0
Hasbeek *et al.* (33), 2011	63	3 y	Central (≤2 cm from PBT and/or) ≤1 cm from heart or mediastinum	60 Gy/8 fx	92.6	64.3	6	0
Chaudhuri *et al.* (34), 2015	34	2 y	Central (per RTOG 0813)	50 Gy/4–5 fx	90	–	3	0
			Ultracentral (GTV abutting central airway)		100	–	0	0
Li *et al.* (35), 2014	82	2 y	Locations not amenable to 50 Gy/4 fx‡	70 Gy/10 fx	96	66.9	4.8	0
Tekatli *et al.* (36), 2016	47	29.3 mo	Ultracentral (PTV overlapping trachea or main bronchi)	60 Gy/12 fx	100	20.1	38	15
Stam *et al.* (37), 2017	104	5 y	GTV ≥1 and <2 cm from PBT	54 Gy/3 fx (median)	–	58	–	–
			GTV <1 cm from PBT		–	14	–	–
Daly *et al.* (38), 2017	42	21.4 mo	Central	50 Gy/5 fx (median)	–	–	4.3	1.1
			Ultracentral				22.2	0
Haseltine *et al.* (39), 2016	10		≤1 cm from PBT	45 Gy/5 fx (median)	77.4	63.9	30.7	3.7
	8	2 y	>1 cm from PBT				7.3	0

*, defined as ≤2 cm from PBT, major vessels, esophagus, heart, trachea, pericardium, brachial plexus, or vertebral body, but 1 cm from spinal canal; †, rate of Grade 2–3 dermatitis and chest wall pain; ‡, per institutional dose constraints. y, years; mo, months; n, number of patients evaluated; SBRT, stereotactic body radiation therapy; LC, local control; OS, overall survival; G3+T, Grade 3+ toxicity; G5, Grade 5 toxicity; PBT, proximal bronchial tree; fx, fractions.

dose-volume risk factors (31).

In a separate Dutch study, 63 patients with central tumors treated with 60 Gy in 8 fractions had 3-year LC of 92.6%, while 4 patients (6%) had late grade III toxicity, but no grade IV/V toxicity (32). In a separate study of 27 Stage I patients (n=13) and patients with isolated recurrences (n=14) at MD Anderson, 50 Gy in 4 fractions was delivered to superiorly and centrally located tumors, defined as 2 cm in all directions of any mediastinal critical structure. With a median follow-up of 17 months, crude LC was 100% and there were no occurrences of esophagitis or grade 2 pneumonitis (33).

An influential report of late grade 5 central airway necrosis in a patient treated with 50 Gy in 5 fractions to a central tumor (40) prompted studies further stratifying central tumors into those that are "ultracentral", with gross or planning target volumes abutting or overlapping the trachea, primary bronchial tree, or esophagus. The first study to retrospectively evaluate this specific cohort determined good outcomes and few toxicities comparable to central and peripheral tumors (35). In an MD Anderson study, 70 Gy in 10 fractions was found to achieve excellent LC (2-year LC 96.2%) with acceptable toxicity for challenging cases not amenable to a 4-fraction regimen, particularly due to concerns of chest wall and brachial plexus toxicity with a four fraction technique (36). In a Dutch retrospective study of 47 patients with ultracentral tumors overlapping the trachea or main bronchus, 60 Gy in 12 fractions was found to be efficacious with regard to local tumor control (LC 100%, median follow-up 29 months), but grade 3+ toxicity was noted in 38% of patients, with 21% of patients having possible or likely treatment related death. Fatal pulmonary hemorrhage was observed in 15% of patients. While the authors noted that the fatal toxicity rates of conventionally fractionated radiation for endobronchial tumors are similar, the authors concluded that the 15% grade 5 toxicity rate is concerning and merits further evaluation (37). Indeed, a recent multi-institutional

retrospective study demonstrated a >3.5-fold increased risk of non-cancer related death in patients with a tumor <1 cm from the proximal bronchial tree (38) and multiple other single-institution experiences echo these concerns (39,40). Thus, while reported institutional experiences have shown reasonably good outcomes in this high-risk cohort, particularly with more protracted regimens, the concern for unacceptable rates of fatal toxicity remains and necessitates further study with long term follow up.

Dose intensity and volume-adapted dosing

A number of dose-response studies have demonstrated the importance of dose-intensity for tumor control (41-45). Biologic effective dose (BED) is an equivalent dose used to compare different dose and fractionation regimens, and is most often calculated using the linear quadratic formula. A relatively large retrospective Japanese study that included T1 and T2 tumors in any location showed improved 5-year LC and survival with $BED_{iso} \geq 100$ Gy_{10} (91.6% *vs.* 57.1% and 53.9% *vs.* 19.7% respectively) (32). Given the variety of dosing schemes available, comparisons utilizing BED are convenient and this finding offer a valuable benchmark for evaluating treatment efficacy, notwithstanding the decreased accuracy of the linear quadratic model at high dose per fraction (46).

Recently, volume has been integrated into dose-response studies and found to be a modifier of treatment response. One study identified 11-month LC of up to 100% for tumors with gross tumor volume (GTV) ≤12 mL but 47% for tumors with GTV >12 mL (47). On this premise, Trakul *et al.* conducted a retrospective analysis of 83 patients treated with a volume-adapted dosing strategy in which tumors <12 mL received single-fractions with BED <100 Gy and tumors >12 mL received multifraction regimens with BED ≥100 Gy. LC at 12 months for these groups was 92.6% and 91.7% and grade 3+ toxicity was 0% and 11.4%, respectively. There was no difference in regional control, distant metastasis, or OS (48). Thus, it appears that dose reduction for smaller tumors may be efficacious and may spare patients from unnecessary toxicity, although longer follow-up and additional studies are needed.

Single-fraction SBRT

Although SBRT is commonly delivered in multiple fractions, single-fraction SBRT has been evaluated in multiple single-institution studies using doses ranging from 19–34 Gy and shown to be comparable with regard to primary tumor control compared to multi-fractionated regimens (49-53). This observation, as well as the possibility that at longer follow-up outcomes are preferentially affected by competing comorbidities in the inoperable population, was the foundation for NRG Oncology RTOG 0915 (Sep 2009–Mar 2011) (54). Eighty-four patients were randomized between a single-fraction (34 Gy in 1 fraction; n=39) or multi-fraction (48 Gy in 4 fractions; n=45) SBRT regimen to determine the optimum dosing that would yield the least chance of grade 3+ toxicity for equivalent cancer-related control in medically inoperable patients. Tissue density heterogeneity corrections were required for dose planning. With a median follow-up of 30.2 months, rates of grade 3+ protocol-specific adverse events were 10.3% and 13.3%, respectively, for single- and multiple-fraction arms. Primary tumor control was excellent for both arms (97.0% *vs.* 92.7%). There was a trend toward improved 2-year OS and disease-free survival with the multiple fraction arm (61.3% *vs.* 77.7% and 56.4% *vs.* 71.1%, respectively). However, the study was not powered to adequately evaluate these endpoints and these did not reach statistical significance. Consequently, 34 Gy in 1 fraction was the recommended arm for further study (55).

In addition, the results of a randomized phase II clinical trial at Roswell Park Cancer Institute (Sep 2008–Apr 2015) comparing 30 Gy in one fraction *vs.* 60 Gy in 3 fractions (without heterogeneity corrections) were recently reported. Rates of grade 3+ adverse events were comparable between the arms (27% and 33% of patients on the single- and multifraction arms respectively) and there was no statistically significant difference in OS (71% *vs.* 61%, P=0.44) or progression-free survival (63% *vs.* 51%, P=0.99) (56).

In addition, a Roswell Park retrospective analysis of 42 patients treated with central lung tumors within 2 cm of the proximal bronchial tree showed no difference in OS, progression-free survival, local failure, nodal failure, or distant failure at 18 months between patients treated with 26–30 Gy in 1 fraction vs those treated with 52.6–60 Gy in 5 fractions. Although the single-fraction cohort had higher cumulative incidence of grade 3+ toxicity, univariate analysis did not identify dose as a significant factor for increased risk of grade 3+ toxicity (57).

Both of the aforementioned 30- and 34-Gy regimens have been shown to be equally safe, efficacious, and with minimal toxicity (58). Thus, in appropriately selected patients, it appears such single-fraction regimens are reasonable alternatives to more fractionated treatments.

Table 2 Select studies evaluating the toxicity of treatment on consecutive and/or nonconsecutive days

Study	n	Follow up	Dose	Fractionation	G2+ toxicity (%)
Stauder *et al.* (59), 2011	84	15.8 mo	54 Gy/3 fx (peripheral)	Consecutive	10.6
			48 Gy/4 fx (central)	Consecutive	14.6
Song *et al.* (60), 2009	32	26.5 mo	40–60 Gy/3–4 fx (central)	Consecutive	33*
Jain *et al.* (61), 2013	54	4 mo	48 Gy/4 fx (≤3 cm tumor)	Consecutive	55.6
			52 Gy/4 fx (>3 cm tumor)	Nonconsecutive	33.3
Verma *et al.* (62), 2017	92	12 mo	48–60 Gy/3–5 fx (≥5 cm tumors)	Consecutive	43
				Nonconsecutive	7
Alite (63), 2016	107	3 y	50 or 60 Gy/5 fx	Consecutive	35
				Nonconsecutive	35.8

*, rate of grade 3+ pulmonary toxicity. y, years; mo, months; n, number of patients evaluated; G2+, grade 2+; fx, fractions.

Consecutive *vs.* non-consecutive fractionation

There is some inconsistency in the literature regarding the relative safety of SBRT administered in daily (consecutive) *vs.* non-consecutive fractions (*Table 2*) and this is reflected by modern trial protocols, some of which require a minimum of 40 h between fractions (64,65) and some of which permit or require daily treatment (54,66). A prospective study from Mayo Clinic showed acceptable rates (12.5–14.3%) of grade 2+ pneumonitis in 84 patients with central or peripheral lung tumors treated in 3 or 4 consecutive daily fractions (59). However, a separate study showed 8 of 9 patients with central lung tumors treated with 40–60 Gy in 3–4 daily fractions developed bronchial strictures and 3 patients (33%) developed grade 3+ pulmonary toxicity (60). Results of a randomized prospective study suggest increased grade 2+ acute toxicity in patients receiving 4-fraction SBRT daily compared to receiving SBRT on non-consecutive days (61). More recently, a multi-institutional analysis evaluating toxicity in patients with tumors >5 cm showed grade 2+ toxicities of 7% *vs.* 43% between non-consecutive (n=46) and daily (n=46) treatment groups respectively, a finding attributed to interfractional normal tissue repair in the former group (62).

Fractionation scheme has also been suggested to influence treatment efficacy. A recent study retrospectively evaluated the LC of tumors treated on consecutive *vs.* non-consecutive days on the basis that differences in treatment timing may exploit re-oxygenation kinetics and promote radiosensitivity. One hundred ninety-two patients who received 50 or 60 Gy in 5 fractions were stratified between those who did and did not get treated daily. There were 18 failures in the entire cohort (15.4%) with 14 of these in the group treated consecutively and 4 treated nonconsecutively. Propensity matching yielded 3-year LC rates of 97.5% and 63.6% for non-consecutively and consecutively treated patients, respectively (63). This finding requires validation in larger independent cohorts and prospective trials.

Patterns of failure

In one of the largest patterns of failure studies to date, Senthi *et al.* retrospectively analyzed the patterns of recurrence for 676 patients treated with SBRT for early-stage NSCLC. With a median follow up of 32.9 months, there were 124 recurrences and actuarial 5-year local, regional, and distant recurrences were 10.5%, 12.7%, and 19.9% respectively. Nearly half (46%) of the recurrences were isolated distant recurrences that occurred at a median of 8.3 months after treatment, suggesting existing subclinical disease undisclosed by baseline ^{18}F-FDG-PET imaging that was required for study inclusion. Roughly one-third of recurrences were isolated locoregional and thus potentially amenable to salvage therapy. Given a combined recurrence and second primary event rate of 6% per patient per 6 months for the first 3 years and 1% for the subsequent 2 years, the authors suggested a follow up of 6-month CT scans for the first 3 years after SBRT (67). This theme of excellent LC and distant-predominant recurrence has been echoed across multiple retrospective studies (43,68,69), prospective studies (26,28,66,69), and a systematic review (70).

SBRT for tumors greater than 5 cm

Patients with large (>5 cm) tumors are underrepresented in SBRT data in part due to the relative infrequency of large, lymph node-negative disease, and concern for significant toxicity with larger volumes. Multiple studies have evaluated the effect of size on local, regional, and distant recurrence and their conclusions are mixed in this regard. Moreover, they evaluate a relatively small proportion of tumors ≥5 cm (71-76). The first single-institution study specifically addressing this population evaluated outcomes after SBRT for 40 patients. Eighteen-month LC, locoregional control, disease-free survival, and OS were 91.2%, 64.4%, 34.6%, and 59.7% respectively. Failures were predominantly distant (32.5%) and the rate of grade 3+ toxicity was acceptable at 7.5% (77).

In the largest multi-institutional study evaluating this population to date, 92 patients, nearly half of which received 50 Gy in 5 fractions, were retrospectively analyzed from 12 institutions. Actuarial 1- and 2-year LC rates were 95.7% and 73.2%, respectively and grade 3+ toxicity occurred in 11% of patients, suggesting relative efficacy and safety of SBRT in this population at high risk of recurrence. Distant metastases, the predominant mode of failure, occurred in 21% of patients at a median follow up of 8 months (78).

This higher propensity of large tumors for distant recurrence is in accordance with a recent National Cancer Database (NCDB) analysis showing survival benefit of large-tumor SBRT patients who received chemotherapy (median OS 30.6 *vs.* 23.4 months) (79), congruent with findings of surgical studies (80,81). Although the NCDB lacks cancer-specific survival endpoints, there is data to suggest benefit in disease-free survival with addition of chemotherapy selectively added for large tumors after SBRT (70). Thus, it appears that modern SBRT dosing regimens are sufficient to achieve adequate LC in large tumors, with acceptable toxicity. Addressing subclinical distant disease through systemic therapy in this at-risk population may be more pertinent than local dose-escalation.

SBRT *vs.* conventionally fractionated radiotherapy

Although the body of evidence in support of SBRT for inoperable patients is extensive, resulting in its adoption as standard of care (22,23), this acceptance came without randomized evidence to support its superiority to conventionally fractionated radiotherapy. This changed with the recent conclusion of SPACE, a Scandinavian phase II randomized trial of 102 patients comparing SBRT, 66 Gy in 3 fractions, *vs.* conventionally fractionated radiotherapy [three-dimensional conformal radiotherapy (3DCRT)], 70 Gy in 35 fractions, in medically inoperable patients with Stage I NSCLC. There was no difference in progression-free survival or OS between the two arms, despite a tendency toward improved disease control rate with SBRT. However, patients treated with 3DCRT experienced worse dyspnea, chest pain, and cough on quality of life (QOL) analysis, although overall toxicity was mild (mostly grade 1–2) in both treatment groups (82). It is notable that with low toxicity and a 3-year OS of nearly 60%, the results of the 3DCRT arm are improved when compared to historical data, likely a function of improved staging and treatment in the past 1–2 decades (11). The authors concluded that SBRT should be the standard treatment for inoperable Stage I NSCLC patients since it is more convenient with less toxicity and improved QOL.

There are two other ongoing randomized trials evaluating similar regimens. The Trans-Tasman Radiation Oncology Group (TROG) 0902 (CHISEL) Australian/New Zealand study, recently closed to accrual with a sample size of 100 patients, compares SBRT (18 Gy × 3 or 12 Gy × 4) with external beam radiation therapy delivered in 66 Gy in 33 fractions or 50 Gy in 20 fractions (83). The Canadian phase III randomized trial LUSTRE entails 2:1 randomization to either SBRT (48 Gy in 4 fractions for peripheral lesions; 60 Gy in 8 fractions for central lesions) or conventionally hypofractionated radiotherapy (CRT) of 60 Gy in 15 fractions. The comparison to hypofractionated CRT, which is standard Canadian practice, and inclusion of central tumors is unique compared to the aforementioned studies. Accrual is expected to be complete in 3 years (84). These studies may help to address remaining concerns regarding the efficacy and safety of SBRT compared with more conventional or hypofractionated radiation treatment schedules.

SBRT in operable patients

Although SBRT has become standard of care in medically inoperable patients (22,23), the role of SBRT in operable patients is less defined (*Table 3*). RTOG 0618 was the first prospective evaluation of the feasibility of SBRT in operable patients, using the dosing established from RTOG 0236 (18 Gy × 3). Early data shows promising 2-year primary tumor failure, local failure, and OS rates of 7.7%,

Table 3 Studies comparing SBRT to lobectomy

Study	n	Follow up	Local failure (%)		Regional failure (%)		Distant failure (%)		Disease-free survival (%)		OS (%)	
			Lobectomy	SBRT	Lobectomy	SBRT	Lobectomy	SBRT	Lobectomy	SBRT	Lobectomy	SBRT
RTOG 0618 (85), 2013	26	2 y	–	19.2	–	11.7	–	15.4	–	65.4	–	84.4
JCOG 04013 (66), 2015	65*	3 y	–	85.4	–	25	–	33	–	54.5	–	76.5
Rosen *et al.* (86), 2016	470†	5 y	–	–	–	–	–	–	–	–	58	40
Verstegen *et al.* (87), 2013	128	3 y	3.1	1.6	9.4	4.7	34.5	14.8	79.7	75	76.9	79.6
Grills *et al.* (88), 2017	254	5 y	5	8	5	18	12	11	72	53	78	61
Shirvani *et al.* (89), 2014	7,597‡	3 y	–	–	–	–	–	–	–	–	75	54.9
Yu *et al.* (90), 2015	1,078	1 y	–	–	–	–	–	–	–	–	73.9	69.7
Chang *et al.* (91), 2015	58	3 y	0	4	4	10	9	3	80	86	79	95

*, number of operable patients evaluated on the trial; †, number of patients included in matched analysis that included SBRT patients who were offered lobectomy but refused; ‡, number of patients treated with either lobectomy or SBRT. y, years; n, number of patients evaluated. SBRT, stereotactic body radiation therapy.

19.2%, and 84.4%, respectively (85). A second Japanese study, JCOG 04013, shows similar 3-year OS of 76.5%, comparing favorably to historical surgical results (66).

In a 2016 NCDB analysis that included only patients free of comorbidities, 13,562 stage I lung cancer patients treated with lobectomy were compared to 1781 patients treated with SBRT. Propensity-matched analysis revealed a 5-year OS of 59% for lobectomy *vs.* 29% for SBRT (86). This is in contrast to a Dutch propensity-matched analysis of 64 SABR and 64 video-assisted thoracoscopic surgery (VATS) lobectomy patients, which showed superior 3-year locoregional control with SABR (93.3% *vs.* 82.6%) with no difference in distant recurrence or OS (87). Contrarily, recent data from a single institution shows higher rates of regional and clinical failure in SBRT compared to lobectomy with lower disease-free and OS, despite similar rates of local recurrence and distant metastasis (88).

In a Surveillance, Epidemiology, and End Results (SEER) analysis of patients over 65 years of age, 9,093 patients were analyzed and split into cohorts receiving lobectomy (n=7,215), sublobar resection (n=1,496), and SABR (n=382). OS was determined to be time-dependent using proportional hazards regression, with SABR associated with better survival within the first 6 months after diagnosis [adjusted hazard ratio (AHR) 0.45] but worse survival after 6 months (AHR 1.66). Propensity score matching of SABR and lobectomy cohorts, which accounted for comorbidities, yielded similar OS in both groups (89). In addition, the authors concluded that the clinical relevance of these findings are confined to the patients well-represented by the matched cohorts (i.e., those with advanced age and multiple comorbidities) and cannot be used to justify the use of SABR over surgery in operable patients. A subsequent propensity-matched SEER analysis in a similar cohort of patients found a significantly lower rate of acute toxicity and early mortality in patients receiving SBRT with no difference in toxicity and higher mortality with SBRT at 24 months. Furthermore, overall mortality was significantly worse with SBRT for patients with longer life expectancy (>5 years), whereas it was equivalent with shorter life expectancies (90). These findings indicate the importance of longitudinal analysis when comparing these modalities as well as the risk of competing comorbidities when selecting the most appropriate treatment modality.

To date, there have been 3 randomized control trials comparing surgery *vs.* SBRT in operable patients (ROSEL, STARS, RTOG 1021/ACOSOG Z4099), all of which have closed due to poor accrual (92). Despite this, a pooled analysis of patients from the STARS and ROSEL trials offers potential insight. In this analysis, a total of 58 patients were analyzed with an estimated 3-year OS of 95% for SABR *vs.* 79% for lobectomy, with a median follow-up of 40.2 months for the SBRT group and 35.4 months for the surgery group. Although this marked difference should be interpreted with caution given the small patient sample, these results suggest a large, randomized comparison between SBRT and lobectomy is warranted (91).

To our knowledge, three phase III studies to answer this question are currently underway, the United States STABLE-MATES trial (93), the U.K. SABRTooth trial (94), and the Veterans Affairs VALOR trial (95). Of these, only the STABLE-MATES trial compares SBRT with sublobar resection (instead of lobectomy). This trial utilizes randomization prior to trial enrollment and also has an observational cohort if patients decline their treatment assignment but elect to be observed after surgery (93). These methods are designed to circumvent the difficulties of accruing patients to disparate treatment modalities. These trials will hopefully provide much needed insight into this ongoing debate.

Particle therapy

Given the emergence of proton therapy and data suggesting efficacy in hypofractionated regimens in the treatment of NSCLC (96-98), it is not surprising that there have been attempts to utilize proton therapy using modern SBRT fractionation schemes due to theoretically higher dose conformity and reduction of radiation dose to normal tissue (99,100). Virtual studies suggest a benefit in proton SBRT, in particular intensity-modulated proton therapy (IMPT), in reducing lung dose as well as dose to other critical structures including the aorta, brachial plexus, heart, pulmonary vessels, and spinal cord in the treatment of centrally or superiorly located stage I NSCLC tumors (101). Early data from Massachusetts General Hospital involving 15 patients shows such treatment is well-tolerated in patients with adverse factors such as pulmonary comorbidities, prior chest irradiation, or multiple primary tumors. Furthermore, this study also suggested proton therapy was efficacious, with a 2-year LC of 100% (102).

Carbon ions share the advantageous Bragg peak of protons while having the additional benefit of higher linear energy transfer, potentially resulting in significantly higher BED (103). Dosimetrically, carbon ion planning can achieve significantly lower conformity index and lung dose compared to photon SBRT in 4-fraction treatment (104). A recent phase I dose-escalation trial evaluating feasibility of single-fraction treatment of peripheral Stage I NSCLC showed 5-year LC of 95% with doses of 48–50 Gy [relative biological effectiveness (RBE)] as well as no grade 3 or higher toxicities (105). A relatively larger study entailing proton (n=43) or carbon ion (n=27) treatment of 70 patients with T2 tumors, showed that 4-year OS, LC, and progression-free survival (PFS) rates were 58%, 75%, and 46% respectively, with grade 3 pulmonary toxicity observed in only 2 patients. The majority of these patients were treated with either 4-fraction (n=16) or 10-fraction (n=36) regimens (106).

While reimbursement uncertainty and technical complexity of charged particles has limited their use in many institutions (107-109), these data suggest that in situations that demand maximal tissue sparing or entail larger tumors in difficult locations, proton or carbon ion therapy are viable modalities worth consideration at equipped centers. Ultimately, prospective trials will be required to validate their relative efficacy and safety compared to historical photon data.

Histologic and molecular predictors of treatment response

Thus far, clinically utilized risk-adapted dosing strategies have primarily accounted for tumor location and size. However, recent evidence suggests heterogeneity in tumor response depends on tumor subtype. Recent studies have shown a significantly higher local failure rate for squamous cell cancers over adenocarcinomas as well as other NSCLCs (88,110,111). Another study showed that heterogeneity exists even within adenocarcinomas, with micropapillary and solid subtypes correlating with higher rates of locoregional and distant failure (112).

Advances in cancer genomics have led to the discovery of the prognostic and therapeutic significance of v-Ki-ras 2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and epidermal growth factor receptor (EGFR) mutations in the setting of metastatic adenocarcinoma (113-116). Recently, such genomic data is being integrated into studies involving early-stage tumors. In one study of 75 patients treated with SBRT (18 Gy × 3 or 10–12 Gy × 5), although histology

was not clearly associated with recurrence, the presence of *KRAS* mutation was associated with significantly lower freedom from recurrence (48% *vs.* 69%) and decreased cancer-specific survival (75% *vs.* 93%) when compared to *KRAS*-wildtype tumors or those with unknown mutation status (117). Similarly, a recent study implicates Kelch ECH associating protein 1/nuclear factor erythroid 2-related factor 2 (KEAP1/NRF2) mutations in promoting radioresistance and local recurrence after radiotherapy for lung squamous cell carcinomas. Of a cohort of 42 patients that were studied, the majority had stage I-II tumors (81%) and received treatment with SABR (74%). The incidence of local failure at 30 months was 70% in KEAP1/NRF2-mutants *vs.* 18% in wildtype tumors. Furthermore, the authors identified Cancer Personalized Profiling by deep Sequencing (CAPP-Seq) analysis of pretreatment plasma as an accurate and noninvasive method to identify KEAP1 mutation. This testing was utilized to verify the association of KEAP1 and local recurrence in an independent cohort of 20 patients. These results imply a potential benefit of KEAP1/NRF2 testing in identifying patients more prone to local recurrence after SBRT (118).

Conclusions

SBRT is the standard of care for the medically inoperable patient with early-stage NSCLC (22-24) and is at least equivalent to conventionally fractionated radiotherapy in this setting (82). SBRT may be a reasonable alternative to surgery in operable patients, although its appropriateness in this context must be further elucidated by ongoing randomized trials (93-95).

As the modality has evolved, the variability in institutional practices has led to a diverse assortment of fractionation schemes. SBRT has been shown to be efficacious with these regimens, particularly if treatment achieves a defined level of dose-intensity (43). Similarly, SBRT can be delivered safely regardless of location (30,32,33), although an important factor in selecting the most appropriate regimen is tumor location with regard to proximity to organs at risk, especially in the case of tumors in close proximity to or abutting mediastinal structures (31,37,39,40). Particularly in such cases, regimens that offer adequate LC with minimal toxicity are best and may entail more protracted fractionation in order to achieve dosimetric objectives (35,36,38). For the appropriately selected patient, a single-fraction regimen may be a reasonable, convenient option in achieving good LC with minimal toxicity (55-57).

There are other potential ways to optimize toxicity profile. For example, treatment on nonconsecutive days, rather than daily, is potentially beneficial in reducing toxicity (61,62). Whether non-consecutive fractionation results in improved disease control needs further evaluation (63). Technological advances in the form of proton or carbon ion therapy may be beneficial in the treatment of higher risk patients, such as those with cardiopulmonary comorbidities or prior thoracic irradiation, for whom maximal dose conformity is warranted to prevent excess toxicity (102,106).

Despite the excellent LC achieved by modern SBRT fractionation regimens, distant recurrence remains the primary mode of failure after treatment (70), likely a result of occult metastatic disease not revealed by pretreatment imaging. This is especially true of larger tumors (>5 cm) and warrants evaluation of integrating systemic therapy into treatment regimens for such patients (77-79). Furthermore, as SBRT becomes increasingly individualized in tandem with advances in cancer genomics and molecular profiling, histo-molecular classification of early-stage NSCLC may provide valuable predictive information in tailoring treatment and follow up (110,112,117,118).

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Footnote

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