Chapter 14

Stereotactic Radiation Therapy: Changing treatment paradigms for stage I non-small cell lung cancer

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Abstract

Purpose of Review
To review recent developments in stereotactic body radiation therapy (SBRT) for stage I non-small cell lung cancer (NSCLC).

Recent Findings
In stage I tumors measuring up to 5 cm in diameter, SBRT can achieve local tumor control rates of up to 97%. SBRT has a favorable toxicity profile and has been safely applied in elderly patients, after previous pneumonectomy, or with severe chronic obstructive airways disease (COPD). Population studies indicate that the introduction of SBRT was associated with increased treatment rates for elderly patients and improved overall survival.

Summary
In patients with stage I NSCLC who do not undergo surgery, SBRT achieves superior survival as compared to treatment using conventionally fractionated radiotherapy. The role of SBRT in operable patients remains to be defined within randomized trials. In patients identified to be at high-risk for surgical complications, SBRT appears to provide an effective alternative with low risks of hospitalization and 30-day mortality. Future treatment algorithms should include individualized assessment of surgical risks, and the consideration of SBRT for high-risk patients, in order to develop a personalized treatment approach.
Introduction

Stereotactic body radiation therapy (SBRT) was first introduced more than a decade ago to treat stage I NSCLC in patients unfit for surgery [1]. SBRT precisely delivers very high radiation doses in a very short period of time (often 60 Gy in only 3-8 fractions), with excellent local control rates and a favorable toxicity profile in tumors measuring ≤5 cm. The goal of this review is to summarize recent developments in the field of SBRT, to define the role of SBRT in the treatment of stage I NSCLC, and to outline challenges and areas of future research that are likely to improve the treatment of patients with stage I NSCLC.

Development of SBRT and Improvements in Local Control

Although surgery has widely been considered to be the standard of care for patients with stage I NSCLC, a substantial proportion of patients are unable or unwilling to undergo an operation, often due to co-morbidities or advanced age [2]. Prior to the advent of SBRT, the treatment for such patients was often conventional conformal radiotherapy (3D-CRT) using typical radiation doses of approximately 55-70 Gy delivered over 4-7 weeks [3]. However, local tumor control with such schemes was suboptimal, with reported local failure rates as high as 60-70% in some series [3]. In the absence of highly effective alternatives to surgery, patients were often untreated, a choice that is associated with poor overall survival [4].

The growing interest in SBRT has been driven by advances in radiotherapy planning and imaging techniques, both of which allow for increased treatment precision [5]. Currently, SBRT treatment plans routinely take into account breathing-related tumor motion through the use of 4-dimensional CT scans that correlate CT images with respiratory phases, allowing for visualization of tumor motion [6]. Integrated imaging devices on the treatment units now allow for CT scans to be performed immediately prior to treatment, with the patient on the radiotherapy couch, thereby confirming that the patient and tumor are positioned correctly [7]. Such ‘image-guidance’ can be done using either x-rays or a cone-beam CT scanner that is installed on the radiotherapy machine.

Image-guided SBRT allows oncologists to reduce the ‘safety margin’ of normal lung treated alongside the tumor [7], allowing for much higher doses to be delivered safely. In contrast to 3D-CRT, a 60 Gy dose can delivered in SBRT in as few as 3 fractions in one week,
with dramatic increases in tumoricidal effect. For example, an SBRT prescription of 60 Gy in 3 fractions may equate to as much as 150 Gy delivered in conventional fractions [8].

Local failure rates after SBRT are generally <10% in studies using adequate doses [9,10], but rates of local recurrence increase as tumor size increases (T2 lesions), and when lower doses of SBRT are prescribed [11-13]. A biologically effective dose (BED) above 100 Gy has been used as a cutoff for adequate dose: below this threshold, local recurrence risk is higher [12]. This threshold is met by prescriptions such as 60 Gy in ≤8 fractions, or 48 Gy in 4 fractions, although there is some uncertainty equating SBRT doses and fractionations [14,15]. Local control outcomes from early SBRT studies have been confirmed in two recent multicenter phase II SBRT trials: one reported a primary tumor control rate of 97% and local control (in the involved lobe) of 91% at 3-years [16]; the other reported a 3-year local control rate of 92% [17].

Evaluation of treatment response after SBRT can be challenging, as the pattern of radiologic changes differs from the conventional patterns seen after 3D-CRT [18-21]. Although symptomatic pneumonitis is uncommon, persistent radiologic findings of fibrosis or ground-glass opacities are common after SBRT, occurring in >50% of patients, and can evolve long after treatment (Figure 1) [18-21]. Differentiating benign changes from recurrent or progressive disease is crucial, since salvage surgery may be offered to selected patients, yet is difficult in practice. Serial CT imaging, PET scanning, and/or biopsy can assist in diagnosis, but misclassification of radiotherapy sequelae as recurrence can occur, resulting in ‘salvage’ resection for lesions that prove to be benign fibrotic lesions [22].

Despite high local control rates, patients remain at risk of recurrence due to systemic relapse. Distant metastasis are the main location of recurrence after SBRT, occurring in approximately 20% [23,24]. Since systemic recurrences are associated with a poor prognosis, the development of effective strategies to prevent or treat such recurrences should be further investigated.
**Figure 1.** Long-term benign CT changes after stereotactic body radiotherapy (SBRT). The tumor was treated with 3 fractions of 20 Gy, with late benign changes appearing after 2 years and regressing thereafter. Reproduced with permission from [22].

**SBRT toxicity**

Although CT changes consistent with radiographic pneumonitis are extremely common after SBRT [20], these findings are often asymptomatic (likely due to the small volume of lung irradiated), and rates of clinical pneumonitis are usually <20% [17]. Common, self-limited side effects occurring in 5-40% of patients include fatigue, cough, dyspnea, chest pain, and skin rash. Less commonly, hemoptysis and rib fracture can occur, whereas life-threatening complications such as esophageal rupture, severe pneumonitis or pneumonia, or major hemoptysis, are rare [9,16,17,25-27].

An important caveat is that treatment of central tumors adjacent mediastinal structures with 60 Gy in 3 fractions or similar dose-fractionation schemes is associated with a higher rate of severe toxicity [25,26]. Lower doses or more fractionated treatments, such as 60 Gy in 8 fractions, appear to be safer based on retrospective reports [9,28,29] (Figure 2). In a recently
published phase II trial, 60 Gy in 4 fractions was associated with acceptable toxicity for central tumors, although one patient died as a result of treatment complications [30]. Currently, the optimal dose for central tumors is the subject of ongoing trials [31].

**Figure 2.** Treatment of a central lung tumor (within close proximity to mediastinal structures) in a high-risk patient after previous pneumonectomy. This patient remains free of disease recurrence or toxicity 7 years post-treatment.

Toxicity can be minimized through careful attention to the radiation tolerance of normal structures, and newer approaches such as volumetric modulated arc therapy have been used to reduce chest wall doses, while minimizing patient discomfort by reducing treatment time [32]. Although the body of research into the tolerance of normal tissues to large fractions of radiotherapy is evolving, several important contouring guidelines and dose constraints have been established recently [16,33,34] and some individual risk calculation is possible to predict the risk of pneumonitis [35], chest wall pain or rib fracture [36,37], skin necrosis [38] and brachial plexus injury [39].
The delivery of SBRT requires more attention to detail as a result of the sophisticated techniques and high doses used. Several guidelines are now available that addressing practical issues involved in implementing an SBRT program [40-42].

**Unmet therapeutic needs in the population & access to care**

SBRT implementation can improve access to care, increasing the number of patients receiving potentially curative treatment. There are considerable variations internationally in the proportion of patients undergoing curative treatment for early stage NSCLC, yet active treatment of lung cancer in the first year after diagnosis is associated with improvements in long-term survival [43]. In a study of elderly patients in a population of 3 million people in North Holland, SBRT introduction was associated with a reduction in the proportion of stage I NSCLC patients going untreated. This corresponded to a 16% absolute increase in the proportion of patients receiving radiotherapy, and this shift was associated with a 6-month median survival improvement in the stage I NSCLC population. On subgroup analysis, this survival improvement was confined to the patients treated with RT, but not seen in patients treated with surgery or those receiving no treatment [44]. By increasing the rates of active treatment, and providing better local control than older 3D-CRT techniques, SBRT may improve survival for elderly patients with stage I NSCLC.

**SBRT as first-line treatment for operable patients**

The high rates of local control attained with SBRT have generated several outcomes comparisons against other treatment modalities [10,24]. Currently, randomized trials are underway comparing SBRT to conventional radiotherapy [45] or surgery [34], but results from these trials are still several years away. Furthermore, accrual to such studies may be difficult, since patients and physicians may wish to avoid randomization when two treatment arms are inherently different. In the interim, clinicians and patients must make decisions based on the available evidence to date.

Direct comparisons of results between surgical and SBRT studies are limited by differences in baseline patient populations: nearly all SBRT patients are medically inoperable, which itself confers a survival disadvantage of 10-20% compared to operable patients [13]. Limited data is available on patients who are considered medically operable but underwent
SBRT. A recent update of a cohort of 87 ‘medically operable’ SBRT patients demonstrated 5-year survival of 72% and 63% for patients with T1 and T2 disease respectively [46], similar to outcomes after surgical resection.

SBRT has been compared to wedge resection in a study that retrospectively evaluated a cohort of 124 patients (58 received SBRT and 69 wedge resection) [47]. Although SBRT patients were older, had higher comorbidity scores and 95% were medically inoperable, they had better local and regional disease control than patients undergoing wedge resection. Distant metastasis and cause-specific survival rates were the same in the two groups, whereas surgical patients had better overall survival, likely reflective of their superior baseline status.

Differences in baseline factors can be reduced, though not eliminated, by matching patients based on propensity scores [48]. Such an analysis was carried out for 114 patients, comparing surgery and SBRT after propensity score matching, and demonstrated similar results in local control and disease-specific survival between the two treatments. [49]

In the absence of actual data from randomized clinical trials, virtual trials can be simulated with a process known as Markov modelling. A hypothetical cohort of patients are taken through different treatment scenarios, and probabilities are assigned to each possible outcome (e.g. operative death, recurrence, successful salvage, etc.), based on published literature. A Markov model simulating a clinical trial comparison of SBRT and surgery for patients with stage I NSCLC of various ages and co-morbidity levels was recently reported [50], and the model predicted a small survival advantage for patients treated with surgery of 2-3% at 5 years for most patient groups. When adjusted for quality of life, the advantage was only one quality-adjusted life month. This effect was highly sensitive to several factors, including the operative mortality rate: once operative mortality increased above 4%, the advantages of surgery disappeared and SBRT was favoured. This analysis suggests the decision in selecting SBRT versus surgery is not a universal one, but depends on individual patient factors and risk level, as well as the quality of available surgical care.

**Treatment of high-risk groups**

In light of data suggesting that operative mortality risk may be a key factor in choosing optimal treatment, it follows that patients at high surgical risk might benefit most from a switch
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to SBRT for first-line treatment. Such high-risk patients include the elderly, patients with severe COPD, and patients who have previously undergone lung resection.

Elderly patients are less likely than their younger counterparts to receive active cancer treatment, usually due to concerns about comorbidity, frailty, or treatment efficacy. Nearly 70% of elderly lung cancer patients have significant comorbidities [51-54], and surgical morbidity and mortality is higher in such patients [55]. In the Netherlands, surgery is performed for 60% of all cases of stage I-II NSCLC, but operative rates vary substantially by age: 79% of younger patients (age <75) undergo surgery, compared to 43% of elderly patients (age ≥75) [56].

SBRT in the elderly (aged ≥75) was evaluated in 193 patients who had a median Charlson co-morbidity score of 4, 25% of whom had severe COPD. Actuarial local control at 3-years was 89%, similar to local control rates in younger patients [57]. Importantly, SBRT was well tolerated: apart from fatigue, all early side effects (such as nausea, cough and dyspnea) were limited to <10% of patients each, and grade 3 or higher toxicity occurred in <10%.

Patients with severe COPD represent a second high-risk group. COPD increases the risk of post-operative complications and reduces the amount of lung that can be safely resected [58][59]. A systematic review of the literature compared outcomes after surgery or SBRT in patients with severe COPD (defined as GOLD III or IV). Although overall survival and local control outcomes were similar between patients treated with surgery or SBRT, surgery was associated with a substantial operative risk (mean 30-day mortality 10%), compared to SBRT (mean 30-day mortality <1%). [60]

A thirdly high risk group is patients who have undergone previous lung cancer surgery. After resection of a primary lung cancer, the risk of developing a new primary lung cancer is more than double the baseline population risk, and the cumulative incidence reaches 15% by 8 years [61,62]. In new cancers arising post-pneumonectomy, surgical options are limited, and are associated with risks of complications or mortality [63]. A report on SBRT for 15 patients with stage I NSCLC previously treated with pneumonectomy demonstrated no local recurrences after a median follow-up of 16 months, and only two patients developed grade 3 toxicity [64].

These data suggest that in high-risk patients, SBRT can be delivered safely, potentially exposing the patient to fewer complications than an operation, with excellent local control. Validated instruments are available to estimate surgical risk [65], and in patients at high risk of
mortality, the presumption that surgery is preferred over SBRT based on historical patterns of practice should not be assumed.

Although most studies on stage I NSCLC report on long-term survival outcomes, these may not be the outcomes most important to patients [66]. High-risk patients, such as the elderly, who undergo surgery are likely to remain in hospital longer, and less likely be discharged home, with discharge to long-term care facilities more common [55]. Surgery is associated with a decreased quality of life, whereas such a decline is not apparent after SBRT [67-69]. These factors take on increased importance if oncologic outcomes between SBRT and surgery are similar.

Conclusion

The field of SBRT has developed rapidly since its introduction over ten years ago. Studies from several institutions worldwide have established its efficacy in the treatment of medically inoperable patients, but its suitability as first-line treatment in operable patients has yet to be defined. As surgical risk rises, the relative attractiveness of SBRT increases. For patients at high risk, clinicians should individualize their recommendations, with a discussion of the risks and benefits of each treatment in the context of the patient’s individual situation. With the advent of an effective alternative to surgery, striving for resection at all costs is no longer necessary.

The future of SBRT holds a great deal of promise. In addition to data from ongoing clinical studies that aim to define the optimal dose of SBRT and its role as first-line treatment, future research will attempt to understand the systemic immunological effects of SBRT, the tolerance of normal tissues to large radiation doses, and the long-term pulmonary and quality of life sequelae after SBRT. Research should also be patient-centered, focusing on personal preferences, risk tolerance and decision-making. Finally, since distant metastases are the main cause of cancer death after treatment with SBRT or surgery for stage I NSCLC despite excellent local control, much is to be gained from addressing systemic risk, through novel chemotherapeutic or targeted agents, or ablative treatments for patients with oligometastatic disease.
References


