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Review

Stereotactic radiotherapy for early lung cancer: Evidence-based approach and future directions

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ABSTRACT

Aim: To review key studies evaluating stereotactic radiotherapy in the setting of early-stage non-small cell lung cancer (NSCLC) for inoperable or high-risk patients, and discuss areas of ongoing research and clinical trials.
Background: The use of stereotactic radiotherapy for the treatment of early stage non-small cell lung cancer (NSCLC) has increased rapidly over the past decade. Numerous studies have reported outcomes for patients treated with SBRT who are unfit for surgical resection, or at high risk of surgical complications.
Materials and methods: A narrative review.
Results: The preponderance of evidence suggests that SBRT is associated with excellent local control (~90% at 3 years) and a favorable toxicity profile. In patients with higher operative risks, such as the elderly and patients with severe COPD, SBRT may provide a less-toxic treatment than surgery with similar oncologic outcomes. Ongoing studies are evaluating the use of SBRT for locally advanced or oligometastatic NSCLC.
Conclusions: A large body of evidence now exists to support the use of SBRT for early-stage NSCLC. Decisions regarding the optimal choice of treatment should be individualized, and made in the context of a multidisciplinary team.

1. Background

Stereotactic body radiation therapy (SBRT), also referred to as stereotactic ablative radiotherapy (SABR), has emerged over the past decade as a standard treatment option for early stage NSCLC. SBRT differs from older techniques (termed 'conventional radiotherapy' (CRT)) in several important ways: SBRT uses advanced imaging technologies (such as four-dimensional CT scans) to account for tumor motion during the respiratory cycle and also for patient positioning prior to treatment (Fig. 1); SBRT treatment plans employ multiple beams (often 7–11 or large arcs) which all converge on the target; SBRT prescriptions delivery very high doses (often 54–60 Gy)

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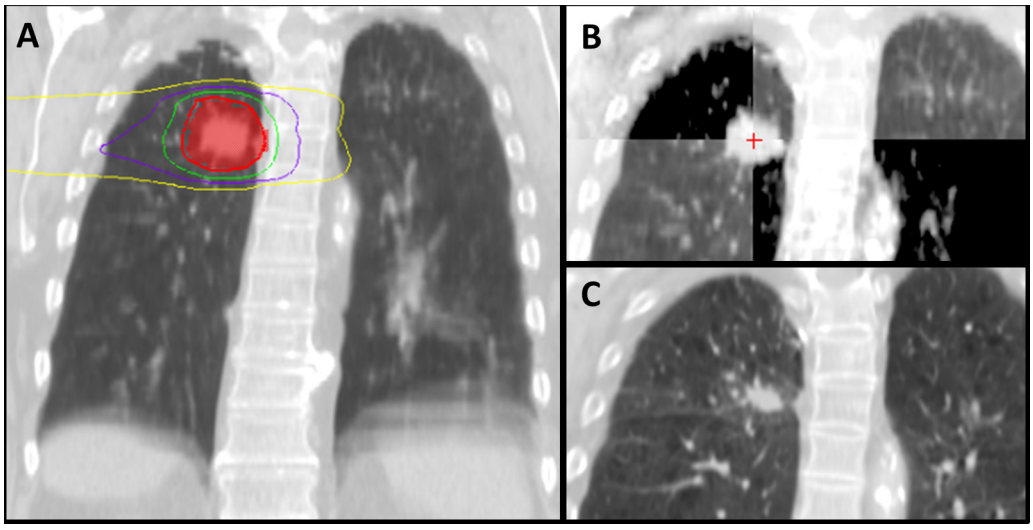

Fig. 1 – Stereotactic body radiotherapy (SBRT) for a T1N0 lung adenocarcinoma. (A) Four-dimensional CT average projection showing the SBRT plan. Red color wash represents the planning target volume (PTV), solid lines represent regions receiving doses of 60 Gy (red), 45 Gy (green), 30 Gy (purple) and 15 Gy (yellow), respectively. (B) Cone-beam CT done at time of treatment and aligned with planning CT scan to confirm setup accuracy. (C) Follow-up scan 2.5 years post-treatment, with stable area of fibrosis measuring 1.9 cm.

in a small number of fractions (often 3–8), while allowing for doses in the center of the tumor that often exceed the prescription dose by 30% or more.[1] These factors, taken together, allow for the precise delivery of potent radiotherapy doses while minimizing dose to normal tissues.

The use of SBRT for early-stage NSCLC has been increasing in Europe, North America, and Asia,[2–4] providing an important tool in the multidisciplinary management of NSCLC at numerous centers worldwide. Given the widespread adoption of SBRT for early-stage NSCLC, the goal of this article is to review key studies evaluating the use of SBRT for NSCLC, and to discuss areas of uncertainty which are being addressed in current research studies.

2. Outcomes of untreated NSCLC

The importance of providing curative-intent treatment for early-stage non-small cell lung cancer, rather than merely observing, is underscored by the poor outcomes observed for patients who do not receive treatment. Population-based data from the Netherlands suggests that the median survival for untreated stage I NSCLC is only approximately 6–7 months.[5,6] Similarly, a U.S. population based study[7] reported that elderly patients (>65 years old) with untreated stage IA or IB NSCLC had a 6-month mortality rate of 33% and a 2-year overall mortality rate of 73%. A Markov model constructed to compare treated vs. untreated elderly patients (≥75 years) with COPD and T1 and T2 NSCLC predicted very poor survival, with 5-year OS of 9.0% for patients with untreated T1 tumors and 3% for patients with untreated T2 tumors. In contrast, patients with treated T1 and T2 tumors were predicted to have a 7–48% five-year OS, depending on COPD GOLD status.[8]

3. Outcomes with SBRT: key studies

Numerous single-institutional studies and pooled analyses have reported outcomes after SBRT treatment for early NSCLC.[9,10] The largest[11] single-center analysis of SBRT efficacy was a retrospective study of 676 patients with T1 or T2 tumors treated with SBRT at the VU University in Amsterdam. All patients were treated using a consistent risk-adapted strategy, with delivered doses of 54–60 Gy in 3-, 5-, or 8-fraction regimens depending on the tumor size and proximity to local structures.[12] In this large cohort with good follow-up (median 33 months), 56% of patients had T1 tumors and 44% had T2 tumors. Local control was excellent, with 2-year and 5-year local recurrence (LR) rates of 4.9% and 10.5%, respectively. Regional recurrence rates were 7.8% and 12.7%, and distant recurrence rates were 14.7% and 19.9%, respectively. Two patterns of recurrence emerged in this study. The first pattern, isolated distant recurrence, was the most common and accounted for 46% of recurrences. Such distant relapse may occur early (median 8.3 months post-treatment), and is attributed to undetected subclinical metastases existing at the time of treatment. The second pattern of recurrence was isolated locoregional recurrence without distant metastasis, occurring in 34% of patients with recurrence, most of whom (83%) did not develop distant recurrences thereafter. In addition, second primary lung cancers (SPLC) occurred in 6% of patients. Risk of recurrence or SPLC is highest in the first 3 years after SBRT: the average rate of these two events was 5.9% per patient per 6 months during years 0–3 post-treatment, falling to 1.2% in years 4–5. Overall, the predominant pattern of failure was out-of-field recurrences, highlighting the importance of standardized follow-up procedures to detect potentially salvageable recurrences, and the

need for improved systemic treatments for patients who ultimately fail distantly.

As the delivery of SBRT requires substantial clinical and technological expertise, the generalizability of SBRT outcomes from single centers to a multi-institutional setting was assessed as part of the Radiation Therapy and Oncology Group (RTOG) 0236 trial. RTOG 0236 prospectively studied medically inoperable patients with peripheral T1N0 or T2N0 NSCLC from several centers, and patients were treated with SBRT to a dose of approximately 54 Gy in 3 fractions using current calculation algorithms.[13] Quality assurance revealed a very high standard of dose delivery to target (tumor coverage was protocol-compliant in 98%), although compliance with normal tissue constraints was lower, with 73% of plans compliant for normal structures. In the 55 evaluable patients (44 with T1 tumors and 11 with T2 tumors), the 3-year control rate of the primary tumor was 97.6%, and the 3-year rate of local control (defined as the absence of recurrence at the primary tumor site or involved lobe) was 90.6%. Overall survival was 55.8% at 2 years, with a median survival of 48.1 months. Protocol-specified grade 3 and grade 4 toxicity occurred in 12.7% and 3.6% of patients, respectively, and there were no reported grade 5 toxicities. An additional 10.9% of patients experienced adverse events attributable to SBRT which were not prospectively protocol-specified. The most frequently-affected normal structures for grade 3 or 4 toxicities (protocol-specified or not) included the lungs (pneumonitis, hypoxia, decreased pulmonary function), skin, and musculoskeletal/soft tissue structures.

Long-term results from RTOG 0236, with a median follow-up of 4 years (7.2 years for surviving patients) have been presented in abstract form, and suggest that late failures can occur within the untreated lobe with longer follow-up. The actuarial 5-year outcomes were as follows: primary tumor recurrence 7%, involved lobar recurrence 20%, regional recurrence 38% and distant recurrence 31%. Overall survival was 40% at 5 years.[14]

Results from SBRT studies from other institutions are well-summarized in a systematic review and meta-analysis by Grutters et al.,[9] who used a random effects analysis to evaluate OS and disease-specific survival for patients with lung cancer treated with conventional radiotherapy (CRT), SBRT, or particle therapy (proton therapy and carbon-ion therapy).[9] The meta-analysis found that, when corrected for differences in percentages of inoperable patients, there was no statistical difference in 2-year overall survival for patients treated with SBRT, proton, or carbon-ion therapy. However, all three of these modalities produced OS significantly greater than CRT. Specifically, 2-year OS was found to be 53%, 70%, 61%, and 74% for CRT, SBRT, proton, and carbon-ion therapy, respectively. Similar patterns were found for 2-year disease-specific survival and 5-year overall survival. Severe adverse events (grade $\geq$3) were infrequent for all modalities, with the majority of studies reporting no adverse events. Toxicity was higher with SBRT vs. CRT, with the estimated risks of grade 3–4 pneumonitis reported as 2% vs. 0.2%, and treatment-related death as 0.7% vs. 0.1%; however, all SBRT-related deaths were from a single study using doses for central tumors which are now known to be excessive.[15]

A more recent systematic review including only publications since 2006 reported on 3771 patients treated with SBRT. Local control at 2 years was 91% (95% confidence interval [CI] 90–93%), with no difference detected between various technologies used for SBRT.[11]

3.1. *The importance of dose*

The overall dose delivered to the tumor is strongly associated with local control, with data suggesting that a Biologically Effective Dose (BED) of $\geq$100 Gy, delivered to the periphery of the tumor, is ideal.[16,17] BED is calculated using a linear-quadratic model of cell kill, and although imperfect, offers a clinically useful method of equating different dose and fractionation regimens.[18,19] BED can be used to model tumor kill and acute radiation effects (BED_{10}) and also late toxicity (BED_3). A BED_{10} of 100 Gy is delivered by a regimen of 50 Gy in 5 fractions; more potent regimens in common clinical use include 48 Gy in 4 fractions (BED_{10} = 106), 60 Gy in 8 fractions (BED_{10} = 105), 55 Gy in 5 fractions (BED_{10} = 116), and 54 Gy in 3 fractions (BED_{10} = 151), although some controversy exists in the use of the BED model to equate different dose-fractionation schemes.[18,19] A retrospective analysis of 257 patients with T1–2 NSCLC treated with SBRT found that outcomes were strongly associated with BED: 5-year local control was 84% in patients receiving a $BED_{10} \geq 100$ Gy, compared to 36% for a $BED_{10} < 100$ Gy.[17] A separate study modeling dose–response found that the dose delivered to the periphery of the target (the planning target volume [PTV] margin) was the strongest predictor of outcome, with higher doses required for equivalent local control if prescribing the dose to the center of the tumor.[16] However, it is unknown whether escalating the BED_{10} far beyond 100 Gy provides any benefit. A meta-analysis of 34 observational studies examined the relationship between BED and OS, and suggested that regimens exceeding a BED_{10} of 146 Gy was associated with inferior survival.[20]

4. Outcomes in special populations

4.1. *Patients with central tumors*

Centrally-located tumors present a therapeutic challenge both for surgeons and radiation oncologists. For patients undergoing surgical resection, more extensive surgery is often required for central tumors, which is associated with increased morbidity and mortality.[21,22] For patients with central tumors undergoing SBRT, a pivotal phase II study reported that a dose of 60–66 Gy in 3 fractions was associated with excessive toxicity and treatment-related death. In this trial of 70 patients with T1 or T2 NSCLC, patients with peripheral tumors had a 2-year freedom from severe toxicity of 83%, compared to only 54% in patients with central tumors.[15] As a result, less potent SBRT fractionation regimens have been used in such patients, with more favorable toxicity profiles.[23] In a systematic review of studies evaluating SBRT for central tumors,[24] the risk of treatment-related death was found to be dependent on BED. Overall treatment-related death was 2.8% (16 out of 563 patients), occurring in 3.6% of patients receiving a $BED_3 \geq 210$ Gy, but only 1% of patients receiving $BED_3 < 210$ Gy;

a BED_3 of 210 Gy corresponds to a dose of 60 Gy in 8 fractions. It was concluded that for central tumors, using a fractionation with a $BED_{10} \geq 100$ Gy and a $BED_3 < 210$ Gy provided the best balance of acceptable toxicity while preserving local control.

The question of optimal dose for central tumors is being addressed by RTOG 0813, a seamless phase I/II trial escalating the dose from 50 Gy in 5 fractions to 60 Gy in 5 fractions. This trial included a phase I component to determine the maximal tolerated dose (MTD) for central tumors, with a phase II component to assess tumor control rate at the MTD. This study has completed accrual ($n = 120$) and data are maturing.[25] A clear recommendation on fractionation schedule should await the results of RTOG 0813, yet based on the data from the meta-analysis above, a schedule of 60 Gy in 8 fractions appears to be safe.

4.2. *Patients with large tumors*

The safe upper-size limit for SBRT has not been clearly defined, but treatment of larger tumors appears to be associated with increasing toxicity. Ong et al. aimed to investigate dose parameters and toxicities associated with the treatment of larger tumors, defined as those with PTV size $\geq 80\,cm^3$.[26] A total of 18 patients were included, with a mean PTV size of 137 cm^3 (a 5 cm spherical tumor, with a standard 5 mm margin, would yield a PTV of 113 cm^3). SBRT for patients with large tumors was feasible, but associated with a higher risk of radiation pneumonitis (scored as grade 2 or 3 in 5 patients [27%]). All five radiation pneumonitis (RP) cases were associated with the use of arc-based radiation delivery without prioritizing the avoidance of the contralateral lung. Eight deaths occurred during a median follow-up of 12.8 months. Five deaths were due to comorbidity, two deaths were found to be potentially treatment related, while another was due to recurrent local disease leading to pulmonary hemorrhage. The best predictor of RP was percentage of contralateral lung volume receiving ≥ 5 Gy, with no patients developing RP if the contralateral V5 was $\leq 26\%$. A separate study of 63 patients with tumors >3 cm (range 3.1–8.5 cm) treated with SBRT reported a 19% rate of grade ≥ 2 pulmonary toxicity, and a 1.5% rate of grade 4 pulmonary toxicity. Overall, the use of SBRT in patients with large tumors is feasible but appears to be associated with higher rates of toxicity, which must be balanced against the potential benefits of treatment, and any alternate treatment options available.

4.3. *Elderly patients*

Lung cancer is a disease of the elderly, and approximately one-third of patients with NSCLC are ≥ 75 years of age.[27] Elderly patients are less likely to receive curative treatment due reasons including frailty, operative risks and/or perceived lack of benefit.[27,28] For such elderly patients, the introduction of SBRT provides a curative-intent treatment option which can be delivered on an outpatient basis, with a lower risk of short-term mortality than operative interventions.[5,29]

At least three population-based studies have evaluated the impact of SBRT introduction for elderly patients. One such study examined practice patterns and outcomes for 875 patients aged ≥ 75 years in the province of North Holland as SBRT was introduced across three time periods: 1999–2001 (period A, no SBRT availability), 2002–2004 (period B, SBRT introduction), and 2005–2007 (period C, full SBRT availability).[5] In each successive period, the proportion of elderly patients receiving radiation therapy increased, from 26% in period A to 42% in period C ($p < 0.01$), and this corresponded to a decrease in the number of patients going untreated. Patients treated in period C experienced a 5-month improvement in overall survival, and on subgroup analysis, only patients in the radiotherapy group sustained this survival improvement. There was no significant improvement in the surgical group, or in the group of patients receiving no treatment. A nested matched-pair analysis comparing SBRT vs. surgery in this population found no differences in long-term survival but higher 30-day mortality in patients receiving surgery (8.3%) vs. SBRT (1.7%).[29] A larger retrospective population-based analysis of 4605 elderly patients (≥ 75 years) confirmed the finding of improved survival associated with SBRT implementation, with lower short-term mortality compared to surgical resection.[6]

A U.S. population-based study used the Surveillance, Epidemiology and End Results (SEER) database linked with Medicare claims to evaluate outcomes for 10,923 patients ≥ 66 years of age with early-stage NSCLC.[7] Five strategies were compared: lobectomy, sublobar resection, conventional RT, SBRT, and no treatment, and used propensity score matching to control for baseline characteristics. Patients receiving SBRT had better survival than those receiving CRT or no treatment. In comparisons with surgery, after propensity matching, patients receiving lobectomy or SBRT showed no significant difference in overall survival or disease-specific survival. During the first 6 months of treatment, the group treated with SBRT had the lowest mortality rate; thereafter patients treated with lobectomy had the lowest mortality rates.

Octogenarians with early-stage NSCLC represent a unique subgroup with a lack of specific data addressing treatment outcomes. This age group was specifically addressed by a recent retrospective study which looked at outcomes of 24 patients aged 80–89 treated with SBRT. All patients were treated at a single center, with radiation doses ranging between 48 and 56 Gy given in 4–5 fractions. The authors reported favorable results, with a 24-month disease-free survival of 77%, and a 0% local failure rate. There were no grade 3–5 treatment toxicities. Although the sample size was small, this study provides data suggesting that SBRT is safe and effective, even in patients ≥ 80 years old.[30]

4.4. *Patients with severe COPD*

COPD is present in approximately 50–70% of patients with lung cancer,[31] and is associated with increased surgical morbidity and mortality.[32,33] The advent of SBRT provides an additional treatment option for patients with severe COPD who are at high surgical risk. A systematic review of the literature compared outcomes in patients with stage I NSCLC and severe COPD who were treated with SBRT or surgical resection. Severe COPD was defined as a Global Initiative for Chronic Obstructive Lung Disease (GOLD)[34] score of III or IV, or predicted post-operative FEV1 of $\leq 40\%$. Locoregional control and long-term overall survival outcomes were similar for patients treated

surgically and with SBRT, but short-term mortality was higher for patients undergoing surgical resection (30-day mortality of 7–25% in the surgical arm vs. 0% in SBRT arm).[35] SBRT appears to be well-tolerated in patients with severe COPD, with grade 3–4 toxicities occurring in <10% of patients.[35] At present, no evidence exists to suggest the use of a different total dose or fractionation for severe COPD patients, compared to others.

5. Unanswered questions

5.1. *Randomized comparisons of SBRT with other treatments*

Until recently, no randomized trials had directly assessed the differences between SBRT and older radiotherapy techniques, although population-based studies provide a high level of evidence when randomized data is not available.[36] Currently, at least two randomized trials are underway comparing SBRT vs. CRT (NCT01968941 and NCT01014130), and one additional trial has been completed. This latter trial enrolled 102 patients with T1–2 NSCLC and randomized them to SBRT (66 Gy in 3 fractions in 1 week) using a 5–10 mm expansion for uncertainty vs. CRT (70 Gy in 35 Gy over 7 weeks) using a 20 mm expansion. The results, recently reported in abstract form,[37] suggested a tendency toward improved disease control at 3 years with SBRT, with similar OS between the two arms, and less toxicity with SBRT.[37] Full results of this trial, along with data from the two ongoing randomized trials, are awaited.

The promising results of SBRT have led to comparisons with surgical resection, which has historically been the gold-standard treatment for early-stage NSCLC.[38] Such comparisons have included single-modality cohort studies compared to historical controls, matched comparisons, systematic reviews, and modeling studies, and have included sublobar resection or lobectomy as surgical comparators.[10,39–43] The results of these comparisons have led to sufficient equipoise for the launch of three randomized trials comparing SBRT vs. surgery, but all have closed due to poor accrual.[44] In the absence of randomized evidence, the choice between various treatment modalities is best made in the context of a multidisciplinary team, with full discussion of treatment options available locally and knowledge of their associated outcomes, including operative mortality risks, which can vary substantially based on several patient and institutional factors.[45,46]

5.2. *Assessment of response after SBRT*

Although the development of symptomatic radiation pneumonitis after SBRT is uncommon, nearly all patients develop asymptomatic lung parenchymal changes in the high-dose region.[47] Such changes can evolve over time, and in some situations can be difficult to distinguish from recurrence as some patients have undergone resection for lesions which proved to be benign fibrosis.[48] PET–CT may be helpful to distinguish recurrence from fibrosis, but low- or moderate-grade FDG uptake can be found after SBRT in the absence of malignancy.[49]

Recently, high-risk features (HRFs) on CT have shown promise as predictors of recurrence. Such HRFs include an enlarging opacity (particularly >1 year post-treatment), sequential enlargement, growth in the cranio-caudal direction, and loss of air bronchograms.[50] One prospective study (NCT02136355) is combining SBRT with surgical resection after extensive imaging with dynamic PET–CT and dynamic contrast enhanced CT, in order to assess new biomarkers of response, to help distinguish recurrence from benign changes, and to measure the true rate of pathological complete response rate after SBRT.

5.3. *SBRT for locally advanced NSCLC*

For patients with locally advanced NSCLC, dose escalation is limited by concerns regarding normal tissue structures.[51] The recent RTOG 0617 randomized trial evaluated dose escalation to 74 Gy in 37 fractions for stage III NSCLC, compared to a standard dose of 60 Gy in 30 fractions, and concluded that the higher dose arm was associated with inferior survival.[52] SBRT has been proposed as an alternative mechanism to deliver higher doses for patients with stage II or III NSCLC, with the potential advantages of more conformal treatment delivery for the primary tumor, and reduced overall treatment duration, avoiding tumor repopulation that may occur with prolonged fractionation schemes.

One prospective single-institution study evaluated the feasibility of a 19.5–20 Gy SBRT boost dose after chemoradiotherapy (with a radiation dose of 60 Gy) in 35 patients with stage II–III NSCLC. The SBRT boost was delivered at a median of 2.0 months after chemoradiotherapy.[53] The treatment was well-tolerated, with 4 patients (11%) developing acute grade 3 pneumonitis and 1 patient (3%) developing late grade 3 pneumonitis. Early follow-up suggested a local control rate of 83%. Longer follow-up data is awaited, along with additional prospective studies which are currently underway (NCT01345851 and NCT01656460).

5.4. *SBRT for oligometastatic NSCLC*

The oligometastatic state, first described by Hellman and Weichselbaum in 1995, refers to a disease state with a limited metastatic burden, where ablation of all metastatic deposits may lead to a prolonged disease-free interval, or even cure.[54] Oligometastases can be ablated using surgical resection, SBRT, or other modalities such as radiofrequency ablation. SBRT can be employed to ablate metastatic deposits at several body sites, including brain, bone, lung, liver and adrenals,[55] and can play a key role in the treatment of oligometastatic NSCLC.[56]

The aggressive treatment of oligometastases has increased in recent years, but randomized evidence to support such aggressive treatment is lacking for most situations.[57] For patients with oligometastatic NSCLC, long-term survival is most associated with the development of metachronous (rather than synchronous) oligometastases, and the presence of node-negative thoracic disease.[56] In patients with low-risk oligometastases (metachronous presentation and N0 disease), 5-year survival is 48%, falling to 14% in patients with synchronous presentation and node-positive disease.[56] Other prognostic factors include definitive control of the primary

tumor, and lower intrathoracic disease burden in patients undergoing thoracic radiotherapy.[56,58,59]

5.5. *Re-irradiation with SBRT*

Outcomes and toxicities from SBRT used in a re-irradiation scenario have been described in a few small retrospective studies and summarized in one systematic review. For example, one small study of 39 patients treated with salvage SBRT following CRT found that SBRT achieved a 2-year local progression free survival rate of 64%, but 23% of patients experienced grade 2–3 radiation pneumonitis, and 3% experienced grade 4 skin toxicity. There were no grade 5 events.[60] In the systematic review, which included 466 patients in 19 studies receiving SBRT in various re-irradiation scenarios, overall rates of grade 1–3 radiation pneumonitis, grade 4 and grade 5 toxicity were 27% (124 patients), <1% (2 patients) and 1.7% (8 patients), respectively.[61] However, grade 5 toxicity rates varied substantially across studies, ranging from 0 to 12%. While further research is required to evaluate the utility and safety of re-irradiation with SBRT, the limited current data suggests that long-term disease control is achievable, but toxicity may be increased and repeat SBRT should be considered with caution.

5.6. *Cost effectiveness of SBRT*

With increasing worldwide pressure on health-care costs, the economic impact of SBRT implementation must also be considered. Several studies have evaluated the cost effectiveness of SBRT relative to other treatment modalities. A 2011 study using Markov modeling and U.S. cost data found that SBRT was cost effective relative to either CRT or radiofrequency ablation (RFA): SBRT had an incremental cost effectiveness ratio (ICER) of $6000/quality adjusted life year (QALY) compared to CRT, and a ICER of $14,000/QALY compared to RFA.[62] This finding was supported by a recent Canadian modeling study comparing costs of radiotherapy, SBRT, sublobar resection, lobectomy, pneumonectomy, and best supportive care for 4318 cases of stage I NSCLC.[63] Authors found that CRT had a lower up-front cost than SBRT, however CRT was less effective overall due to costs associated with recurrence. SBRT achieved both higher QALY and lower costs (i.e. "dominated") compared to sublobar resection, CRT and best supportive care. Lobectomy was the most cost-effective strategy of all, with an ICER of ~$56,000 compared to SABR.[63] Other U.S. data supports the general finding that for clearly operable patients, lobectomy is the most-cost effective option, whereas for marginally operable patients, SBRT dominates the other treatment options.[64]

6. Conclusions

A large body of evidence now exists to support the use of SBRT for early-stage NSCLC. The preponderance of evidence suggests that SBRT is associated with excellent local control (~90% at 3 years) and a favorable toxicity profile. In patients with higher operative risks, such as the elderly and patients with severe COPD, SBRT may provide a less-toxic treatment with similar oncologic outcomes. SBRT appears to be safe for central tumors, if normal tissue dose constraints are respected. Further research is required to determine the optimal use of SBRT in comparison to surgical resection, for assessment of response after SBRT, and to determine if SBRT can provide benefits for patients with locally advanced or oligometastatic NSCLC.

Conflict of interest

Dr. Palma's research group holds a patent for advanced image analysis for assessment of response after SABR. The authors have no other conflicts of interest to declare.

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