clinical reviews

Stereotactic Body Radiotherapy for the Management of Early-Stage Non–Small-Cell Lung Cancer: A Clinical Overview

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INTRODUCTION

Lung cancer is a significant source of worldwide morbidity and mortality.[1] In the United States, there will be an estimated 236,740 new cases and 130,180 lung cancer deaths in 2022.[2] The majority of lung cancers are non–small-cell lung cancer (NSCLC) in histology.[3] Among patients with NSCLC, the diagnosis of localized disease is increasing. In 2018, 28% of lung cancer diagnoses were localized disease, an increase from 17% in the mid-2000s.[2] Since lung cancer screening was first recommended in 2013, the number of early-stage diagnoses has notably increased, rising at a rate of 4.5% per year from 2013 to 2018.[2]

The standard of care for a patient with medically *operable* early-stage NSCLC has long been surgical resection.[4] For those patients deemed *inoperable* because of their high surgical risk, the current standard has emerged over the past 25 years and is now considered to be stereotactic body radiotherapy (SBRT; also known as stereotactic ablative radiotherapy)[4]—defined as very high dose, precisely focused radiation given over a limited number of treatments (typically ≤ 5) to discrete targets using rigorous delivery and motion management techniques. Having been shown to be safe, effective, and favorable for a vulnerable patient population, SBRT has revolutionized the treatment of early-stage NSCLC and is the subject of the present review.

THE ORIGINS OF SBRT IN THE TREATMENT OF EARLY-STAGE, MEDICALLY INOPERABLE LUNG CANCER

Inasmuch as surgery was deemed the gold standard for curative management of early-stage lung cancer, clinicians had long wondered if lesser surgeries might be beneficial for high-risk, vulnerable patients given the potential deleterious impact of extensive resection on individuals with impaired lung function and other comorbidities.[5] However, limited surgeries had historically provided inferior outcomes compared with standard resection. In 1995, Ginsberg and Rubenstein published the results of the Lung Cancer Study Group phase III randomized trial comparing lobectomy with limited resection, which showed that sublobar resections were associated with significantly increased rates of locoregional recurrence and with trends toward worse survival.[6] In the years since its publication, further investigation into this question has produced mixed results and lobectomy remains standard.[7]

Considering the factors associated with the risk of developing lung cancer, it is not surprising that a significant proportion of patients with early-stage lung cancer would present with a tenuous cardiopulmonary reserve, excluding them from surgical intervention. Criteria for the designation of medical inoperability in historic trials have been typically predicated on selected pulmonary function values and predicting pulmonary reserve after resection. For example, a recent trial included a baseline forced expiratory volume in 1 second $< 40\%$ predicted, postoperative forced expiratory volume in 1 second $< 30\%$ predicted, severely reduced diffusion capacity, baseline hypoxia and/or hypercapnia, exercise oxygen consumption $< 50\%$ of predicted, and severe pulmonary hypertension, to classify patients as having an unacceptable surgical risk.[8] For high-risk patients, a combination of surgery and radiotherapy was sometimes used to minimize the surgical risk by using limited resections and then incorporating radiotherapy (RT). For example, in some cases involving wedge resections, postoperative (adjuvant) conventionally fractionated external beam radiotherapy (EBRT) to the tumor bed was delivered in fractional doses of 1.8-2 Gy per fraction over 4-6 weeks. In other cases, brachytherapy (delivery of radiation via the implantation of radioactive materials, usually seeds, directly within the tumor or tumor bed) was used after limited resection. Such combination approaches had variable results.[9,10]

When the risk posed by resection was considered too great, patients were then conventionally referred for the local management of their disease using RT. That said, radiation oncologists historically were aware of the limitations in using routine forms of RT to manage early-stage lung cancer because of challenges in defining the target and delivering an effective dose. Thus, the goal of treatment was typically the best achievable local tumor control. A number of retrospective studies looking at EBRT alone for early-stage lung cancer showed that it was invariably associated with inferior outcomes compared with surgery.[9,11,12] Factors contributing to inferior outcomes with EBRT alone include

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the use of clinical staging limiting a full understanding of disease extent (ie, optimal target delineation), baseline patient frailty leading to impaired tolerance for treatment, and treatment fields used with traditional EBRT that incorporated large amounts of noncancer bearing lung.[8,9] Results from such studies made it therefore apparent that to deliver potentially more effective radiation, there had to be methods developed to better identify the target in the lung so as to limit the normal lung irradiated. This would also mean accounting for tumor motion because of breathing.

When considering how to improve the efficacy of RT when treating cancer, radiobiologic principles have suggested that delivering higher doses per fraction and over a short time interval (eg, days instead of weeks) would result in a substantially more effective total dose because it results in a higher biologically equivalent dose (BED) and thus an increased tumoricidal effect. BED is a measurement of the true biologic dose delivered, taking into account dose per fraction, total dose, and the alpha-beta ratio—a quantification of the inherent radiosensitivity of a given tumor or tissue.[13] The concept of delivering high-dose radiation safely and rapidly to discrete targets was pioneered by Leksell in the 1950s in Sweden for the treatment of intracranial lesions. Using a stereotactic head frame for localization of tumors in space, he created a robust and consistently reproducible system for identifying the brain target and then ensuring precise delivery of large single doses. This approach became known as stereotactic radiosurgery (SRS).[14] Its efficacy and safety profile became well established over subsequent decades so that utilization of SRS for tumors of the central nervous system became routine.

The first report of applying the SRS concept to sites of extracranial disease was published in 1994 and was an innovation of the same group in Sweden, the Karolinska Institute, which had pioneered SRS in the 1950s. Their landmark report detailed the components of a stereotactic body frame and fixation device to rigidly but noninvasively immobilize patients for accurate target localization and motion characterization. Hence, the technique became known as SBRT.[15,16] They described a range of exploratory doses from 7.7 to 30 Gy in one to four fractions that were delivered to tumors of the lung and abdomen with very high local control rates (approximately 80%) and, most remarkably, minimal toxicity. This report triggered a wave of trials and clinical studies of SBRT, particularly as it was applied to lung tumors (both primary and metastatic) in patients who were not surgical candidates. Over the subsequent 25 years, from the late 1990s into the 2000s, a large body of evidence from numerous institutional experiences and nonrandomized prospective trials of SBRT for patients with lung cancer accumulated and consistently demonstrated its extremely high rates of local control while at the same time resulting in very low rates of treatment-related side effects (see Table 1).[17-73] Notwithstanding this consistent theme in the published results for lung SBRT, that is, that it achieves excellent local control, the definition of local control after this form of therapy can be difficult because distinguishing true tumor failure from radiation-induced lung damage is often challenging.[9] With regression of the physical tumor after SBRT, there is concurrent development of fibrotic lung parenchyma in response. Many treated patients develop radiographic changes of fibrosis that may be mistaken for recurrence, and interpretation of images may require an experienced reader.[9] Positron emission tomography–based imaging can be of utility for assessing ambiguous cases although biopsy may occasionally be required, which brings with it its own risks in a vulnerable pulmonary patient.[9]

Considering the medically fragile population being treated, the results provided in Table 1 were considered by many oncologists as practice-changing. Figure 1 provides an illustrative case. By 2010, on the basis of comparisons with historical outcomes reported for conventional RT and given the very limited number of other treatment options for this population, SBRT was recognized as the (pragmatic) standard of care for the medically inoperable patient.[9,18] That said, SBRT was formally compared with conventional RT in two important randomized prospective trials, whose results were both published in the late 2010s. In 2016, *Stereotactic Precision And Conventional radiotherapy Evaluation* (SPACE), a randomized phase II trial, was the first of the two studies to be published.[19] It enrolled 49 medically inoperable patients with peripheral tumors to SBRT (prescribed as 66 Gy in three fractions to the isocenter so that the periphery of the planning target volume received 45 Gy in three fractions) and 53 patients to conventional RT (70 Gy in 35 fractions with 3D conformal RT). At a median follow-up of 37 months, no difference was found between the two arms in terms of progression-free survival, overall survival, or local control, with less toxicity and better quality-of-life (QOL) scores observed in the SBRT arm. However, there was an imbalance in prognostic factors between the two arms, so that any potential benefits of the SBRT approach might have been masked by the inclusion of patients with poor performance status, no pathologic diagnosis, or incomplete staging because of omission of ^{18}F-fluorodeoxyglucose-positron emission tomography in a substantial proportion of patients.[19] TROG 09.02 CHISEL[20] was a randomized (2:1) phase III trial that randomly assigned 66 medically inoperable patients to SBRT (54 Gy in three fractions or 48 Gy in four fractions) and 35 patients to conventional RT (66 Gy in 33 fractions). At a median follow-up of over 2 years and in contrast to the SPACE trial, CHISEL showed statistically significant improvements in local control and, most importantly, overall survival in the SBRT group compared with the conventional RT group with comparable toxicity between the two arms. Given that staging processes, patient characteristics, and tumor factors were balanced between arms, CHISEL was considered the landmark study to demonstrate the superiority of SBRT and confirm it as the standard of care.

TABLE 1. Selected Studies in Lung SBRT for Early-Stage Lung Cancer

Year	Reference	Design	No. of Patients	Population	Dose Schedule	F/U	LC	OS	Toxicity
2004	Onishi et al[21]	MI RR	245	Stage I NSCLC	18-75 Gy in 1-22 fractions	Median: 24 months	LC: 85.5%	3-Year, operable, BED ≥ 100 Gy: 88.4%	Grade 3 or higher pulmonary toxicity: 2.4%
				Operable and inoperable	Median BED of 108		Local recurrence for BED ≥ 100 Gy: 8.1% (LC: 91.9%)	BED < 100 Gy: 69.4%	
2007	Onishi et al[22]	MI RR	257	Stage I NSCLC	18-75 Gy in 1-22 fractions	Median: 38 months	LC: 86.0%	5-Year, operable, BED ≥ 100 Gy: 70.8%	Grade 3 or greater pulmonary toxicity: 5.4%
				Operable and inoperable	Median BED of 111		Local recurrence for BED ≥ 100 Gy: 8.4% (LC: 91.6%)	BED < 100 Gy: 30.2%	
2003	Timmerman et al[23]	Phase I	37	T1, T2 N0M0	Dose escalation to 20 Gy in three fractions	Median: 15.2 months	LC: 83.8%	At a median F/U of 15.2 months, OS: 64.0%	G3 or higher pulmonary toxicities: 5.4%
				Medically inoperable			All LFs received < 18 Gy per fraction		No appreciable decline in cardiopulmonary function per examination, laboratory results, PFTs, imaging
2005	McGarry et al[24]	Phase I	47	T1, T2, N0M0	Dose escalation as above	T1 mean: 27.4 months	LC: 78.7% LF: 4/19 T1 LF: 6/28 T2	NA	G3 toxicity, T2 group with tumors > 5 cm: 3 of 5 patients treated with 24 Gy per fraction
				Medically inoperable		T2 mean: 19.1 months			
2006	Timmerman et al[25]	Phase II	70	T1, T2, N0M0	60-66 Gy in three fractions	Median: 17.5 months	LC, 2-year: 95.0%	OS, 2-year: 54.7%	2-Year freedom from severe toxicity in peripheral tumors 83.0%; 54.0% in central tumors G3-5: 5 of 48 with peripheral tumors, 10.4% G3-5: 6 of 22 with central tumors, 27.3%
				Medically inoperable					
2009	Fakiris et al[26]	Phase II	70	T1, T2, N0M0	60-66 Gy in three fractions	Median: 50.2 months	LC, 3-year: 88.1%	OS, 3-year: 42.7%	2-Year freedom from severe toxicity in peripheral tumors 83.0%; 54.0% in central tumors G3-5: 5 of 48 with peripheral tumors, 10.4% G3-5: 6 of 22 with central tumors, 27.3%
				Medically inoperable					
2010	RTOG 0236[27]	Phase II	55	T1, T2, N0M0	54 Gy in three fractions	Median: 34.4 months	LC, 3-year: 97.6%	OS, 3-year: 55.8%	G3/4: 16.4% (9 of 55)
				Medically inoperable					
				Peripheral					

(continued on following page)

TABLE 1. Selected Studies in Lung SBRT for Early-Stage Lung Cancer (continued)

Year	Reference	Design	No. of Patients	Population	Dose Schedule	F/U	LC	OS	Toxicity
2018	RTOG 0236[28]	Phase II	55	T1, T2, N0M0 Medically inoperable Peripheral	54 Gy in three fractions	Median: 48 months for all patients 86.4 months seven patients still living	LC, 5-year: 92.7%	OS, 5-year: 40.0%	G3/4: 30.9% (17 of 55)
2014	Videtic et al[29]	Institutional review	80	T1, T2, N0M0 Medically inoperable Peripheral	30 Gy in one fraction (69%) 34 Gy in one fraction (31%)	Median, 30 Gy: 18.7 months 34 Gy: 17.8 months	30 Gy, LC, 1 year: 98.0% 34 Gy, LC, 1-year: 86.2%	30 Gy, OS, 1 year: 75.0% 34 Gy, OS, 1 year: 64.0%	30 Gy, no toxicity: 92.7% 34 Gy, no toxicity: 84.0% No G3 or higher toxicity
2015	RTOG 0915[30]	Phase II	84	T1, T2, N0M0 Medically inoperable Peripheral	34 Gy in one fraction 48 Gy in four fractions	Median: 30.2 months	34 Gy, 1-year LC: 97.0% 48 Gy, 1-year LC: 92.7%	34 Gy, 2-year OS: 61.3% 48 Gy, 2-year OS: 77.7%	34 Gy, G3 or higher: 10.3% 48 Gy, G3 or higher: 13.3%
2019	RTOG 0915[31]	Phase II	84	T1/T2 N0M0 Medically inoperable Peripheral	34 Gy in one fraction 48 Gy in four fractions	Median: 4 years for all patients 6 years for those alive at analysis	34 Gy, 5-year LC: 89.4% 48 Gy, 5-year LC: 93.2%	34 Gy, 5-year OS: 29.6% 48 Gy, 5-year OS: 41.1%	34 Gy, G3 or higher: 2.6% 48 Gy, G3 or higher: 11.1%
2018	RTOG 0618[53]	Phase II	26	T1/T2 N0M0 Medically operable Peripheral	54 Gy in three fractions	Median: 48.1 months	4-Year LC: 96.0%	4-Year OS: 56.0%	G3 AEs: 7.7% No G4/G5 AEs
2019	RPCI[32]	Phase II	98	T1/T2 N0M0 Medically inoperable Peripheral	30 Gy in one fraction 60 Gy in three fractions	Median: 53.8 months	30 Gy, 2-year LC: 94.9% 60 Gy, 2-year LC: 97.1%	2-Year OS: 73.0% 2-Year OS: 62.0%	30 Gy, thoracic G3 AEs: 16.3% 60 Gy, thoracic G3 AEs G3: 12.2% No grade 4/5 AEs
2019	RTOG 0813[34]	Phase I/II	100	T1/T2 N0M0 Medically inoperable Central	Five fractions, dose escalating, 10-12 Gy per fraction	Median: 37.9 months	2-Year LC, 10 Gy per fraction: 87.5% 2-Year LC, 12 Gy per fraction: 87.9%	2-Year OS, 10 Gy per fraction: 75.0% 2-Year OS, 12 Gy per fraction: 72.7%	12 Gy per fraction probability of DLT: 7.2%
2021	Videtic et al[33]	RR	229	T1/T2 N0M0 Medically inoperable Peripheral	30 Gy in one fraction (27.9%) 34 Gy in one fraction (72.1%)	Median, 30 Gy: 36.7 months 34 Gy: 17.2 months	2-Year LC: 92.7%	Median OS: 44.1 months	G3 toxicity: 0.9% No G4/G5 AEs

Abbreviations: AE, adverse event; BED, biologic equivalent dose; DLT, dose-limiting toxicity; F/U, follow-up; G, grade; LC, local control; LF, local failure; MI, multi-institutional; NSCLC, non–small-cell lung cancer; OS, overall survival; PFTs, pulmonary function tests; RCPI, Roswell Park Cancer Institute; RR, retrospective review; RTOG, Radiation Therapy Oncology Group.

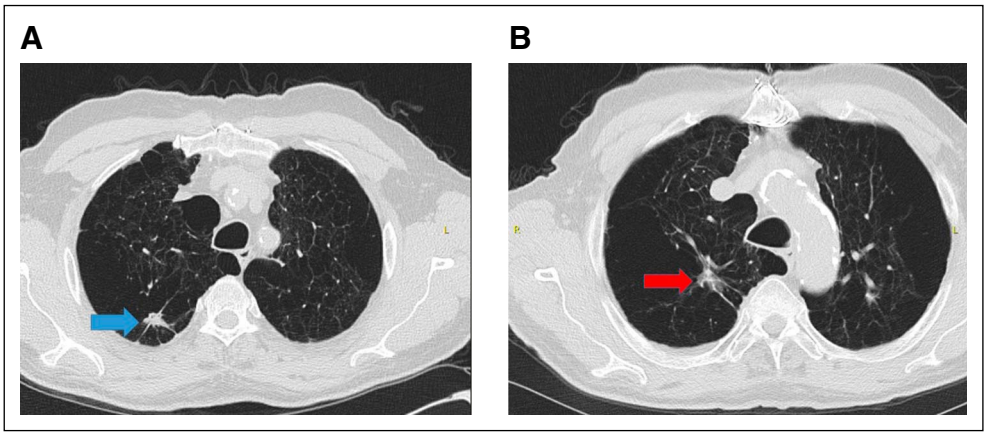

FIG 1. Case of a 72-year-old male with medically inoperable (by severely impaired pulmonary function), American Joint Committee on Cancer, 8th edition, T1aN0M0 stage IA1 adenocarcinoma of the RUL of the lung, enrolled in the RPCI-124407 trial, randomly assigned to 60 Gy in three fractions completed on March 2012. (A) Representative pretreatment computed tomography axial slice of January 2012 demonstrating RUL lung cancer (blue arrow). (B) Representative computed tomography axial slice of April 2022 demonstrating stable fibrotic response in treated RUL lung cancer 10 years after SBRT (red arrow). RPCI, Roswell Park Cancer Institute; RUL, right upper lobe.

CLINICAL APPLICATIONS: EVOLUTION OF SBRT AND SELECTION BY PATIENT AND TUMOR FACTORS

Pioneering work in the application of SBRT to early-stage lung cancer came particularly from multiple groups in Japan. In 2004, Onishi et al[21] published the results of a multi-institutional retrospective review analyzing the use of SBRT for the treatment of stage I NSCLC in 245 medically inoperable *and* operable patients treated from 1995 to 2003. In this study, a variety of dosing and fractionation schedules were used (18-75 Gy in 1-22 fractions) yielding very low rates of toxicity (2.4% grade 3 or higher) and very high local control rates (over 90%) for patients treated with high doses (8.1% recurrence rate in patients treated at a BED $\geq$ 100 Gy). Of particular note in this series were the medically operable patients whose 5-year survivals matched, stage for stage, historic results from their surgical counterparts. A 2007 update with a median follow-up of 38 months showed continuous rates of low toxicity (5.4% grade 2 or higher).[22] A correlation between local control and the BED of the SBRT delivered also became evident, when they showed a local recurrence rate of 8.4% with a BED $\geq$ 100 Gy versus 42.9% for BED $<$ 100 Gy. Further analysis of operable patients showed that for BED $\geq$ 100 Gy, the 5-year OS was 70.8% compared with a 5-year OS of 30.2% for BED $<$ 100 Gy ($P < .05$).[21,22]

In 2003, the initial report from the first phase I lung SBRT study conducted in North America was published by Timmerman and colleagues from Indiana University,[23] showing that doses of 20 Gy per fraction were tolerable and feasible. Follow-up data in 2005 showed that local control was a function of dose: of 47 patients treated, 10 experienced local failures, 9 of whom received doses of $\leq$ 16 Gy per fraction.[24] In 2006, the same group published phase II data in which 70 patients with early-stage NSCLC were treated with 60- 66 Gy in three fractions, again showing impressive rates of local control (2- and 3-year local control rates of 95% and 88%, respectively) and overall minimal toxicity.[25,26] However, it was noted that a greater proportion of severe toxicity (including 4 of 6 grade 5 toxicities) was observed in what eventually came to be termed *centrally located* tumors (with centrality defined as a tumor located within 2 cm of the proximal bronchial tree) as distinct from other tumors in the lung now termed peripheral (ie, 10.4% grade 3-5 toxicity for peripheral tumors; 27.3% for central tumors). This finding was novel as this toxicity profile had not been previously identified with less potent (by BED) SBRT schedules, such as those frequently used in Japan.

In 2010, the first *multi-institutional* phase II study investigating the safety and efficacy of SBRT in early-stage lung cancer, Radiation Therapy Oncology Group (RTOG) trial #0236, was published, with a later update in 2018.[27,28] Fifty-five medically inoperable patients with peripherally located tumors were treated at a dose of 54 Gy in three fractions (modeled after the Indiana University trials, with the original dose adjusted by a tissue correction factor). Three- and 5-year local control rates were 97.6% and 92.7%, respectively, with a 5-year overall survival of 40% observed. With regard to safety, 27.3% of patients experienced grade 3 toxicity at extended follow-up.

At their inception, studies of SBRT feasibility and efficacy had mimicked the single-shot approach used conventionally with SRS for brain tumors. Although investigations of lung SBRT over the decades had tended to favor schedules with multiple fractions, albeit five or less, the late 2000s saw active investigations formally studying single-fraction SBRT (SF-SBRT) for peripherally located lung tumors.[29] In 2015, Videtic et al[30] published the results of RTOG 0915, a randomized phase II study comparing 34 Gy

in one fraction with 48 Gy in four fractions for peripherally located tumors. This study had a primary end point of grade 3 or higher toxicity at 1 year, and the final results showed similar outcomes for each arm (10.3% *v* 13.3%, one *v* four fractions, respectively) and for 1-year local control rates (97% *v* 92.7%, one *v* four fractions, respectively). Long-term results of this study continued to show no differences in outcomes between the SF-SBRT and the four-fraction schedule.[31] The Roswell Park Cancer Institute published the results of their randomized phase II trial #124407 in 2017 that compared 30 Gy in one fraction with 60 Gy in three fractions. The results of this study showed no significant differences between the two arms in terms of adverse events, overall survival, or 2-year local control.[32] Recently published single-institutional data looking at 10 years of implementing SF-SBRT continue to show the same promising results.[33]

Central Tumors

After early work suggested increased toxicity for central lung tumors when using the Indiana University three-fraction SBRT schedule, the RTOG conducted trial #0813, a prospective phase I/II trial investigating the maximally tolerated dose, safety, and efficacy of SBRT for centrally located early-stage NSCLC.[34] Of interest, this trial used a broader definition of centrality than the previous RTOG 0236 trial such that lesions immediately adjacent to mediastinal structures or pericardial pleura were also included. In this trial, SBRT was delivered in a stepwise 5-fraction schedule starting at 10 Gy to a maximum of 12 Gy per fraction (total doses 50-60 Gy). RTOG 0813 results were published in 2019 and showed that the fractional maximally tolerated dose for central tumors was 12 Gy. Two-year local control and overall survival rates were similar across the fractionation schedules, with no evident improvement in control with increased dose (87.5% *v* 87.9% for the 10 Gy– and 12 Gy–per fraction cohorts, respectively). Current thinking is that SBRT for centrally located tumors should not exceed this dosing threshold, especially in the absence of clear local control benefits.

Multiple other studies investigating the treatment of central tumors have been published using a variety of dosing/fractionation schemes.[35-44] Although local control rates are consistently high (80%-90%), severe side effects remain a concern with most studies reporting at least one grade 5 toxicity. It has been posited that severe toxicity is more pronounced for *ultracentral* tumors, that is, those within 1 cm of the proximal bronchial tree or invading the trachea or mainstem bronchi. Further studies differentiating between these two entities have shown significant rates of toxicity including grade 5 toxicity (as high as 21%) for ultracentral tumors.[41-44]

As an illustrative example, the Nordic HILUS nonrandomized phase II study published in 2021 evaluated 65 patients stratified into two groups—group A, including patients with tumors within 1 cm of the proximal bronchial tree, and group B, including all other patients.[42] All patients were treated with SBRT, 56 Gy in eight fractions. There was significant toxicity observed in this study, including a grade 5 toxicity rate of 15%, with most toxicity and treatment-related death occurring in group A and leading to the conclusion that SBRT for ultracentral tumors comes with a substantial risk for serious/fatal toxicity. In response to the Nordic HILUS study, multiple editorials have been published, which review the radiation planning and delivery techniques used by the study, exploring the possibility that different approaches in dose constraints, organ-at-risk delineation, and motion management/image guidance could have resulted in better outcomes.[45,46] The optimal dose and fractionation schedule for the treatment of central and ultracentral tumors remain a matter of controversy and are the subject of active investigation. Given their very high-risk nature, the management of ultracentral cases should be discussed in an expert multidisciplinary setting, as should the appropriateness of SBRT. If SBRT is recommended for ultracentral cases, clinicians may consider it being performed at a center of expertise.

Another consideration when treating centrally located tumors is radiation dose to the heart. A number of studies have shown correlations between radiation doses to the heart and its substructures and noncancer-related deaths. As such, significant care is required to avoid unnecessary heart dose to prevent such treatment-related toxicity.[47-49] These findings, which have been identified in studies of inoperable patients, could potentially have a bearing on decision making in cases of operable patients considering SBRT and who might otherwise benefit from surgery.

The Operable Patient

As noted above, publications from the SBRT work of Onishi et al in the early 2000s included results for operable and inoperable patients and showed promising results in both populations, comparable with surgical series.[21,22] Not surprisingly, lung SBRT for the patient with operable early-stage lung cancer became an active area for study where it was compared with resection.[50-52] Despite this interest, few such studies have ever been completed, due primarily to low accrual rates. This poor accrual has been attributed in part to the difficulty with being randomly assigned to a treatment where the injury potential of one modality (surgery) is greater than another (SBRT).

In an attempt at salvaging possible insights from unfinished trials, Chang et al[51] in 2015 published a pooled analysis of the accumulated data from the *Stereotactic Ablative Radiotherapy (SABR) in Stage I* (STARS) and *Radiosurgery Or Surgery for operable Early stage (stage 1A) non-small cell Lung cancer* (ROSEL) trials, each randomized study comparing SBRT with lobectomy with mediastinal lymph node dissection. The results of this highly critiqued and controversial analysis of the 58 patients who were analyzable revealed 3-year overall survival that favored SBRT (95%)

over surgery (79%; $P = .037$). Ten percent of the SBRT group experienced grade 3 or higher toxicity versus 44% in the surgery group. A 2021 analysis compared this study's SBRT cohort with a cohort of patients with stage IA NSCLC treated with video-assisted thoracoscopic surgery (VATS), using a propensity-matched analysis.[52] No differences were found in local, regional, or distant recurrence between the two groups, with no significant difference in overall survival in the SBRT group compared with the VATS group.

In addition, in 2018, Timmerman et al[53] published the results of RTOG 0618, which evaluated SBRT for patients with operable early-stage NSCLC, reserving surgical resection for salvage of local failures. This was not a study comparing modalities, but it did define the long-term benefits of SBRT in fit patients, with a 4-year local control rate of 96% and no grade 4/5 toxicity. Notwithstanding these findings, current guidelines do not recommend SBRT as an alternative to surgery for operable patients outside of a clinical trial.[18]

When considering special populations, multiple large database reviews have suggested that markers of morbidity and mortality in the postinterventional setting favor SBRT[54,55] compared with surgery. Postinterventional morbidity and mortality may be highest in individuals age over 70 years, and this has prompted some to advocate for preferential use of SBRT in the elderly, operable population.[54]

Ongoing phase III trials continue to address the question of surgery and SBRT. The *Sublobar Resection (SR) versus Stereotactic Ablative Radiotherapy (SAbR) in High-Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)* (STABLEMATES) trial is a randomized phase III study of sublobar resection versus SBRT in high-risk patients, with a 3-year overall survival primary end point.[56] The *Veterans Affairs Lung Cancer Surgery Or Stereotactic Radiotherapy* (VALOR) is a randomized phase III trial of resection versus SBRT in operable patients being cared for in Veterans Affairs clinical centers.[57]

SBRT for Large Tumors and for Salvage

Treatment options for the inoperable population are intrinsically limited, with frailty and comorbidity often precluding invasive interventions. This is even more so for patients with atypical cancer needs. The large, multi-institutional studies that provided a prospective scientific basis for lung SBRT (RTOG 0236, 0813, 0915, 0618) per protocol only allowed tumors ≤ 5 cm in maximal diameter. Mindful that larger tumors have an increased propensity for locoregional and distant spread,[18] the use of SBRT for definitive management of such cases elicited concern since the larger treatment volumes required were assumed, theoretically, to increase the risk of toxicity. Necessity, nonetheless, prompted the use of SBRT for inoperable patients with tumors > 5 cm in size and was based on strictly following the standard planning constraints (independent of size) provided by the RTOG protocols for the organs at risk. In the first series published looking at large tumor outcome with SBRT, 40 patients with a median tumor size of 5.6 cm (range, 5.1-10) had an 18-month local control rate of 91.2% and a 7.5% rate of grade 3 or higher toxicity.[58] Further validating the use of SBRT in this setting, a 2019 review of the literature on this subject found corroboration across multiple large tumor studies (all of which involved fractionated SBRT) regarding the safety and efficacy of this approach.[59] Another observation in this report was that, for a given SBRT dose, local control decreases with increasing tumor size. Although one of the earliest SF-SBRT publications documented treating tumors up to 10 cm, there have been no publications to date on the relationship between SF-SBRT dose and outcomes as a function of tumor size.[60]

Definitive SBRT has also been used as a means of salvage for local-only failures after previous surgery or SBRT. Hearn et al[61] reported on successful salvage SBRT for 22 patients with local failure after previous primary lung SBRT. Sittenfeld et al[62] showed that similar to SBRT for primary early-stage NSCLC, salvage SBRT in 48 patients who had local relapse after surgical resection of their primary NSCLC offered high rates of local control with limited toxicity.

SBRT and QOL

QOL parameters are key considerations when treating patients with lung cancer, especially when caring for those patients with multiple concurrent medical comorbidities for whom any form of intervention may trigger unanticipated detrimental effects. Mindful of its excellent cancer outcomes and minimal treatment-related side effects, multiple studies have also confirmed the favorable QOL outcomes achievable with lung SBRT.[63-65] A prospective QOL assessment for SBRT patients treated at the Cleveland Clinic observed no degradation in patient-reported QOL or pulmonary function tests over 1 year.[63] A 2016 systematic review of nine early-stage lung cancer studies analyzing the impact of SBRT on QOL found no significant changes across numerous QOL domains.[64] A 2018 phase II trial looked at the early impact of SBRT on QOL outcomes and showed significant improvement in QOL scores after SBRT for those with low initial pretreatment scores.[65] By contrast, an analysis of postsurgical resection QOL showed clinically significant decreases in domains related to physical functionality at 6 months, which in some cases persisted for 2 years.

A common toxicity concern with potential QOL considerations is chest wall toxicity. Symptoms typically develop between 6 and 12 months after SBRT and, in the majority of cases, resolve with medical management and time.[66,67] Multiple retrospective reviews on this subject have been published with rates of post-SBRT chest wall pain on par with those observed post-VATS (21%-34% *v* 25%-47%).[66,67] In addition, SF-SBRT has not been found to consistently increase the risk of chest wall toxicity over SBRT delivered in multiple fractions.[66] Although the risk of

post-treatment chest wall pain and rib fracture increases for lesions abutting the chest wall, this is not considered a contraindication to SBRT and distance from the chest wall was removed from the 2022 NCCN guidelines as a factor for determining SF-SBRT eligibility.[4,66] Dosimetric constraints correlating with post-SBRT chest wall syndromes have been published and can help to guide treatment planning decisions in cases of abutment.[67]

SBRT AND PUBLIC HEALTH

Lung SBRT's favorable treatment profile has had an impact on the patterns of referral for patients seeking lung cancer treatment. A time trend analysis investigating the impact of SBRT on the care of the elderly (≥75 years old) found that, from 1999 to 2007, SBRT resulted in a 16% absolute increase in RT utilization and resulted in a 5-month improvement in overall survival for an age-matched population.[68] Interest in implementing SBRT developed quickly after the first reports on lung SBRT became well known. In the United States, a 2013 survey of American radiation oncologists revealed that more than 50% of those queried had adopted this technology and were predicting further increased usage in the future.[69]

The COVID-19 pandemic prompted re-evaluation of routine cancer treatment practices in consideration of the disease's risk of transmission; this prompted means of limiting physical exposure that occurs within complex medical systems.[2] There were also calls for shifts in RT practice, with an emphasis placed on shorter treatment delivery schedules to meet this need. For example, a 2020 review strongly advocated for the increased use of SF-SBRT for patients with inoperable early-stage lung cancer since it would minimize the chance of any COVID-19–related patient and provider exposures.[70] Similarly, a 2020 ESTRO-ASTRO consensus statement recommended SF-SBRT for patients with early-stage NSCLC treated in the pandemic setting.[71]

Lung SBRT has also been shown to be cost-effective. When comparing SBRT with standard conformal RT and radiofrequency ablation in a Markov model involving medically inoperable NSCLC, SBRT was the most cost-effective treatment strategy by a significant margin.[72] SF-SBRT for NSCLC has been estimated to be 40% less expensive compared with three-fraction SBRT using 2009 Medicare rates.[70] A cost-effectiveness analysis for operable stage I NSCLC suggested that SBRT dominates VATS resection in the majority of simulation models.[73]

SBRT AND IMMUNOTHERAPY (IO)

Multiple early reviews analyzing institutional early-stage lung cancer cohorts described distant recurrence as the predominant mode of failure after SBRT, mimicking the patterns of failure seen with surgical resection for same-stage patients.[74,75] Distant dissemination was seen as the most common failure pattern in RTOG 0236, at approximately 30% on long-term follow-up.[28] With SBRT local control rates consistently around 90%, prevention of distant failure has been considered as critical for optimizing overall survival. However, this goal has presented a significant clinical challenge since SBRT patients likely will not be able to tolerate conventional chemotherapy because their medical fragility lends itself to more severe side effects.[76]

The advent of IO in the past 5 years has revolutionized the treatment of lung cancer. In that regard, it potentially offers an avenue to improving distant control in the early-stage SBRT population given its favorable toxicity profile compared with conventional chemotherapy and also for the possible combinatorial effects enhancing its efficacy when it interacts with RT. Serving as an in vivo vaccine, RT causes increased exposure of the immune system to tumor antigen–stimulating T-cell activation, while also increasing vascular permeability and altering the tumor microenvironment eliciting a favorable antitumor immune response.[77,78] This can enhance treatment response within, and possibly even outside of, the irradiated field.[79-81] The landmark PACIFIC study showed a survival benefit to consolidative durvalumab postchemoradiotherapy in the locally advanced setting.[82] The secondary analysis of KEYNOTE-001 and a retrospective review of patients with metastatic lung cancer treated with IO at the Massachusetts General Hospital have suggested that patients treated with prior RT experience greater IO benefit.[83,84] This has led to direct investigation of combinatorial IO and SBRT in the metastatic setting with promising results.[85-87]

By extrapolation, this combinatorial approach is also now being tested in the early-stage setting. Multiple ongoing clinical trials including PACIFIC-4, SWOG 1914, and Keynote 867 are currently investigating this therapeutic combination.[88-90] PACIFIC-4 is a multicenter study testing durvalumab versus placebo (given concurrent with and after SBRT) for patients with unresected early-stage node-negative NSCLC.[88] SWOG 1914 is a randomized phase III trial of induction/consolidation atezolizumab with SBRT versus SBRT alone in the treatment of early-stage NSCLC.[89] Similarly, Keynote 867 is a prospective randomized trial investigating SBRT with or without pembrolizumab in the treatment of unresected stage I/II NSCLC.[90]

Many details on how to integrate IO and SBRT, including the ideal dose/fractionation of SBRT when given in combination with IO and the actual immunomodulatory potential of SBRT, remain to be answered.[80,81] Interestingly, shorter SBRT delivery schedules (such as SF-SBRT) may provide the most potent immunomodulatory doses.[70] It has been theorized that shorter treatment schedules result in greater lymphocyte sparing important for the optimal functionality of IO.[70]

DISCUSSION

SBRT is a safe, effective, curative, patient-friendly, and cost-effective treatment for inoperable early-stage lung cancer. Since its origins in the 1990s, its principles and practices have been refined over the past 25 years through a number of

critical prospective trials and institutional series. Its use has expanded broadly and will likely continue to do so given the increasing diagnosis of early-stage disease as lung cancer screening becomes more mainstream. Its increasing application to the operable population and for complex clinical scenarios will continue to evolve. Its integration with other components of lung cancer care such as chemotherapy and IO is an active area of investigation that is in its early stages but promises to offer patients the possibility of highly effective cancer cures with minimal treatment-related burden.

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REFERENCES

1. WHO. Cancer: Key facts. 2022. https://www.who.int/news-room/fact-sheets/detail/cancer
2. Siegel RL, Miller KD, Fuchs HE, Jemal A: Cancer statistics, 2022. CA Cancer J Clin 72:7-33, 2022
3. Thomas KW, Gould MK. Overview of the Initial Evaluation, Diagnosis, and Staging of Patients With Suspected Lung Cancer. Jan 21, 2020. https://www.uptodate.com/contents/overview-of-the-initial-evaluation-diagnosis-and-staging-of-patients-with-suspected-lung-cancer
4. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (Version 1.2022). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
5. Jensik RJ, Faber LP, Milloy FJ, Monson DO: Segmental resection for lung cancer: A fifteen year experience. J Thorac Cardiovasc Surg 66:563-572, 1973
6. Ginsberg RJ, Rubinstein LV: Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Ann Thorac Surg 60:615-623, 1995
7. West H, Vallieres E, Schild SE. Management of Stage I and Stage II Non-Small Cell Lung Cancer. September 28, 2021. https://www.uptodate.com/contents/management-of-stage-i-and-stage-ii-non-small-cell-lung-cancer
8. Videtic GMM: Stereotactic body radiation therapy and lung cancer, in Lo Simon, The Bin, Mayr Nina, et al (eds): Stereotactic Body Radiation Therapy: Lung Cancer. London UK: Future Medicine Ltd, 2013, pp 5-19
9. Videtic GMM, Stephans KL: The role of stereotactic body radiotherapy in the management of non-small cell lung cancer: An emerging standard for the medically inoperable patient?. Curr Oncol Rep 12:235-241, 2010
10. Fernando HC, Landreneau RJ, Mandrekar SJ, et al: Impact of brachytherapy on local recurrence rates after sublobar resection: Results from ACOSOG Z4032 (Alliance), a phase III randomized trial for high-risk operable non-small-cell lung cancer. J Clin Oncol 32:2456-2462, 2014
11. Sibley GS: Radiotherapy for patients with medically inoperable stage I non-small cell lung carcinoma: Smaller volumes and higher doses—A review. Cancer 82:433-438, 1998
12. Qiao X, Tullgren O, Lax I, et al: The role of radiotherapy in the treatment of stage I non-small cell lung cancer. Lung Cancer 41:1-11, 2003
13. Hall EJ, Giaccia AJ: Time, dose, and fractionation in radiotherapy, in Hall EJ & Giaccia AJ (eds): Radiobiology for the Radiologist (ed 8), Philadelphia, PA: Wolters Kluwer, 2019, pp 417-436
14. Leksell L: The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 102:316-319, 1951
15. Lax I, Blomgren H, Näslund I, Svanstrom R: Stereotactic radiotherapy of malignancies in the abdomen: Methodological aspects. Acta Oncol 33:677-683, 1994
16. Blomgren H, Lax I, Näslund I, Svanstrom R: Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator: Clinical experience of the first thirty-one patients. Acta Oncol 34:861-870, 1995
17. Uematsu M, Shioda A, Tahara K, et al: Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: A preliminary experience. Cancer 82:1062-1070, 1998
18. Videtic GMM, Donington J, Giuliani M, et al: Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive summary of an ASTRO evidence-based guideline. Pract Radiat Oncol 7:295-301, 2017
19. Nyman J, Hallqvist A, Lund JÅ, et al: SPACE—A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. Radiother Oncol 121:1-8, 2016
20. Ball D, Mai GT, Vinod S, et al: Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): A phase 3, open-label, randomised controlled trial. Lancet Oncol 20:494-503, 2019
21. Onishi H, Araki T, Shirato H, et al: Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: Clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 101:1623-1631, 2004
22. Onishi H, Shirato H, Nagata Y, et al: Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: Updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2:S94-S100, 2007
23. Timmerman R, Papiez L, McGarry R, et al: Extracranial stereotactic radioablation: Results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 124:1946-1955, 2003
24. McGarry RC, Papiez L, Williams M, et al: Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: Phase I study. Int J Rad Oncol Biol Phys 63:1010-1015, 2005
25. Timmerman R, McGarry R, Yiannoutsos C, et al: Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 24:4833-4839, 2006

26. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al: Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: Four-year results of A prospective phase II study. Int J Rad Oncol Biol Phys 75:677-682, 2009
27. Timmerman R, Paulus R, Galvin J, et al: Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 303:1070-1076, 2010
28. Timmerman RD, Hu C, Michalski JM, et al: Long-term results of stereotactic body radiation therapy in medically inoperable stage I non-small cell lung cancer. JAMA Oncol 4:1287-1288, 2018
29. Videtic GMM, Stephans KL, Woody NM, et al: 30 Gy or 34 Gy? Comparing 2 single-fraction SBRT dose schedules for stage I medically inoperable non-small cell lung cancer. Int J Rad Oncol Biol Phys 90:203-208, 2014
30. Videtic GM, Hu C, Singh AK, et al: A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer: NRG oncology RTOG 0915 (NCCTG N0927). Int J Radiat Oncol Biol Phys 93:757-764, 2015
31. Videtic GM, Paulus R, Singh AK, et al: Long-term follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A randomized phase II study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer. Int J Radiat Oncol Bio Phys 103:1077-1084, 2019
32. Singh AK, Gomez-Suescun JA, Stephans KL, et al: One versus three fractions of stereotactic body radiation therapy for peripheral stage I to II non-small cell lung cancer: A randomized, multi-institution, phase 2 trial. Int J Radiat Oncol Biol Phys 105:752-759, 2019
33. Videtic GM, Reddy CA, Woody NM, Stephans KL: Ten-year experience in implementing single-fraction lung SBRT for medically inoperable early-stage lung cancer. Int J Radiat Oncol Biol Phys 111:436-442, 2021
34. Bezjak A, Paulus R, Gaspar LE, et al: Safety and efficacy of a five-fraction stereotactic body radiotherapy schedule for centrally located non-small-cell lung cancer: NRG Oncology/RTOG 0813 trial. J Clin Oncol 37:1316-1325, 2019
35. Owen D, Sio TT: Stereotactic body radiotherapy (SBRT) for central and ultracentral node-negative lung tumors. J Thorac Dis 12:7024-7031, 2020
36. Roach MC, Robinson CG, DeWees TA, et al: Stereotactic body radiation therapy for central early-stage NSCLC: Results of a prospective phase I/II trial. J Thorac Oncol 13:1727-1732, 2018
37. Chang JY, Li QQ, Xu QY, et al: Stereotactic ablative radiation therapy for centrally located early stage or isolated parenchymal recurrences of non-small cell lung cancer: How to fly in a "no fly zone". Int J Radiat Oncol Biol Phys 88:1120-1128, 2014
38. Modh A, Rimner A, Williams E, et al: Local control and toxicity in a large cohort of central lung tumors treated with stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 90:1168-1176, 2014
39. Arnett ALH, Mou B, Owen D, et al: Long-term clinical outcomes and safety profile of SBRT for centrally located NSCLC. Adv Radiat Oncol 4:422-428, 2019
40. Sio TT, Mohindra P, Yu NY, et al: The search for optimal stereotactic body radiotherapy dose in inoperable, centrally located non-small-cell lung cancer continues. J Clin Oncol 37:2697-2699, 2019
41. Tekatli H, Haasbeek N, Dahele M, et al: Outcomes of hypofractionated high-dose radiotherapy in poor-risk patients with "ultracentral" non-small cell lung cancer. J Thorac Oncol 11:1081-1089, 2016
42. Lindberg K, Grozman V, Karlsson K, et al: The HILUS-trial-a prospective Nordic multicenter phase 2 study of ultracentral lung tumors treated with stereotactic body radiotherapy. J Thorac Oncol 16:1200-1210, 2021
43. Chang JH, Poon I, Erler D, et al: The safety and effectiveness of stereotactic body radiotherapy for central versus ultracentral lung tumors. Radiother Oncol 129: 277-283, 2018
44. Cong Y, Sun B, Wang J, et al: Outcomes and toxicity of stereotactic body radiation therapy for advanced stage ultra-central non-small cell lung cancer. Thorac Cancer 10:1567-1575, 2019
45. Rosenberg SA, Mak R, Kotecha R, et al: The Nordic-HILUS trial: Ultracentral lung stereotactic ablative radiotherapy and a narrow therapeutic window. J Thorac Oncol 16:e79-e80, 2021
46. Swaminath A, Ritter T, Louie AV, et al: Performing SBRT in the fly-with-caution zone: Are we heeding the advice of daedalus? Int J Radiat Oncol Biol Phys 112: 586-589, 2022
47. Reshko LB, Kalman NS, Hugo GD, Weiss E: Cardiac radiation dose distribution, cardiac events and mortality in early-stage lung cancer treated with stereotactic body radiation therapy (SBRT). J Thorac Dis 10:2346-2356, 2018
48. Wong OY, Yau V, Kang J, et al: Survival impact of cardiac dose following lung stereotactic body radiotherapy. Clin Lung Cancer 19:e241-e246, 2018
49. Stam B, Peulen H, Guckenberger M, et al: Dose to heart substructures is associated with non-cancer death after SBRT in stage I-II NSCLC patients. Radiother Oncol 123:370-375, 2017
50. Zheng X, Schipper M, Kidwell K, et al: Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: A meta-analysis. Int J Radiat Oncol Biol Phys 90:603-611, 2014
51. Chang JY, Senan S, Paul MA, et al: Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: A pooled analysis of two randomised trials. Lancet Oncol 16:630-637, 2015
52. Chang JY, Mehran RJ, Feng L, et al: Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): Long-term results of a single-arm, prospective trial with prespecified comparison to surgery. Lancet Oncol 22:1448-1457, 2021
53. Timmerman RD, Paulus R, Pass HI, et al: Stereotactic body radiation therapy for operable early-stage lung cancer: Findings from the NRG Oncology RTOG 0618 trial. JAMA Oncol 4:1263-1266, 2018
54. Stokes WA, Bronsert MR, Meguid RA, et al: Post-treatment mortality after surgery and stereotactic body radiotherapy for early-stage non-small-cell lung cancer. J Clin Oncol 36:642-651, 2018
55. Bryant AK, Mundt RC, Sandhu AP, et al: Stereotactic body radiation therapy versus surgery for early lung cancer among US Veterans. Ann Thorac Surg 105: 425-431, 2018
56. Sublobar resection or stereotactic ablative radiotherapy in treating patients with stage I non-small cell lung cancer, the STABLE-MATES trial. https://www.cancer.gov/about-cancer/treatment/clinical-trials/search/v?id=NCI-2015-01676&r=1
57. Veterans affairs lung cancer surgery or stereotactic radiotherapy (VALOR). https://clinicaltrials.gov/ct2/show/NCT02984761
58. Woody NM, Stephans KL, Marwaha G, et al: Stereotactic body radiation therapy for non-small cell lung cancer tumors greater than 5 cm: Safety and efficacy. Int J Radiat Oncol Biol Phys 92:325-331, 2015
59. Verma V, Simone II CB: Approaches to stereotactic body radiation therapy for large (≥5 centimeter) non-small cell lung cancer. Transl Lung Cancer Res 8: 70-77, 2019
60. Fritz P, Kraus HJ, Blaschke T, et al: Stereotactic, high single-dose irradiation of stage I non-small cell lung cancer (NSCLC) using four-dimensional CT scans for treatment planning. Lung Cancer 60:193-199, 2008
61. Hearn JW, Videtic GM, Djemil T, Stephans KL: Salvage stereotactic body radiation therapy (SBRT) for local failure after primary lung SBRT. Int J Radiat Oncol Biol Phys 90:402-406, 2014

62. Sittenfeld SMC, Juloori A, Reddy CA, et al: Salvage stereotactic body radiation therapy for isolated local recurrence after primary surgical resection of non-small-cell lung cancer. Clin Lung Cancer 22:e360-e365, 2021
63. Videtic GMM, Reddy CA, Sorenson L: A prospective study of quality of life including fatigue and pulmonary function after stereotactic body radiotherapy for medically inoperable early-stage lung cancer. Support Care Cancer 21:211-218, 2013
64. Chen H, Louie AV, Boldt RG, et al: Quality of life after stereotactic ablative radiotherapy for early-stage lung cancer: A systematic review. Clin Lung Cancer 17: e141-e149, 2016
65. Adebahr S, Hechtner M, Schrader N, et al: Early impact of pulmonary fractionated stereotactic body radiotherapy on quality of life: Benefit for patients with low initial scores (STRIPE trial). J Thorac Oncol 14:408-419, 2019
66. Bartl AJ, Mahoney M, Hennon MW, et al: Systematic review of single-fraction stereotactic body radiation therapy for early stage non-small-cell lung cancer and lung oligometastases: How to stop worrying and love one and done. Cancers (Basel) 14:790, 2022
67. Manyam BV, Videtic GMM, Verdecchia K, et al: Effect of tumor location and dosimetric predictors for chest wall toxicity in single-fraction stereotactic body radiation therapy for stage I non-small cell lung cancer. Pract Radiat Oncol 9:e187-e195, 2019
68. Palma D, Visser O, Lagerwaard FJ, et al: Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small cell lung cancer: A population-based time-trend analysis. J Clin Oncol 28:5153-5159, 2010
69. Pan H, Rose BS, Simpson DR, et al: Clinical practice patterns of lung stereotactic body radiation therapy in the United States: A secondary analysis. Am J Clin Oncol 36:269-272, 2013
70. Ng SS, Ning MS, Lee P, et al: Single-fraction stereotactic body radiation therapy: A paradigm during the coronavirus disease 2019 (COVID-19) pandemic and beyond? Adv Radiat Oncol 5:761-773, 2020
71. Guckenberger M, Belka C, Bezjak A, et al: Practice recommendations for lung cancer radiotherapy during the COVID-19 pandemic: An ESTRO-ASTRO consensus statement. Radiother Oncol 146:223-229, 2020
72. Sher DJ, Wee JO, Punglia RS, et al: Cost-effectiveness analysis of stereotactic body radiotherapy and radiofrequency ablation for medically inoperable, early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys 81:e767-e774, 2011
73. Wolff HB, Alberts L, van der Linden N, et al: Cost-effectiveness of stereotactic body radiation therapy versus video assisted thoracic surgery in medically operable stage I non-small cell lung cancer: A modeling study. Lung Cancer 141:89-96, 2020
74. Bradley JD, El Naqa I, Drzymala RE, et al: Stereotactic body radiation therapy for early-stage non-small-cell lung cancer: The pattern of failure is distant. Int J Radiat Oncol Biol Phys 77:1146-1150, 2010
75. Senthi S, Lagerwaard FJ, Haasbeek CJ, et al: Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small cell lung cancer: A retrospective analysis. Lancet Oncol 13:802-809, 2012
76. Lin AJ, Roach M, Bradley J, Robinson C: Combining stereotactic body radiation therapy with immunotherapy: Current data and future directions. Transl Lung Cancer Res 8:107-115, 2019
77. Citrin DE: Recent developments in radiotherapy. N Engl J Med 377:1065-1075, 2017
78. Chandra RA, Keane FK, Voncken FEM, Thomas CR Jr: Contemporary radiotherapy: Present and future. Lancet 398:171-184, 2021
79. Abuodeh Y, Venkat P, Kim S: Systematic review of case reports on the abscopal effect. Curr Probl Cancer 40:25-37, 2016
80. Xing D, Siva S, Hanna GG: The abscopal effect of stereotactic radiotherapy and immunotherapy: Fool's Gold or El Dorado? Clin Oncol 31:432-443, 2019
81. Buchwald ZS, Wynne J, Nasti TH, et al: Radiation, immune checkpoint blockade and the abscopal effect: A critical review on timing, dose and fractionation. Front Oncol 8:612, 2018
82. Antonia SJ, Villegas A, Daniel D, et al: Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 377:1919-1929, 2017
83. Shaverdian N, Lisberg AE, Bornazyan K, et al: Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: A secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol 18:895-903, 2017
84. Hwang WL, Niemierko A, Hwang KL, et al: Clinical outcomes in patients with metastatic lung cancer treated with PD-1/PD-L1 inhibitors and thoracic radiotherapy. JAMA Oncol 4:253-255, 2018
85. Theelen WSME, Peulen HMU, Lalezari F, et al: Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non-small cell lung cancer: Results of the PEMBRO-RT phase 2 randomized clinical trial. JAMA Oncol 5:1276-1282, 2019
86. Welsh J, Menon H, Chen D, et al: Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: A randomized phase I/II trial. J Immunother Cancer 8:e001001, 2020
87. Theelen WSME, Chen D, Verma V, et al: Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: A pooled analysis of two randomised trials. Lancet Respir Med 9:467-475, 2021
88. Durvalumab vs placebo with stereotactic body radiation therapy in early stage unresected non-small cell lung cancer (NSCLC) patients/osimertinib following SBRT in patients with early stage unresected NSCLC harboring an EGFR mutation (PACIFIC-4). http://clinicaltrials.gov/ct2/show/NCT03833154
89. A randomized phase III trial of induction/consolidation atezolizumab (NSC #783608) plus SBRT versus SBRT alone in high risk, early stage NSCLC (SWOG 1914). https://www.swog.org/clinical-trials/s1914
90. Efficacy and safety study of stereotactic body radiotherapy (SBRT) with or without pembrolizumab (MK-3475) in adults with unresected stage I or II non-small cell lung cancer (NSCLC) (MK-3475-867/KEYNOTE-867). https://clinicaltrials.gov/ct2/show/NCT03924869

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Stereotactic Body Radiotherapy for the Management of Early-Stage Non–Small-Cell Lung Cancer: A Clinical Overview

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