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The Role of Stereotactic Body Radiotherapy in the Management of Non-Small Cell Lung Cancer: An Emerging Standard for the Medically Inoperable Patient?

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Abstract The standard of care for early-stage lung cancer is surgical resection. Many patients with this diagnosis have comorbidities that preclude oncologic resection. Randomized data show that limited resection is inadequate for local disease control and may negatively impact on survival. Stereotactic body radiotherapy (SBRT) has emerged as a novel radiation modality with significant applications in the inoperable, early-stage lung cancer population. Retrospective and prospective studies published in the past decade have established the feasibility, safety, and efficacy of SBRT in these patients using a variety of dose regimens and technologies. To date, lung SBRT results demonstrate excellent local control with very little acute toxicity, and suggest improved overall survival compared to historical controls of fractionated radiotherapy. Ongoing prospective trials are exploring dose and fractionation schedules in the inoperable population, and are starting to explore the role of SBRT for the operable patient.

Keywords Early-stage lung cancer · Medically inoperable · Stereotactic body radiotherapy · Local control · Toxicity · Survival

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Introduction

Lung cancer is the most common malignancy worldwide, with over 1 million cases now being diagnosed yearly [1]. In the United States, cancer statistics for 2009 estimated 219,440 new cases and 159,390 deaths due to lung cancer, making it the leading cause of cancer mortality in both men and women [2]. Almost 75% of lung cancers are non-small cell (NSCLC) in histology [3]. Approximately 15% to 20% of NSCLC patients present with localized disease (stage I) [2]. Standard therapy for stage I NSCLC is surgical resection, consisting of either lobectomy or pneumonectomy, as well as nodal dissection, with 5-year overall survival (OS) ranging from 50% to 70% [4]. A significant proportion of NSCLC patients, however, present with impaired cardiopulmonary reserve, placing them at increased risk of perioperative complications and long-term disability with standard anatomic resections; these patients are deemed medically inoperable [5]. Despite substantial patient comorbidities, observation alone leads to unacceptable outcomes; lung cancer was shown to be cause of death in 53% of 75 stage I medically inoperable patients not receiving definitive therapy in a study by McGarry et al. [6]. Treatment options frequently offered to this population include limited surgical resection [7] or conventional radiotherapy (RT) [8]; however, outcomes appear inferior to anatomic resection [9].

Recent technologic advances across a range of disciplines are now changing the treatment landscape for the medically inoperable patient. The possibility of lung cancer cure without substantial treatment-related morbidity appears to be real. Among these emerging technologies, stereotactic body radiotherapy (SBRT) potentially offers high-risk patients one of the least invasive and most tolerable means of achieving this cure, and is the subject of the present review.

Lung Cancer and the Medically Compromised Patient: Surgery

In 1973, Jensik et al. [7] suggested that nonstandard (lesser) resections might be adequate operations for early-stage lung cancer in a compromised patient, with parenchyma-sparing wedge resections especially promoted for those with limited pulmonary function. Ginsberg and Rubinstein [9] subsequently demonstrated in the pivotal Lung Cancer Study Group (LCSG) trial that attempts at lung sparing come with an increased risk of lung cancer failure. Their 1995 report on 276 stage I NSCLC patients randomized to limited resection (32.8% had wedge resection) versus standard lobectomy found an increase in recurrence rates (18% vs 6%) in those with sub-lobar resection [9]. Although this study showed no statistically significant difference in overall survival, there was an observed 30% increase in overall death rate (P=0.08) and an observed 50% increase in death with cancer rate (P=0.09) in patients undergoing sub-lobar resection [9]. Thus, lobectomy was still judged to be the surgical procedure of choice for stage I lung cancer.

Prior to publication of the LCSG trial results, surgeons had in fact recognized the problem of local failures with very limited resections. Postoperative external beam RT had been employed by some groups as a method of adding further local therapy to sub-lobar resection, with some series suggesting feasibility and safety but others noting challenges in defining the postoperative target [10, 11]. The use of intraoperative brachytherapy in the setting of limited resections (using radioactive iodine seeds) had also been employed as a means of limiting normal tissue toxicity and maximizing delivery of radiation dose to prevent local failures. Some published series reported that the brachytherapy was well tolerated with satisfactory local control rates and limited radiation-associated toxicity [12]. However, others noted risks to this combined approach; for example, McKenna et al. [13] reported two deaths and a range of cardiovascular and pulmonary complications in their report of 48 patients receiving wedge resections and brachytherapy. The American College of Surgeons Oncology Group (ACOSOG) recently completed trial #Z4032, in which high-risk NSCLC patients with tumors 3 cm or smaller were randomized to sub-lobar resection with or without intraoperative brachytherapy [14]. Final results have not yet been reported.

Lung Cancer and the Medically Compromised Patient: Radiotherapy

Medically inoperable early-stage NSCLC patients have also been offered external beam RT alone using conventional techniques as primary management for medically inoperable lung cancer. Treatment results have been consistently inferior to the 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. [15] reported local recurrence to be the most common cause of failure, ranging up to 70%. Similarly, in Sibley's report [8] on clinical stage I NSCLC treated with RT 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 explain 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 to surgically staged patients [16]. Also, the underlying comorbidities that 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 [8]. Lastly and most critically, high local failure rates after conventional RT represent inadequate dose to tumor; on the other hand, more dose to control cancer would further compromise lung function in these patients. As reference, Martel et al. [17] have suggested that at least 84 Gy delivered by conventional RT would be required to achieve local control rates of at least 50% for lung cancer, a dose far greater than typically administered. Mindful of this, there have been a number of trials in dose escalation with conventional fractionation. Several have shown improved outcomes with higher doses, 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].

Principles of and Approaches to SBRT

The efficacy and safety of RT 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, small doses (or fractions, typically 1.8–2 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 to 70 Gy at 2 Gy/fraction reflect what has proven safe in clinical trials (eg, Radiation Therapy Oncology Group [RTOG] study #7301 [19]), even though cancer outcomes have been modest with such doses.

Given these recognized limitations in cancer control with conventional RT doses, concepts and techniques previously developed for brain tumor radiosurgery were tested in extracranial sites. These principles include very high doses per fraction; rapid dose drop-off in the surrounding normal tissues; RT delivery over few sessions; and administration only to small (eg, <5 cm) discrete targets without regional micrometastatic spread (ie, without nodal involvement) and applicable to organs whose functional structures could support focal ablation of physiologic units without compromising overall functionality (eg, liver, lung) [20]. In 1994, Lax and colleagues [21] reported the first non-brain SBRT experience: a method for performing extracranial high-dose irradiation in the setting of abdominal malignancies using a custom body cast with stereotactic coordinates. This innovative approach was eventually extended to testing in early-stage lung cancer because tumors are discrete, and only small volumes of lung would likely be fibrosed by aggressive RT (ablation), thus not compromising the overall functioning. The move to lung cancer was also facilitated by technologies that 1) could allow accurate staging of malignant targets (eg, CT, positron emission tomography [PET] allowing elimination of elective nodal treatment); and 2) could account for tumor motion during the SBRT delivery [20, 21]. For chest malignancies there have been a number of solutions to managing the problem of tumor movement during treatment, including implantation of radiographic fiducials in/around tumors to facilitate their localization; tracking of tumor motion by computer-assisted robots; timing of RT delivery only to selected phases of the breathing cycle when tumor position is known; physical restriction of respiratory range to limit tumor motion; and employing breath control techniques when delivering RT, such as breath holding at full inspiration [20]. Over the past decade, a range of publications have now described stereotactic experiences principally in Japan [22, 23••, 24], Europe [25–27•, 28], as well as at Indiana University in the United States [29••, 30, 31], with respect to the range of technological approaches and dose regimens they have employed [20]. Thus, a survey of SBRT lung schedules shows a range of prescriptions: from 60 Gy in three fractions to 50 Gy in five fractions, 48 Gy in four fractions, and 30 Gy in one fraction [20]. The biological equivalent (ie, effective) dose of these regimens is substantially higher than the absolute value of the total dose given due to delivery in large fraction sizes over short periods of time [32]. For example, 60 Gy in three fractions is closer to being equivalent to 150 Gy when converted to conventional 2 Gy-fractionation.

SBRT in the Medically Inoperable Lung Cancer Patient: Selection, Staging, and Work-up

Given that lung SBRT patients generally have significant medical comorbidities, approaches to staging and work-up are frequently intended to be noninvasive and minimally harmful. Although pathologic confirmation of malignancy by biopsy is the gold standard, this is not readily achievable in some patients due to medical contraindications. For those non-biopsied patients, treatment is then offered on the basis of a clinical diagnosis of cancer; that is, based only on radiographic criteria such as serial CT chest scans showing a growing lesion and an accompanying FDG-PET scan either demonstrating high (SUV >5) metabolic activity on a single scan, or progression of intermediate activity over serial scans. Non-biopsied SBRT patients may represent up to 30% of some practices; studies to date suggest reassuringly that they have outcomes similar to the biopsy-proven cases [33•]. Similarly, mediastinoscopy is rarely carried out in these patients. CT-based, and more recently PET-based, staging has been used to characterize and clinically define the mediastinal lymph nodes.

Contraindications to SBRT are relatively few. Any tumor with suspected hilar or mediastinal disease requires further investigation prior to SBRT. Although baseline assessments usually include spirometry and diffusion capacity for carbon monoxide, there is no evidence to date to suggest that there are threshold pulmonary function (PFT) values to exclude patients from being offered SBRT. SBRT has been documented as a safe and effective treatment strategy of new stage I lung cancer after pneumonectomy [34], and is well tolerated by elderly patients [35]. While not a contraindication to therapy, proximity of tumor to critical structures, predominately the central airways, does require special considerations during treatment delivery and is discussed in more detail below.

SBRT Results in Medically Inoperable Lung Cancer: Outcomes

Figure 1 is a representative case documenting the results of SBRT for a typical medically inoperable patient. At the

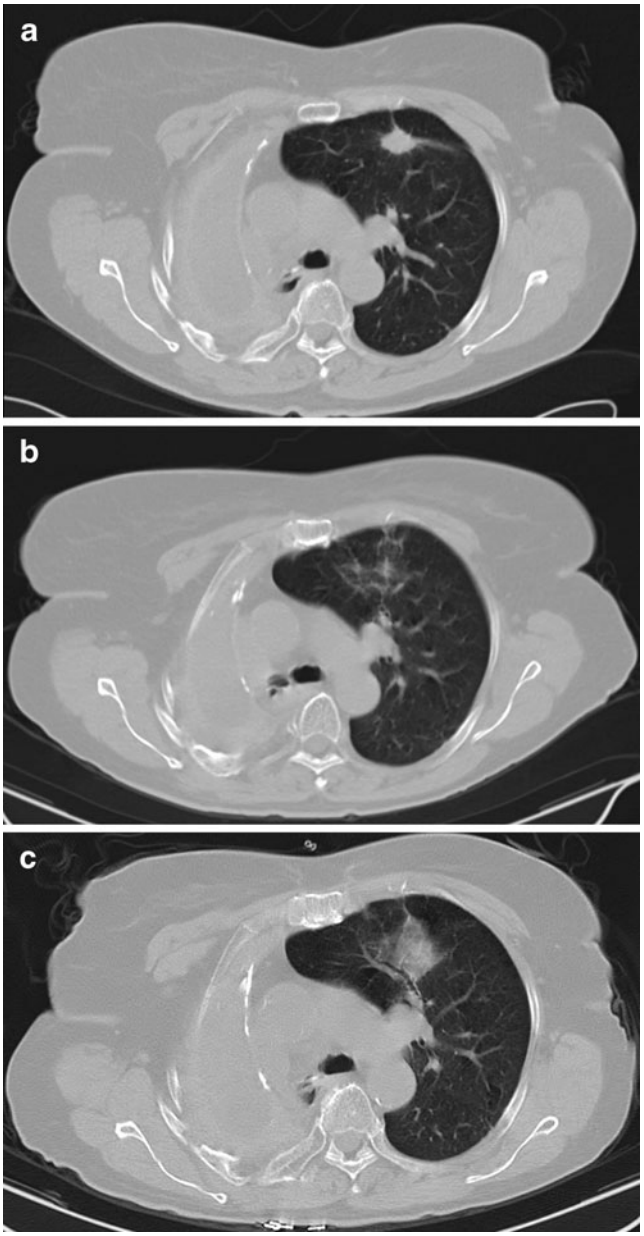

Fig. 1 A 76-year-old medically inoperable patient with a growing lesion in the upper lobe of the left lung: selected axial CT images of the chest before and following stereotactic body radiotherapy. **a**, Before treatment. **b**, 1 year after treatment. **c**, 4.5 years after treatment

time of treatment in 2004, the patient was a 76-year-old woman with stable chronic obstructive pulmonary disease (COPD) who lived independently but required continuous supplemental oxygen by nasal prongs. Her relevant past medical history revealed two previous primary lung cancers: one in 1992 in the right upper lobe treated with lobectomy alone and a second lesion of the right lung diagnosed in 1998 and treated with completion pneumonectomy. In 2003, she developed a left upper lobe spiculated lesion that was followed for a year, as biopsy was medically contraindicated. Using serial CT and PET imaging, a clinical diagnosis of malignancy in the left lung was made and prompted treatment. The images presented (Fig. 1a–c) reflect the radiographic changes following SBRT of 50 Gy in five fractions to the left upper lobe lesion. The patient had no untoward side effects from her therapy and no significant changes in her COPD symptoms. PET imaging over the years revealed no evidence of local or distant recurrence.

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 [22, 23••, 24–27•, 28, 29••, 30, 31, 33•, 36••]. That said, 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. Many treated patients develop radiographic changes of fibrosis that may be mistaken for recurrence, and interpretation of images may require an experienced reader [37•, 38]. PET-based imaging can be of utility for assessing ambiguous cases [39•], though biopsy may occasionally be required. It also 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: using radiobiological parameters, SBRT doses are felt to require a biologically equivalent dose of at least equivalent 100 Gy_{10} [23••, 25, 26, 28] to achieve the same kind of control rates as a schedule of 50 Gy in five fractions, for example. The Gy_{10} value represents a conversion factor for making comparison between dose and fractionation schedules using a mathematical model based on tissue responses [32].

Similar to lung resection, SBRT is truly a local therapy. As long as adequate dose is given to achieve local control, regional and distant control rates are likely determined by the combination of appropriate patient selection and inherent tumor biology. With primarily PET staging employed in most SBRT series, mediastinal or hilar nodal failures appear to be rare, ranging from 0% to 10% [23••, 24, 25, 27•, 29••, 30, 33•]. 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 [23••, 24, 25, 27•, 29••, 30, 33•]. Taking into consideration the limitations in staging, the age of most patients receiving SBRT, and the multiple comorbidities precluding surgery, 3-year to 5-year actuarial survival rates in excess of 50% reported for this population remain provocative and intriguing [40] in comparison to historical conventional RT survival rates ranging from 15% to 45%. In that respect, the recently published results of RTOG 0236 are instructive. Based on foundational phase I and II trials from Indiana University [29••, 30, 31], the RTOG initiated a prospective phase I/II trial (RTOG 0236) in medically

inoperable peripherally located early-stage NSCLC measuring 5 cm or less utilizing a regimen of 60 Gy in three fractions over 8 to 14 days. The study went on to enroll 59 patients over a multi-institutional setting, and closed in October 2006. The study results have just recently been published and were remarkable for a 3-year primary tumor control rate of 97.6%, a local-regional control rate of 87.2%, and a median overall survival of 48.1 months with no treatment-related deaths reported [36].

SBRT Results in Medically Inoperable Lung Cancer: 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 4% [20, 22, 23••, 24–27•, 29••, 30, 31, 33•, 36••]. 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 [37•], 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. The exception to the low rates of SBRT toxicity was 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 [29••, 30]. 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 [22, 23••, 24, 33•].

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 [22, 23••, 24–27•, 29••, 33•, 36••]. Furthermore, on average there is little to no decrease in the pulmonary function of treated patients [41, 42]. In the Cleveland Clinic experience [42], 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 [33•, 43•, 44]. 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 [14]. Similar symptoms such as soft-tissue fibrosis [45], skin reaction [46], and brachial plexopathy [47] have been described; however, these occur in less than 1% of treatments and are likewise preventable with changes in treatment planning.

Ongoing Clinical Trials

Within the RTOG, trials are currently exploring dose/fractionation issues for medically inoperable patients and the feasibility and safety of SBRT for selected operable patients. RTOG 0813 is a phase I/II study to establish the maximally tolerated dose of SBRT for early-stage, centrally located NSCLC. RTOG 0915 is a 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 0618 is a phase II trial in operable patients seeking to demonstrate that sustained (>2 years) high local control is achievable in this population.

Currently in Japan, a single-arm phase II study is being run 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.

In Europe, there is an ongoing randomized trial of either surgery or SBRT for stage IA NSCLC (ROSEL) in the Netherlands. In Scandinavia, a randomized phase II study (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 45 Gy in three fractions and the conventional RT is 66 Gy in 22 fractions.

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 comparing the current standard of 60 Gy in three fractions set by RTOG 0236 to the most successful arm of RTOG 0915, with end points of efficacy and toxicity.

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. It is nonetheless controversial since that practice is currently ill-defined in the standard surgical population and is relatively contraindicated in the medically compromised with more advanced disease.

Among the most provocative findings published in the lung cancer SBRT literature have been the results of Onishi et al. [23••], in which the survival of a subgroup of medically operable patients treated with SBRT was comparable to similar-stage patients treated with video-assisted thoracopic surgery or lobectomy. In the United States, defining the role of SBRT in potentially operable patients is becoming an active area of investigation. There are currently ongoing discussions between the RTOG and the ACOSOG to develop a phase III protocol comparing wedge resection (with or without brachytherapy) to SBRT in potentially operable high-risk patients.

Conclusions

SBRT has established itself as a safe and effective treatment for medically inoperable stage I NSCLC and is considered by many clinicians now to have become the standard of care for this population. However, further clinical studies are warranted, 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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