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REVIEW

- 1 Long-term outcomes of interventions for radiation-induced xerostomia: A review
Ma SJ, Rivers CI, Serra LM, Singh AK

MINIREVIEWS

- 14 Stereotactic body radiation therapy for non-small cell lung cancer: A review
Prezzano KM, Ma SJ, Hermann GM, Rivers CI, Gomez-Suescun JA, Singh AK

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Stereotactic body radiation therapy for non-small cell lung cancer: A review

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Abstract

Stereotactic body radiation therapy (SBRT) is the treatment of choice for medically inoperable patients with early stage non-small cell lung cancer (NSCLC). A literature search primarily based on PubMed electronic databases was completed in July 2018. Inclusion and exclusion criteria were determined prior to the search, and only prospective clinical trials were included. Nineteen trials from 2005 to 2018 met the inclusion criteria, reporting the outcomes of 1434 patients with central and peripheral early stage NSCLC. Patient eligibility, prescription dose and delivery, and follow up duration varied widely. Three-years overall survival ranged from 43% to 95% with loco-regional control of up to 98% at 3 years. Up to 33% of patients failed distantly after SBRT at 3 years. SBRT was generally well tolerated with 10%-30% grade 3-4 toxicities and a few treatment-related deaths. No differences in outcomes were observed between conventionally fractionated radiation therapy and SBRT, central and peripheral lung tumors, or inoperable and operable patients. SBRT remains a reasonable treatment option for medically inoperable and select operable patients with early stage NSCLC. SBRT has shown excellent local and regional control with toxicity rates equivalent to surgery. Decreasing fractionation schedules have been consistently shown to be both safe and effective. Distant failure is common, and chemotherapy may be considered for select patients. However, the survival benefit of additional interventions, such as chemotherapy, for early stage NSCLC treated with SBRT remains unclear.

Key words: Lung cancer; Non-small cell lung cancer; Stereotactic body radiation therapy;

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Core tip: Stereotactic body radiation therapy (SBRT) offers excellent local and regional control for early stage non-small cell lung cancer (NSCLC), and is often the treatment of choice for medically inoperable patients. This literature review provides an updated analysis of prospective clinical trials evaluating clinical outcomes following SBRT for early stage NSCLC.

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INTRODUCTION

Early studies have demonstrated the efficacy of conventionally fractionated radiotherapy for the treatment of stage I non-small cell lung cancer (NSCLC). Haffty *et al*^[1] reported on 43 patients with stage I NSCLC from 1970-1983 who had been deemed medically inoperable or who had refused surgical resection. When treated with a median of 59 Gy in 2 Gy per fraction, 5 year overall survival was reported at 21%. Subsequent studies have demonstrated efficacy for radiation doses exceeding 60 Gy^[2,3]. In particular, T1 tumors treated with > 65 Gy had significantly reduced risk of recurrence compared to T2 and T3 tumors or doses ≤ 65 Gy^[3]. A more modern analysis of stage I, node negative patients staged with computed tomography (CT) and treated with a median dose of 63.2 Gy showed increased cause-specific survival in the subset of patients who received ≥ 65 Gy^[4]. While conventionally fractionated radiotherapy can provide a reasonable alternative to surgical resection in medically inoperable patients, the 5-year overall survival rates reported in these early studies were suboptimal at 10%-30%^[1-4]. As the delivery of radiation has improved over time, SBRT has emerged as an alternative to very precisely deliver a high dose of radiation in a small number of fractions^[5].

Surgery remains the standard of care for medically operable early stage NSCLC. Stereotactic body radiation therapy (SBRT) also referred to as stereotactic ablative radiotherapy (SABR), has become the preferred treatment option for medically inoperable patients with significant comorbidities or for patients who decline surgery. This article will review major concepts in the use of SBRT for primary early-stage NSCLC, including technical considerations and reported outcomes and toxicities from major clinical trials, with a specific emphasis on fractionation and future directions.

SBRT AS DEFINITIVE TREATMENT FOR NSCLC

We conducted a comprehensive literature search for journal articles written in English and published between January 2000 and July 2018. The inclusion criterion was any prospective clinical trial reporting clinical outcomes of primary early stage NSCLC definitively treated with SBRT. The exclusion criteria were the following: (1) review articles, case reports, or letters to editors; (2) studies that did not report the most updated outcomes when multiple publications resulted from the same patient cohort; (3) duration of follow-up shorter than one year; (4) sample size fewer than 30; (5) multiple primary lung tumors; and (6) lung oligometastasis or advanced stage NSCLC.

The search was completed in July 2018. Studies included were identified by performing a search of literature existing in the PubMed database. The PubMed electronic database was queried for search terms including "SBRT", "stereotactic body radiotherapy", and "SABR", along with their respective acronyms, and "lung" or "NSCLC". This database query initially produced 3920 results. Of these, 3631 studies were in the English language. Limiting this selection to prospective clinical trials reduced the results to 269 entries. After a thorough review of the literature, any study

meeting the above criteria but not listed in PubMed was additionally included. By applying our inclusion and exclusion criteria, these studies and their reference lists were evaluated by two reviewers to determine their suitability for inclusion (Figure 1).

Nineteen studies meeting our criteria were selected for inclusion in this review (Table 1). Publication years ranged from 2005 to 2017. The mean number of patients included in the trials was 75 (range 31 to 180), with a median follow-up between 16 to 86 mo. Dose fractionation schedules varied widely. Using a α/β ratio of 10, the total biologically effective doses (BED) included were $> 100 \text{ Gy}_{10}$ in almost all studies, except for two. Shibamoto *et al*^[6] treated four patients, whose tumors were less than 1.5 cm in diameter, with 44 Gy in 4 fractions. Similarly, a small number of patients were treated with BED $< 100 \text{ Gy}$ in the dose escalation study authored by McGarry *et al*^[7].

Survival and tumor control

Two of the earliest studies for early stage NSCLC treated with SBRT were reported by McGarry *et al*^[7] and Nagata *et al*^[8], who both showed promising local and regional control rates, and distant failure only recorded in patients with T2 disease. In the United States, Timmerman *et al*^[9] reported initial results of a phase I study, demonstrating that SBRT was well tolerated, with updated results finding that the majority of local failure was seen in patients receiving $\leq 48 \text{ Gy}$ ^[7]. Of the included studies that estimated 3-year results, reported overall survival percentages ranging from 43% to 95% and local control rates as high as 98%^[10-17]. In the four studies with 5-year outcomes, local control was reported between 79%-85%^[6,18-20]. Distant control at three years ranged from 76%-97%^[10-17]. Reported outcomes from the included studies are tabulated in Table 1.

Fractionation for peripheral tumors

Radiation Therapy Oncology Group (RTOG) 0236 was a phase II North American multicenter study of 55 medically inoperable patients with peripheral NSCLC treated with 54 Gy in 3 fractions. The study initially reported 3-year local control rate of 91% and distant failure in 22%^[21]. Updated 5-year results showed 5-year local control of 80% and distant failure of 31%^[18]. With promising results from the RTOG 0236 3-fraction regimen for peripheral NSCLC, a multicenter, phase II study, I-124407, was undertaken to compare 30 Gy in 1 fraction and 60 Gy in 3 fractions. This study evaluated 98 patients with a median follow up of 27 mo and showed 2-year overall survival of 71% for single fraction and 61% for 3 fraction regimens. There was no difference in survival or toxicity between the regimens^[22].

Similarly, building on the results of the 4 fraction regimen by Nagata *et al*^[8], the comparison of 34 Gy in 1 fraction and 48 Gy in 4 fractions was investigated in a multicenter phase II study, RTOG 0915, by Videtic *et al*^[23]. The study assessed 94 patients with a median follow up of 30 mo, showing 2-year overall survival of 61% for single fraction and 78% for 4 fraction regimens. No difference in overall survival, primary tumor control, and toxicity was seen between these regimens.

As conventionally fractionated radiation therapy has also improved over time, the multicenter Scandinavian phase II SPACE trial is the only publication that has reported results comparing SBRT (66 Gy in 3 fractions) to conventionally fractionated radiotherapy (70 Gy in 35 fractions). Despite an imbalance in the number of patients with T2 tumors and of male gender (both of these negative prognostic factors were increased in the SBRT arm), there was no statistically significant difference in 1-, 2-, or 3-year overall survival (81% vs 89%, 68% vs 72%, 54% vs 59%, respectively, for SBRT vs conventionally fractionated arms). Favorable results were also reported for local control (86.4% in the SBRT arm vs 85.7% in the conventional fractionation arm)^[14].

Central tumors

Timmerman *et al*^[23] reported a phase II study of 70 medically inoperable patients with both peripheral and central tumors treated with 60-66 Gy in 3 fractions. With a median follow up of 17.5 mo, the study initially reported 2-year local control of 95% with grade 3-4 toxicity seen in 8 patients (11%) and treatment-related death in 6 patients (9%). Central location was initially shown to be an adverse prognostic factor for toxicity, but this did not remain significant in the updated report by Fakiris *et al*^[17].

The NRG/RTOG 0813 phase I/II trial evaluated NSCLC patients with centrally located tumors, defined as within 2 cm of the proximal bronchial tree or adjacent to the mediastinal or pericardial pleura. Successively accruing patients into a dose-escalating 5-fraction SBRT schedule, ranging from 10-12 Gy/fraction, the study was designed to determine the maximal tolerated dose. The highest dose level allowed by the protocol, 12 Gy/fraction, was achieved, with only 7.2% dose-limiting toxicities reported in the preliminary phase I analysis. Two-years overall survival rates were

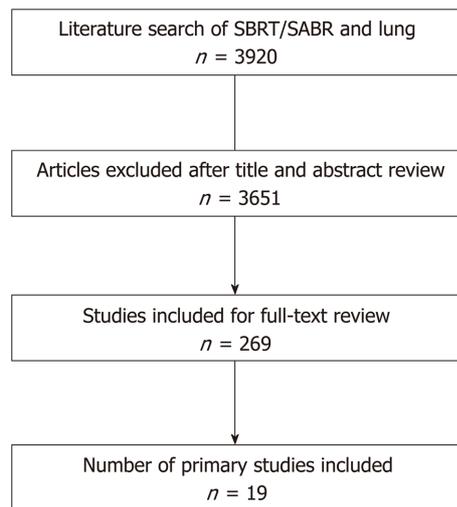


Figure 1 Methods flow chart. SBRT/SABR: Stereotactic body radiation therapy/stereotactic ablative radiotherapy.

reported at 70%^[24].

SBRT for operable patients

While many of these trials included medically inoperable patients only, a multicenter Japanese phase II Japan Clinical Oncology Group (JCOG) 0403 study stratified patients who received SBRT for T1N0M0 non-small cell lung tumors into medically operable and inoperable categories. All patients received 48 Gy in 4 fractions. Overall survival at 3 years was reported as 59.9% in the inoperable group *vs* 76.5% in the operable group^[12]. Despite being comprised of a relatively older population (median age of 79 years), their results were similar to other studies with younger median age populations^[15,25].

Among operable patients only, lobectomy was compared with SBRT in two phase III trials, STARS (NCT00840749) and ROSEL (NCT00687986), both of which were closed early due to slow accrual. Nonetheless, Chang *et al*^[15] reported a pooled analysis of 58 patients who were enrolled, with a median follow up of 40 mo for SBRT and 35 mo for surgery. In the STARS trial, peripheral and central lung tumors received 54 Gy in 3 fractions and 50 Gy in 4 fractions, respectively. In the ROSEL study, only peripheral lung tumors were included and received either 54 Gy in 3 fractions or 60 Gy in 5 fractions. Overall survival at 3-years was 95% for SBRT and 79% for surgery. Local control at 3 years was 96% for SBRT and 100% for surgery. Distant failure at 3 years was 3% for SBRT and 7% for surgery.

Toxicity

In the collected studies, several toxicity measures were analyzed, with all papers citing National Cancer Institute Common Criteria grading of lung toxicity. The reported toxicities from included studies can be referred to in [Table 2](#).

Grade 3 toxicity ranged from 3%-20%, with grade 5 (or fatal) toxicities only detailed by three studies. Fakiris *et al*^[13] noted 12 grade 3-5 toxicities, with the potential treatment-related grade 5 toxicities reported as pneumonia ($n = 3$), hemoptysis ($n = 1$), and respiratory failure ($n = 1$). RTOG 0915 reported one patient death in the single-fraction arm approximately 2 wk after treatment, with the death thought to be unconnected to SBRT. The four-fraction arm had a patient fatality 319 d after treatment due to respiratory failure thought to be related to SBRT. No difference in toxicity was reported between the single fraction *vs* multi-fraction arms in either RTOG 0915 or I-124407^[22].

Rates of toxicities did appear to increase with greater follow-up. For example, 9 patients (16%) with a median follow up of 34 mo were initially reported to have grade 3-4 toxicities in RTOG 0236, but updated results at 4 years found 17 patients (31%) treated with 54 Gy in 3 fractions reporting grade 3-4 toxicities^[18,21]. Rib fractures were recorded in 0-18% of patients in the included studies^[26]. Late toxicities such as esophageal perforation and fatal pulmonary hemorrhage were documented in the 5 fraction arm of the NRG/RTOG 0813 dose escalation trial for centrally located lung tumors^[24].

In the pooled analysis of the STARS and ROSEL studies, Chang *et al*^[15] recorded treatment-related grade 3 toxicities in 10% of patients who underwent SBRT, contrasted with 44% of patients treated surgically who suffered grade 3-4 toxicities,

Table 1 Study characteristics and tumor control results

Study	No.	F/u (median)	Age (median)	Loc	Stage	Dose/fx	OS	LC	RC	DC
Miyakawa <i>et al</i> ^[20] , 2017	71	44	77	C + P	T1-2N0M0	48-52 Gy/ 4 fx	5-yr 65%	5-yr 85%	NA	NA
Sun <i>et al</i> ^[80] , 2017	65	86	71	C + P	T1-2N0M0	50 Gy/4 fx	7-yr 48%	7-yr 92%	7-yr 86%	7-yr 86%
Singh <i>et al</i> ^[22] , 2017, I-124407	98	27	NA	P	T1-2N0M0	30 Gy/1 fx and 60 Gy/3fx	2-yr 71% (30 Gy) 2-yr 61% (60 Gy)	NA	NA	NA
Bezjak <i>et al</i> ^[24] , 2016, RTOG 0813	71	33 (57.5 Gy) 30 (60 Gy)	NA	C	T1-2N0M0	57.5-60 Gy/5 fx	2-yr 70% (57.5 Gy) 2-yr 88% (60 Gy)	2-yr 90% (57.5 Gy) 2-yr 88% (60 Gy)	2-yr 95% (57.5 Gy) 2-yr 88% (60 Gy)	2-yr 84% (57.5 Gy) 2-yr 85% (60 Gy)
Navarro-Martin <i>et al</i> ^[11] , 2016	38	42	74	P	T1-3N0M0	54 Gy/3 fx	3-yr 66%	3-yr 94%	3-yr 79%	3-yr 87%
Nyman <i>et al</i> ^[14] , 2016, SPACE	102	37	74 (mean)	P	T1-2N0M0	66 Gy/3 fx	3-yr 54%	3-yr 86%	3-yr 93%	3-yr 76%
Chang <i>et al</i> ^[13] , 2015, STARS and ROSEL	31	40	67	C + P	T1-2N0M0	54 Gy/3 fx, 50 Gy/4 fx, 60 Gy/5 fx	3-yr 95%	3-yr 96%	3-yr 90%	3-yr 97%
Lindberg <i>et al</i> ^[19] , 2015	57	42	75 (mean)	P	T1-2N0M0	45 Gy/3 fx	5-yr 30%	5-yr 79%	3-yr 81% for regional/ distant control	NA
Nagata <i>et al</i> ^[12] , 2015, JCOG 0403	169	47 (inop) 67 (op)	78	NA	T1N0M0	48 Gy/4 fx	3-yr 60% 5-yr 43% (inop) 3-yr 77% 5-yr 54% (op)	3-yr 87% (inop) 3-yr 85% (op)	3-yr 92% (inop) 3-yr 75% (op)	3-yr 78% (inop) 3-yr 67% (op)
Shibamoto <i>et al</i> ^[6] , 2015	180	53	77	C + P	T1-2N0M0	44-52 Gy /4 fx	5-yr 52%	5-y 83%	5-yr 84%	5-yr 76%
Videtic <i>et al</i> ^[13] , 2015, RTOG 0915	94	30	75	P	T1-2N0M0	34 Gy/1 fx and 48 Gy/4 fx	3-yr 56%	3-yr 98%	NA	NA
Timmerman <i>et al</i> ^[18] , 2014, RTOG 0236	55	48	72	P	T1-2N0M0	54 Gy/3 fx	5-yr 40%	5-yr 80%	5-yr 62% (local-regional control)	5-yr 79%
Taremi <i>et al</i> ^[26] , 2012	108	19	73 (mean)	C + P	T1-2N0M0	48 Gy/4 fx or 54-60 Gy/3 fx (P) 50-60 Gy /8-10 fx (C)	4-yr 30%	4-yr 89%	4-yr 87%	4-yr 83%
Bral <i>et al</i> ^[46] , 2011	40	16	73 (mean)	C + P	T1-3N0M0	60 Gy/3-4 fx	2-yr 52%	2-yr 84%	2 nodal recurrences	6 distant recurrences
Ricardi <i>et al</i> ^[16] , 2010	62	28	74	P	Stage I	45 Gy/3 fx	3-yr 57%	3-yr 88%	3-yr 94%	3-yr 76%
Fakiris <i>et al</i> ^[17] , 2009	70	50	70	C + P	T1-2N0M0	60-66 Gy/ 3 fx	3-yr 43%	3-yr 88%	3-yr 91%	3-yr 87%
Koto <i>et al</i> ^[10] , 2007	31	32	77	C + P	T1-2N0M0	45 Gy/3 fx or 60 Gy/8 fx	3-yr 72%	3-yr 78% (T1) 3-yr 40% (T2)	3-yr 94%	3-yr 81%
McGarry <i>et al</i> ^[7] , 2005	47	27 (Stage IA) 19 (Stage IB)	71 (Stage IA) 74 (Stage IB)	C + P	T1-2N0M0	24-72 Gy/ 3 fx	NA	2-yr 81%	2-yr 81%	2-yr 79%
Nagata <i>et al</i> ^[8] , 2005	45	30 (Stage IA)	77 (Stage IA)	C + P	T1-2N0M0	48 Gy/4 fx	2-yr 90% (Stage IA)	1-yr 100%	2-yr 91%	2-yr 88% (Stage IA)

22 (Stage IB) 73 (Stage IB)

2-yr 72%
(Stage IB)2-yr 77%
(Stage IB)

No.: Number of patients treated with SBRT; F/u: Follow up in months; Loc: Tumor location; P: Peripheral; C: Central; Dose/fx: Total dose/fraction; OS: Overall survival; LC: Local control; RC: Regional control; DC: Distant control; Inop: Medically inoperable; Op: Medically operable; NA: Not available; RTOG: Radiation therapy oncology group; JCOG: Japan clinical oncology group.

including bleeding, fistula, hernia, anemia, weight loss, and cardiac arrhythmias. One patient died of surgical complications.

When compared to conventionally fractionated radiotherapy, toxicity was shown to be less prevalent in the SBRT arm of the SPACE trial, including rates of esophagitis (8% *vs* 30%), borderline significant pneumonitis (19% *vs* 34%) and dyspnea (67% *vs* 81%)^[14]. Additionally, patient-reported quality of life data showed significantly worse dyspnea and chest pain in the three dimensional conformal radiation therapy arm compared to SBRT^[14].

DISCUSSION

Despite the widely varying dose fractionation regimens, patient populations, and primary outcomes included in these prospective trials, results were similarly favorable. High rates of local control and overall survival have been reported, along with favorable toxicity outcomes. These included studies comparing fractionation schemes, operable *vs* non-operable candidates, and tumor location have paved the way for additional questions to be addressed in future studies.

We acknowledge the limitations of this review. The included studies treated patients over a large time frame with multiple inclusion criteria, differing tumor location, dose fractionation regimens, and prescription methods. Techniques of SBRT delivery were also inconsistent. Different versions of Common terminology criteria for adverse events were used to assess toxicities due to various publication years. Notably, a validity assessment of included studies to evaluate the risk of bias and confidence of results was not undertaken. Unpublished studies are unable to be adequately assessed, and this, too, may lead to an important bias leaning toward the effectiveness of treatment or the under-estimation of toxicities. Despite these limitations, published outcomes with SBRT are consistently promising. Because of this promise, increased attention should be paid to delivering regimens that can improve patients' quality of life.

Survival and tumor control

Survival and tumor control results were excellent in the included prospective studies, compared to historic controls in this patient population. As radiation techniques have evolved, the delivery of high dose radiation in fewer fractions has also become more precise. The use of intra-fraction volumetric imaging with cone beam CT can reduce target error compared to use of patient setup or bony anatomy alone^[27,28]. Intra-fraction imaging is recommended as best practice per ESTRO ACROP guidelines^[29]. Because a faster treatment delivery time is likely associated with less patient movement and therefore more accurate treatment delivery, the use of a flattening-filter free setting can help to optimize treatment delivery as well^[30-32]. The use of heterogeneity corrections has also been shown in RTOG 0236 to have a significant effect on prescription dose and tumor coverage, and should be considered standard in SBRT treatments^[33]. Taken together, these technological advances may also be contributing to improved outcomes in this patient population.

Using an α/β ratio of 10, the vast majority of patients were treated with total BED > 100 Gy₁₀, which has been shown to improve outcomes in NSCLC patients treated with SBRT^[34]. Others have argued that biologically effective dose calculations, and the linear quadratic model on which they are constructed, may not be applicable for high fractional doses of radiation^[35]. The radiobiological principles upon which the linear quadratic model is based, however, do not account for differences in re-oxygenation, the effects on tumor vasculature and the enhanced host immunity that hypofractionation can produce. Nevertheless, the use of BED > 100 Gy₁₀ has been adopted as a recommendation for SBRT delivery by the National Comprehensive Cancer Network guidelines and American College of Radiology appropriateness criteria^[36,37].

Fractionation for peripheral tumors

Better staging and delivery techniques have helped improve outcomes compared to historical data with conventionally fractionated radiation therapy. The SPACE trial

Table 2 Toxicity results

Study	Grade 3 + toxicity	Reported adverse events
Miyakawa <i>et al</i> ^[20] , 2017	Grade 3-5, 5.6%	Radiation pneumonitis
Sun <i>et al</i> ^[80] , 2017	Grade 3, 5%	Dermatitis, radiation pneumonitis, chest wall pain
Singh <i>et al</i> ^[22] , 2017, I-124407	Grade 3, 30%	NA
Bezjak <i>et al</i> ^[24] , 2016, RTOG 0813	Grade 3-5, 16%-21%	Respiratory and cardiac toxicities, esophageal perforation, pulmonary hemorrhage
Navarro-Martin <i>et al</i> ^[11] , 2016	Grade 3, 10%	Cough, dyspnea, dermatitis
Nyman <i>et al</i> ^[14] , 2016, SPACE	Grade 3, 14%	Dyspnea, cough, skin reactions
Chang <i>et al</i> ^[13] , 2015, STARS and ROSEL	Grade 3, 10%	Chest wall pain, cough, fatigue, rib fracture
Lindberg <i>et al</i> ^[49] , 2015	Grade 3-4, 30%	Rib fracture, dyspnea, ventricle tachycardia, cough, fatigue, fibrosis, lung infection, pain, pericardial effusion
		Inop: Dyspnea, hypoxia, pneumonitis, chest pain, cough
Nagata <i>et al</i> ^[12] , 2015, JCOG 0403	Grade 3-4, 13% (inop) Grade 3, 6% (op)	Op: Dyspnea, hypoxia, pneumonitis, chest pain
Shibamoto <i>et al</i> ^[6] , 2015	Grade 3, < 10%	Radiation pneumonitis, pleural effusion, esophagitis, rib fracture, dermatitis
Videtic <i>et al</i> ^[13] , 2015, RTOG 0915	Grade 3-5, 12%	DLCO changes, pneumonitis, PFT changes, 2 treatment-related deaths
Timmerman <i>et al</i> ^[18] , 2014, RTOG 0236	Grade 3-4, 31%	Hypocalcemia, hypoxia, pneumonitis, PFT decreased
Taremi <i>et al</i> ^[26] , 2012	Grade 3, 11%	Fatigue, cough, chest wall pain, rib fracture
Bral <i>et al</i> ^[46] , 2011	Grade 3, 20%	Pneumonitis, cough
Ricardi <i>et al</i> ^[16] , 2010	Grade 3-4, 3%	Radiation pneumonitis
Fakiris <i>et al</i> ^[17] , 2009	Grade 3-5, 16%	Apnea, pneumonia, pleural effusion, hemoptysis, respiratory failure, skin erythema
Koto <i>et al</i> ^[10] , 2007	Grade 3, 3%	Pneumonitis
McGarry <i>et al</i> ^[7] , 2005	Grade 3-4, 15%	Pneumonitis, hypoxia, dermatitis, pericardial effusion, tracheal necrosis
Nagata <i>et al</i> ^[8] , 2005	None	None

RTOG: Radiation therapy oncology group; JCOG: Japan clinical oncology group; Inop: Medically inoperable; Op: Medically operable; DLCO: Diffusing capacity of the lungs for carbon monoxide; PFT: Pulmonary function test.

recently demonstrated equivalent survival outcomes compared with SBRT^[14]. Although patients treated with SBRT reported better quality of life and decreased toxicity profiles, the improvement of survival and local control seen in conventionally fractionated radiation therapy during the past several decades is still notable^[14]. Other trials, such as CHISEL study (NCT01014130) and LUSTRE trial (NCT01968941) are currently ongoing and will further investigate the role of conventionally fractionated radiation therapy.

Given the decreased number of visits and favorable toxicity profiles, SBRT offers increased patient convenience and improved quality of life outcomes compared to conventionally fractionated radiation therapy. It would seem that this advantage would be even greater with a decreasing number of SBRT fractions. Amongst the prospective studies included in this review, widely varying dose fractionations have been studied, with only a few comparisons evaluated. Of note, the 5-fraction regimen, which is a commonly used fractionation schema nationwide^[38], has very limited prospective data, and no prospective, comparative data showing superiority. On the other hand, single-fraction dosing, which has been tested in both RTOG 0915 and I-124407, did not show a difference in toxicity or survival outcomes compared to multi-fraction regimens^[13,22].

A follow-up study to RTOG 0915 was not funded because the issue of fractionation was not deemed to be of high enough priority by the National Cancer Institute. In the absence of federal funding for further prospective trials of fractionation, retrospective reviews will have to suffice. Our retrospective review of all patients treated with single- *vs* three-fraction regimens for peripheral early-stage NSCLC at our institution was concordant with the results from our prospective trial^[22] and did not show any significant difference in overall survival, progression-free survival, local failure, nodal failure, or distant failure at 24 mo, despite including patients with lower performance status in the single-fraction cohort^[39]. A propensity matched cohort analysis of the 3-

fraction SBRT regimen used at our institution and a 5-fraction regimen used at another academic institution showed comparable overall survival, progression-free survival, local control and distant control rates^[40]. This is consistent with other retrospective analyses^[41]. Most recently, we expanded the two-institution analysis to include 163 patients comparing single-fraction *vs* five-fraction SBRT and again found no difference in survival outcomes or local control^[42].

Overall, with robust prospective and retrospective evidence showing high rates of local control and comparable safety outcomes to multi-fraction regimens, our institution has adopted the single-fraction radiation schedule for peripheral, early-stage NSCLCs.

Central tumors

Since the definition of a “No Fly Zone” in the 2006 publication by Timmerman *et al*^[23] the spatial proximity of organs at risk, such as main airways, large blood vessels, the heart and esophagus has been the basis of the distinction between centrally and peripherally located NSCLC. Although updated results 3 years later by Fakiris *et al*^[17] showed there was no difference in survival and toxicity between central and peripheral tumors, several subsequent trials have investigated central or peripheral tumors separately. Overall survival outcomes reported from NRG/RTOG 0813 were noted to be comparable to elderly, medically inoperable patients with peripheral early stage tumors. Despite the safety concerns for the treatment of central tumors, this trial also demonstrated reasonable toxicities, though we await the published manuscript.

A literature review of 20 publications reporting outcomes for 563 central lung tumors treated with SBRT included a majority of single-institution retrospective analyses, with only four prospective studies including 68 patients. Tumor location did not appear to impact overall survival, with overall treatment-related mortality reported as 2.7%. As might be expected, Grade 3 and 4 toxicities were more prevalent for central tumors, but occurred in < 9% of patients^[43].

We have previously reported a case of single-fraction SBRT for a solitary metastasis of squamous cell carcinoma in the right hilum which resulted in complete response of the tumor, but sudden grade 4 bronchopulmonary hemorrhage 13 mo after treatment^[44]. Given their location near critical organs, treatment of central tumors is inherently risky, with any fractionation schema predisposing to increased toxicity rates compared to tumors located peripherally.

The recently reported Nordic HILUS-Trial was a prospective, multi-center, non-randomized phase II trial of SBRT for central lung tumors (either primary NSCLC or metastasis), which treated patients with 8 fractions of 7 Gy/fraction, and stratified patients based on tumor location near a mainstem bronchus *vs* a lobar bronchus. Initial results have been published in abstract form. Twenty-one of the 74 included patients developed grade 3 or higher toxicities, with seven patients suffering fatal effects of hemoptysis ($n = 6$) or pneumonitis ($n = 1$)^[45]. The LungTech trial (EORTC 22113-08113), which aims to evaluate efficiency and toxicity of SBRT in patients with centrally located tumors, is ongoing.

SBRT for operable candidates

In our review, despite widely varying inclusion criteria, dose fractionation schemas, and institutional protocols, most trials demonstrated excellent local and regional control for early stage NSCLC^[6-8,10-19,22,24,26,46]. Among operable patients treated with SBRT, 3-year overall survival was 77%-95%. Grade 3-4 toxicity rates were 10%-30% with a few treatment-related deaths, most notably observed in treatment of central lung tumors^[6-8,10-19,22,24,26,46]. These findings are comparable to perioperative complication rates of 15%-25% and the 30-d postoperative mortality rate of 1.7% seen in video-assisted thoracic surgery and open lobectomy in recent trials^[47,48].

In the JCOG 0403 trial, the lower median overall survival reported for the patients deemed medically inoperable was likely complicated by the increased number of comorbidities and decreased performance status of that group, making any direct comparison problematic^[12]. It would be similarly challenging to draw conclusions about SBRT as a viable alternative to lobectomy from the results of the STARS and ROSELS pooled analysis due to the small sample size and short follow up time^[15]. More recently, a brief report was issued regarding results from the single-arm, phase 2 NRG Oncology RTOG 0618 trial, which evaluated SBRT for operable, peripheral T1-2 NSCLC. Of the 26 patients evaluated, only 1 patient had a primary tumor recurrence, and there were no lobular failures at a median follow-up of 48.1 mo. Four-year overall survival was reported as 56%, and median overall survival 55.2 mo^[49].

Regardless, distant failure rates of up to 34% are common for both SBRT and surgery^[6-8,10-19,22,24,26,46,47]. This is likely due to the fact that despite negative findings in initial nodal sampling, nearly 20% of patients are upstaged pathologically from clinical Stage I^[47]. Additional studies have reported up to 30%-35% pathologic

upstaging at the time of surgery^[50,51]. The incidence of occult mediastinal lymph node metastasis in patients with negative uptake on positron emission tomographic/computed tomographic (PET/CT) imaging was as high as 22%, especially in centrally located NSCLC tumors^[52,53]. These findings are unsurprising since PET/CT, mediastinoscopy, and minimally invasive biopsy techniques such as endobronchial ultrasound transbronchial needle aspiration are less sensitive for nodal metastasis compared to nodal dissection^[54-57].

A randomized trial of lung resection combined with nodal dissection published results showing improved survival among early stage NSCLC^[58]. Despite including three-quarters of patients with stage II-III disease, the distant failure rate for patients undergoing systematic nodal dissection was a promising 22.5% without adjuvant chemotherapy *vs* 30.7% of patients who had mediastinal lymph node sampling^[58]. However, if lymph nodes are sampled extensively prior to surgery to rule out nodal metastasis, systematic nodal dissection does not improve survival or reduce distant failure^[59]. At this time, there is no evidence that clinically early stage NSCLC will benefit from intensive lymph node staging prior to SBRT^[60], and several trials are currently investigating the potential role of invasive lymph node staging (NCT01786590, NCT02719847).

Our institution has undertaken a pilot study to evaluate the role of trans-cervical extended mediastinal lymphadenectomy (TEMLA) in combination with SBRT for Stage III NSCLC. The methodology of this study has been previously described^[61]. TEMLA was completed and then followed by either surgical resection or single-fraction SBRT to the primary site, followed by 10 Gy SBRT directed to the mediastinum and/or positive surgical margin. Ten patients completed the study with preliminary results suggesting that the regimen is both well tolerated and provides good regional control^[62]. These findings further suggest that SBRT may be potentially expanded for use in regionally advanced disease.

Toxicity

The SBRT technique allows for a high radiation dose to be delivered to a tumor target while maintaining a rapid drop-off gradient. Since it is assumed that an ablative dose delivered to the target alone should be safe, the toxicity associated with treatment must be related to dose inadvertently deposited in surrounding tissues^[63]. These include toxicities such as chest wall pain and rib fractures in treatment of peripheral tumors, and decline in pulmonary function tests, pneumonia, and pleural or pericardial effusions in treatment of tumors in the central chest region^[23,46,64,65]. These studies collectively show that toxicity is similar between varied fractionation schema. As mentioned above, toxicity may be increased in central tumors despite the use of prolonged fractionation courses.

Future directions

The use of chemotherapy has been retrospectively assessed in patients with T1-3N0M0 NSCLC who underwent SBRT, and was found to reduce distant failure and improve overall survival. However, only 26% of the patients ($n = 17$) received adjuvant chemotherapy^[66]. Subsequently, the STEREO trial was opened to investigate the use of adjuvant chemotherapy in medically inoperable patients with early stage NSCLC treated with SBRT (NCT01300299), but given the difficulty in accruing participants (likely due to significant underlying comorbidities of this population), the study was discontinued. Improved overall survival after surgery and adjuvant chemotherapy for stage IB T2N0M0 has been demonstrated in several studies^[67-69], but this finding has not been reproduced in larger prospective trials^[70-74]. Even when patients were staged clinically and had potential occult nodal metastasis^[47,50,51], neoadjuvant or adjuvant chemotherapy with surgery for early stage NSCLC did not improve survival^[75]. However, adjuvant chemotherapy may be beneficial in select patients with resected early stage NSCLC, such as the tumor size > 4 cm and solid or micropapillary subtypes of adenocarcinoma^[70,76]. Chemotherapy may reduce the risk of distant failure observed in patients treated with either surgery or SBRT alone, but its survival benefits for early stage NSCLC remain unclear.

In addition, other ongoing studies for early stage NSCLC evaluating other treatment regimens and modalities include: immunotherapy with SBRT (NCT02581787, NCT03050554), neoadjuvant SBRT and surgery^[77,78], SBRT dose escalation specifically for T2N0M0 large tumors^[79], radiofrequency ablation^[37], and proton therapy (NCT00875901).

In conclusion, this review shows that SBRT remains the standard of care for medically inoperable patients with early stage NSCLC. While survival and local control outcomes of conventionally fractionated radiation therapy have been shown to be comparable, SBRT still offers better toxicity and quality of life outcomes. Prospective trials evaluating fractionation schema have not shown a clear benefit to

multi-fraction regimens for peripheral, early stage NSCLC, and as such, our institution has adopted a single-fraction SBRT scheme. Additionally, further work is being done to evaluate the role of SBRT for regional nodal disease in stage III NSCLC patients. Additional studies are underway to evaluate various modalities and therapy schedules in this challenging patient population.

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