The development of stereotactic body radiotherapy (SBRT) for medically inoperable early stage non-small cell lung cancer: an international phenomenon

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Abstract

Introduction Lung cancer is the most common malignancy worldwide. The standard of care for early stage lung cancer is surgical resection. Patients with this diagnosis frequently have co-morbidities making surgery not feasible. Limited resections result in inadequate disease control. Historic alternatives to surgery such as conventional radiotherapy provide poor outcomes and undue toxicity. Over the past decade, stereotactic body radiotherapy (SBRT) has emerged as a novel radiation modality with significant applications in the medically inoperable, early stage lung cancer population. A range of international retrospective and prospective reports has established SBRT's feasibility, safety and efficacy in these patients using a variety of dose regimens and technologies.

Results SBRT results consistently show excellent local control, little acute toxicity, and improved overall survival compared with historical controls of fractionated radiotherapy. Ongoing prospective trials are defining the optimal SBRT regimen in the inoperable population and starting to explore its role for the operable patient.

Keywords Early stage · Lung cancer · Inoperable · Stereotactic body radiotherapy · Review

Introduction

In 2008, the results of the most recent global survey of cancer revealed that there were about 12.7 million cancer

cases and 7.6 million cancer deaths estimated to have occurred worldwide, with 56% of the cases and 64% of the deaths in the economically developing world [1]. Lung cancer was the most commonly diagnosed cancer as well as the leading cause of cancer death in males globally [1], and among females, it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death. Overall, lung cancer accounted for 13% (1.6 million) of the total cancer cases and 18% (1.4 million) of the deaths in 2008 [1]. In the USA, lung cancer rates have been slowly declining, even though it remains the number one cancer killer of men and women. In contrast, lung cancer rates have been increasing in non-Western countries for the past two decades [2]. Smoking still remains the leading cause of lung cancer, but in other populations, risk factors such as indoor coal burning, cooking fumes, and infections may play important roles in the development of lung cancer (among Asian women, for example) [2].

Almost 75% of lung cancers are non-small cell (NSCLC) in histology [3]. Approximately 10–15% of NSCLC patients present with localized disease (stage I) [4]. Standard therapy for stage I NSCLC is surgical resection, either lobectomy or pneumonectomy, as well as nodal dissection, with 5-year overall survival ranging from 50% to 70% [5]. A significant proportion of NSCLC patients, however, present with impaired cardiopulmonary reserve, placing them at increased risk of peri-operative complications and long-term disability with standard anatomic resections; these patients are deemed medically inoperable [6]. For example, a report from the Swedish Lung Cancer Registry for the interval 2002–2006 showed that the fraction of patients with stage I disease planned for surgery during that period was 76% and the fraction considered inoperable was 15% [7]. Most of the inoperable patients had coexisting diseases with the

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majority suffering from pulmonary disabilities such as chronic obstructive pulmonary disease.

Despite the presence of co-morbidities, observation alone for the inoperable patient is not appropriate care: Lung cancer was shown to be the direct cause of death in 53% of 75 stage I medically inoperable patients not receiving definitive therapy in a study by McGarry et al. [8]. Until the past decade, the few alternatives to standard surgery for the inoperable population included limited surgical resection [9] or conventional radiotherapy (RT) [10], despite the fact that outcomes were recognized to be potentially inferior to anatomic resection [11]. In recent years, however, technologic advances across a range of disciplines have accelerated to the point that lung cancer cures for the medically inoperable may be achievable and without severe treatment-related morbidity. Foremost among these emerging approaches, stereotactic body radiotherapy (SBRT) has gained the greatest interest because it is likely one of the least invasive and most tolerable means of achieving such outcomes for high-risk patients. Such a rapid breakthrough has only been possible through the cumulative efforts of researchers across the world and highlights lung SBRT's development as truly an international phenomenon. This "globalization" effect can explain why it is now possible to read reports that SBRT has become the preferred treatment for patients with medically inoperable stage I NSCLC in countries as distant as The Netherlands is from Japan [12] and helps to inform in the present review.

Radiotherapy for early lung cancer and the rise of SBRT

The efficacy and safety of RT in eradicating tumor reflect the interplay between total dose delivered to the malignant tumor, the rate of dose delivery (daily fractionation), and the volume (and type) of tumor-bearing organ irradiated. Essentially, conventional RT is fractionated to spare normal tissues. That is, modest doses (or fractions, typically 1.8 to 2 Gy) are delivered daily over extended time intervals (typically weeks) to achieve a desired total dose which is expected to have a certain efficacy against tumor while causing minimal harm to normal structures. On all fronts, the lung is an extremely challenging structure to irradiate: It has limited tolerance to radiation, in general, and to high doses, in particular; delayed side effects are more severe with large daily fractions; tumor volumes are typically large, resulting in a large proportion of the normal organ being exposed to dose; and the RT target has to include not only the definable malignant lesion but account for tumor motion, potential microscopic spread, and the inherent daily uncertainties in patient position and set-up for treatment. Hence, for lung cancer, the standard RT doses of 60–70 Gy at 2 Gy/fraction reflect what has proven safe in clinical trials, e.g., Radiation Therapy Oncology Group

(RTOG) study #7301 [13], even though cancer outcomes have been modest with such doses.

Prior to the advent of SBRT, medically inoperable early stage NSCLC patients were typically offered external-beam RT alone using conventional techniques as primary management. Treatment results were consistently inferior to surgical results reported for operable patients. In a review of 18 studies published from 1988 to 2000 on conventional RT for stage I NSCLC, where the median RT dose was 60 Gy in 30 fractions, Qiao et al. [14] reported local recurrence to be the most common cause of failure, ranging up to 70%. Similarly, in Sibley et al.'s [10] report on clinical stage I NSCLC treated with radiotherapy alone using modern techniques and staging, with a median RT dose of 64 Gy, overall and progression-free survival rates at 5 years were 48% and 28%, respectively. In that study, 49% of patients had local failure as part of their relapse pattern.

Many factors likely explained the discrepancy in outcomes for patients treated with conventional RT compared to standard surgery. RT-only patients typically would have been staged clinically, resulting in underestimating true disease extent compared with surgically staged patients [15]. Also, the underlying co-morbidities which make the patient not appropriate for surgery also negatively influence patient survival; in that regard, most studies show cause-specific survival to be substantially higher than overall survival in the medically inoperable treated with RT [10]. Historically, treatment volumes for stage I disease were often large, to encompass not only the primary tumor, but not infrequently, the regional draining lymph nodes prophylactically. Lastly, high local failure rates after conventional RT ultimately reflected inadequate dose to tumor, but the caveat was that more dose to control cancer would further compromise lung function in these patients. Martel et al. proposed that a minimal dose of 84 Gy by conventional RT would achieve local control rates of at least 50% in lung cancer [16], a dose far greater than ever routinely administered. In fact, there had been a number of dose escalation trials using conventional fractionation. Several have shown improved outcomes with higher doses [17], but not all have shown improved survival. In addition, use of alternate over conventional fractionation schemes has also been investigated as a means of improving RT outcomes but has been associated with significantly increased pulmonary toxicity [18].

The recognized limitations in the efficacy of conventional RT in early lung cancer eventually had their (re)solution when clinicians explored the feasibility of applying techniques already in use for brain tumor stereotactic radiosurgery (SRS) and extending them to extracranial sites. Originally developed for intracranial lesions in the 1950s through the pioneering work of Leksell [19] at the Karolinska Hospital in Sweden, the concept of SRS treatment was that narrow radiation beams from several directions would focus on the

target while sparing the adjacent normal tissues with high accuracy. This technique would then allow delivery of high doses to the target leading to high control of the tumor without causing significant toxicities associated with the treatment. The first commercial SRS system became available in 1967, and by the 1980s, SRS had become a standard part of neurosurgical practice. In brief, SRS implied: very high RT dose per fraction; rapid dose drop-off in surrounding normal tissues; total dose delivery over few sessions; administration only to small (e.g., <5 cm) discrete targets without regional micrometastatic spread (i.e., without nodal involvement), rigorous tumor localization in three-dimensions; and application to organs whose functional structures support focal ablation of physiologic units without compromising overall functionality [20].

Echoing the earlier Swedish breakthroughs, Lax and his colleagues from the Karolinska reported in 1994 the first non-brain radiosurgical experience: a method for performing extracranial high-dose irradiation in the setting of abdominal malignancies using a custom body cast with stereotactic coordinates [21]. This innovative approach was eventually extended to testing in the lung. From clinical work started at the Karolinska in 1991, Blomgren et al. [22] published the first report on SBRT using the stereotactic body frame in 1995, for 42 tumors in the lung and liver of 31 patients treated with SBRT. Treatment was reported safe, and the local control rate was 80%. In parallel in Japan, and beginning in 1994, Uematsu et al. [23] began their own pioneering lung SBRT work based on a frameless system (FOCAL unit) that consisted of a linear accelerator, an X-ray simulator, CT, and a table. In this first report, they described 66 lung tumors (23 primary and 43 metastatic lung cancers) in 45 patients treated using this system, with RT schedules of 30–75 Gray in 5–15 fractions over 1–3 weeks. Local progression was observed only in two of the 66 tumors (3%). These early experiences in the 1990s prompted simultaneous exploration of SBRT in a number of countries, followed by an exponential growth in publications over the next decade, and with Japan, the USA, Germany, and The Netherlands emerging as leaders in establishing this treatment modality as a truly international venture. A comparison between American and Japanese approaches to introducing SBRT are revealing in that regard.

There were only a few centers in the USA engaged in SBRT research, but, among them, the University of Indiana Radiation Oncology group led by Timmerman and his colleagues provided American leadership in developing SBRT through rigorous conduct of a series of prospective trials in medically inoperable stage I NSCLC patients. A formal phase I dose escalation toxicity study with 47 patients was followed by a 70-patient phase II study in the same population [24, 25]. Among other results, these studies

showed that there existed a strong dose–response relationship for lung SBRT and that a specific dose schedule (60 Gy in three fractions) was safe and effective but only for peripherally located tumors. Critically, they had identified central tumor location, based on a fixed relationship to the tracheobronchial tree, as a risk factor for major toxicity with their dose schedule, as well as large tumor size [26]. With local control at 3 years an impressive 88%, these studies provided the basis for the RTOG's first national trial of SBRT.

Japanese investigators had clearly been early leaders in implementing and developing SBRT lung programs. What was notable from that country was the broad distribution and number of clinicians involved in SBRT work and that most publications that have ended up coming out of their experiences are primarily retrospective series. Results were published in 2009 from a survey that had been conducted in Japan in 2005 to determine the status of SBRT practice [27]. These revealed that, of more than 700 radiation oncology departments, 53 had started SBRT programs and that a total of 1,111 patients with lung cancer had been treated. One of the most important publications from this era was a large review in 2004 by Onishi et al. [28] of 257 patients from 14 institutions because its conclusion regarding effective dose and the role of SBRT in operable patients helped set treatment parameters for SBRT. Characteristic of Japanese studies, this study noted considerable variation in immobilization, respiratory motion management approaches, and dose/fractionation schedules (e.g., 30–84 Gy in 1–14 fractions) across institutions. With respect to specific outcomes, Onishi and colleagues reported that 5-year actuarial local control rates were 84% for patients receiving a biologically equivalent dose (BED) of radiation of 100 Gy₁₀ or more (based on assumed tumor alpha/beta ratio of 10) and 37% for those receiving less than 100 Gy₁₀. (Using a simple radiobiological mathematical model, differing SBRT dose schedules are converted to comparable biologically equivalent doses or BEDs. The Gy₁₀ value represents the dose modified by the alpha/beta conversion factor allowing comparisons between different dose and fractionation schedules [29]). Most remarkable in Onishi's results was that 5-year overall survival for medically operable patients receiving in the higher SBRT dose range was 71%, a result similar to historic results from conventional surgery. Overall, Japanese investigators have tended to use more modest dose levels throughout their experiences compared with American counterparts. For example, Nagata et al. [30] from Kyoto University reported excellent result for a series of 45 patients treated with a dose of 48 Gy in four fractions to the isocenter, a dose biologically less potent than the dose fractionation schemes used in comparable prospective North American trials. This schedule

in fact became the regimen subsequently tested in the larger Japan Clinical Oncology Group (JCOG) 0403 trial for peripheral T1N0 stage I patients, which recently completed accrual.

Lung SBRT: overview of outcomes

Local control

From centers spanning the globe, the consistent theme in the published results for lung SBRT is that it achieves outstanding local control for stage I NSCLC patients, with nearly all series reporting 85% to 95% control rates [23–26, 28, 30–43] (see Figs. 1 and 2). Two of the most recent publications merit particular notice because of their precedent

Fig. 1 56-year-old male, aphasic and wheelchair-bound secondary to a stroke, biopsy-proven adenocarcinoma of the right upper lobe lung T2N0M0 (AJCC 6th), medically inoperable. Selected axial CT images of the chest before and following stereotactic body radiotherapy (50 Gy/5 fractions completed 1/13/2006): **a** Before treatment (arrow pointed at tumor); **b** 5 years after treatment

Fig. 2 Representative axial CT image from the plan for the patient presented in Fig. 1. Purple line planning target volume (PTV); orange 0 Gy isodose cloud; blue 30 Gy isodose cloud

setting prospective nature. Timmerman et al. [40] reported the results of RTOG 0236, which was the first North American multi-institutional cooperative group prospective trial using SBRT for lung cancer and reported a primary tumor control rate of 97% and local control (in the involved lobe) of 91% at 3 years. In parallel, Baumann et al. from Scandinavia reported a 3-year local control rate of 92% as the result from the Nordic Study Group's prospective phase II study of SBRT's impact on 3-year progression-free survival in medically inoperable lung cancer [41]. It is interesting to note that tumor size may influence control, with some reports suggesting a trend towards a better outcome for smaller lesions (stage IA vs. IB). This correlation has been noted in several papers, including Danish experience coming from Aarhus University [43] and Dutch work by Lagerwaard and co-workers [34], showing better clinical outcome for tumors smaller than 30 mm, and was recently confirmed by Baumann in their prospective study [41].

A common SBRT theme is that defining local control after this form of therapy can be difficult because distinguishing true tumor failure from radiation-induced lung damage is often challenging. Many treated patients develop radiographic changes of fibrosis that may be mistaken for recurrence, and interpretation of images may require an experienced reader [44, 45]. Positron emission tomography (PET)-based imaging can be of utility for assessing ambiguous cases [46], though biopsy may occasionally be required. Understanding the radiographic changes as also a function of dose may be critical since, as noted earlier, it appears that there is a dose–response relationship with SBRT for lung cancer since local failure rates appear to rise when the treatment dose is less than a certain biological threshold.

Patterns of failure

Notwithstanding that nodal staging in most contemporary SBRT series is primarily with PET and not surgically based, mediastinal or hilar nodal failures appear to be rare, ranging from 0% to 10% [28, 30–43]. Much like in surgical series, distant failure remains the predominant pattern of failure for patients treated with SBRT. Distant metastasis occurs in 15% to 30% of stage I patients treated with SBRT [30–43]. Taking into consideration the limitations in staging, the age of most patients receiving SBRT, and the multiple comorbidities precluding surgery, this failure pattern translates into 3- to 5-year actuarial survival rates in some series in excess of 50% for this population and remain provocative in comparison to historical conventional RT survival rates ranging from 15% to 45% [47].

Survival

Overall survival rates have been typically reported at the 2-year mark, in keeping with the compromised nature of the medically inoperable population and range broadly with a median around 50% at 2 years [37], even if only a few studies have an acceptable median follow-up time (longer than 2 years). The trends in improved survival for this vulnerable population compared with historic results with conventional RT suggest that SBRT is leading to improvements in cancer-specific mortality and thus overall survival. The most provocative findings with respect to survival were seen in the aforementioned results of Onishi et al. [28]. In their review, the 5-year survival rate for their 87 operable patients irradiated with a BED dose of 100 Gy₁₀ or greater were 90% for stage IA and 84% for stage IB disease; these clinical results were as good as those historically obtained by surgery.

Patient selection

A consistent percentage of SBRT patients, ranging from 3% to 69% [42], do not have a pathologic confirmation of malignancy because of the challenges of safely and feasibly obtaining tissue for diagnosis. Factors include the peripheral location and small size of many SBRT tumors, which makes them inaccessible to bronchoscopic biopsy and the poor pulmonary function regarded as a relative contraindication for transthoracic biopsy because of the risk of pneumothorax. In the absence of the histologic evidence of malignancy, patients are judged to have a so-called “clinical diagnosis of malignancy”, based on the presence of a new or growing lesion with CT characteristics of malignancy that is associated with elevated or increasing 18FDG-PET uptake. Results from a number of clinical series show equivalent outcomes for the non-biopsied as compared with the biopsied

patients [37]. Some authors believe this clinical approach to diagnosis may be justified in a country such as The Netherlands where a diagnosis of benign disease is typically made in less than 5% of patients undergoing surgery [12], but may not be suitable to populations with a higher likelihood of benign lung disease. For example, one report had documented the use of only a single computed tomography and PET scan without other supportive data which led to nearly one third of resected PET-positive nodules turning out to be granulomas [48].

Toxicity

Even with the remarkably high radiation doses employed for SBRT, there has consistently been remarkably little toxicity reported with this form of treatment, with grade 3 or higher rates typically less than 5% [28, 30–43]. These low rates of toxicity are presumably due to both the precision of treatment delivery and the structural physiology of lung tissue. While treatment may cause lung parenchymal changes (seen on CT imaging of the chest) after therapy in many patients [44], the functional impact (as evidenced by symptom development) is typically minimal, likely because adequate remaining lung tissue is preserved. It is also likely that the high doses employed in SBRT may obliterate blood vessels in the treated area, thereby mitigating ventilation–perfusion mismatch felt to play a role in the symptomatic toxicity of standard RT. That said, tumor location clearly plays a critical role in the risk and development of treatment-related morbidity as reported by Timmerman et al. following their experience of treating “central” lung tumors, defined as lying within 2 cm of the tracheobronchial tree, in the setting of their phase II series leading to the RTOG SBRT standard of 60 Gy in three fractions [26]. In that phase II experience, patients with tumors treated in the central lung had 2-year freedom from severe toxicity of only 54%. In contrast, central lesions have routinely been safely treated with slightly lower doses (such as 50 Gy in five fractions) with similar local control and toxicity as seen in treatment of peripheral lesions to higher doses [31, 37]. Perhaps most remarkable is that, in spite of the high baseline prevalence of pulmonary comorbidities in patients treated with lung SBRT, the incidence of symptomatic radiation pneumonitis is very low, ranging from 0% to 5% in reported series [30–43]. Furthermore, on average, there is little to no decrease in the pulmonary function of treated patients [49, 50]. In the Cleveland Clinic experience [50], individual patients after treatment were noted to have fluctuations in pulmonary function tests from baseline in both the positive and negative direction, with these results ultimately falling into a normal distribution so that no association between treatment and PFT changes could be made.

Recently, for patients with large peripheral tumors late chest wall pain or rib fracture is an increasingly noted delayed side effect, though symptoms are typically mild to moderate. Chest wall symptoms are reported in 5% to 15% of patients with peripheral lesions and appear to be related to treatment dose, fractionation, and beam arrangement [37, 51, 52]. With advances in understanding of the causative factors and improved treatment planning, rates of toxicity may be lowered for future patients. Overall, the prospect of chest wall toxicity remains mild in comparison with surgical alternatives [15].

Lung SBRT: quality considerations

The use of very high doses of radiation over a few treatments combined with the need for extreme accuracy and reproducibility in RT delivery have made high-level quality control an imperative in administering SBRT. Implementation of such highly technical therapy outside the expertise and constraints of single institutions has presented new challenges to the radiation research community. In developing and implementing the first North American collaborative group trial in SBRT, the RTOG developed de novo a working process for carrying out multicenter trials for SBRT in lung sites [53]. This process included a stringent but workable plan for scrutiny of site qualifications and quality assurance. Site qualifications were reviewed via an accreditation process, a phantom irradiation review, and via digital submission of plans prior to enrolling the first patient on protocol. Dosimetry constraints were devised not just to ensure target coverage, but also to require rapid falloff of dose to surrounding normal tissue and respect organ tolerance limits. These efforts facilitated rapid implementation of the first cooperative group SBRT trial, RTOG 0236 for medically inoperable patients with peripherally situated lung cancer, to enroll patients rapidly despite rigorous quality assurance.

In a similar vein, the European Organization for Research and Treatment of Cancer (EORTC) issued recommendations in 2010 regarding the planning and delivery of high-dose, high-precision RT for lung cancer because there was a genuine concern that advanced radiotherapy techniques were diffusing too slowly into routine practice and were not being introduced without proper preparation and quality assurance [54].

In a recent review of lung SBRT by the International Atomic Energy Agency (IAEA) [55], it was interesting that the authors speculated on a rationale for introducing SBRT to the developing world. This was because several characteristics seem to make SBRT attractive to developing nations, including shortened treatment times with fewer fractions, which could then provide more cost-effective care for both patients and hospitals. However,

they clearly recognized the most obvious barriers to implementation of SBRT in any developing nation would be the lack of a modern and comprehensive diagnostic and therapeutic infrastructure and quality control to support such a venture. In a separate note, they commented on the fact that, for the developed world, SBRT appeared to provide potential economic advantages since information from Japan has shown that SBRT is more cost-beneficial than surgery.

Clinical trials of interest

Within the collaborative group setting, the RTOG has designed trials to explore dose/fractionation issues for medically inoperable patients and the feasibility and safety of SBRT for selected operable patients. RTOG 0618 was recently completed phase II trial in operable patients seeking to demonstrate that sustained (>2 years) high local control is achievable in this population. RTOG 0915 is a recently completed randomized phase II study in medically inoperable patients with peripheral tumors, comparing 34 Gy in a single fraction to 48 Gy in four fractions, with a primary end point of toxicity. RTOG 0813 is an ongoing phase I/II study to establish the maximally tolerated dose of SBRT for early stage, centrally located NSCLC. Recently, in collaboration with the American College of Surgeons Oncology Group (ACOSOG), the RTOG jointly opened a phase III protocol (ACOSOG Z4099/RTOG1021) comparing limited resections (with or without brachytherapy) to SBRT in potentially operable high-risk patients.

The M.D. Anderson Cancer Center at the University of Texas is leading the ongoing industry-sponsored Lung Cancer STARS (STereotActive Radiotherapy vs. Surgery) international randomized study, sponsored by Accuray, comparing CyberKnife-based SBRT with surgical resection in stage I NSCLC, with the primary endpoint of overall survival at 3 years.

In Japan, a single-arm phase II study was recently completed by the Japanese Clinical Oncology Group (JCOG 0403) as a dose exploration study consisting of 48 Gy in four fractions delivered over 4 to 8 days, with a planned accrual of 165 patients, of which a planned subset of operable patients is included. JCOG 0702 is an ongoing phase I dose escalation study of SBRT in patients medically inoperable or unfit for surgery with pathologically proven T2N0M0 NSCLC, to determine the recommended dose.

In Europe, a randomized trial of either surgery or SBRT for stage IA NSCLC (ROSEL) in The Netherlands was closed in 2011 due to poor accrual. In Scandinavia, a randomized phase II study (Stereotactic Precision and Conventional radiotherapy Evaluation (SPACE)) is comparing SBRT versus conventionally fractionated radiotherapy for stage I medically inoperable NSCLC patients, in which the

SBRT is given as a dose of 66 Gy in three fractions and the conventional RT is 70 Gy in 35 fractions.

The Trans-Tasman Radiation Oncological Group (TROG) is leading a randomized phase III trial of 54 Gy in three fractions compared with radiotherapy to a total dose of 60–66 Gy in 30–33 daily 2 Gy fractions over 6 weeks, with or without chemotherapy

Future directions

Establishing a standard SBRT schedule with uniform planning approaches for medically inoperable tumors is a widely accepted goal. Thus, within the RTOG, there are future plans for a randomized phase III trial for peripheral lung tumors comparing the current standard of 60 Gy in three fractions set by RTOG 0236 to the most successful arm of RTOG 0915, with the primary endpoint being survival. Further delineating the tolerance of normal tissues to large radiation doses, as well as the long-term, implications of SBRT on normal structures and quality of life remains a shared multi-institutional goal. Since distant failure remains the predominant pattern of failure for medically inoperable early stage lung cancer patients treated with SBRT, the appropriate use of adjuvant systemic or biologic therapies has also become a question of great interest and is currently the subject of discussion within collaborative groups, especially since that practice is currently ill-defined in the standard surgical population and is relatively contraindicated in the medically compromised with more advanced disease.

Conclusions

SBRT has established itself as a safe and effective treatment for medically inoperable stage I NSCLC through the numerous efforts of radiation specialists worldwide. As a result, it is now considered by many clinicians to have become the standard of care for this frail population. Within the discipline, it has served as a model on how to advance complex clinical questions through high-quality collaborative research nationally and internationally. Given the relative short time interval over which most lung SBRT research has been conducted, ongoing clinical studies in all matters relevant to this modality are warranted, but especially with a view to understanding the long-term results of this form of RT. Understanding the time interval and potential for delayed forms of toxicity will no doubt play a crucial role in defining the appropriateness of SBRT for operable patients.

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