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Follow-up of patients after stereotactic radiation for lung cancer: a primer for the nonradiation oncologist.

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Follow-Up of Patients after Stereotactic Radiation for Lung Cancer

A Primer for the Nonradiation Oncologist

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Background: The use of stereotactic ablative radiotherapy (SABR) as primary treatment for early stage non–small-cell lung cancer, or for ablation of metastases, has increased rapidly in the past decade. With local recurrence rates reported at approximately 10%, and a patient population that is becoming increasingly fit and amenable to salvage treatment, appropriate multidisciplinary follow-up care is critical. Appropriate follow-up will allow for detection and management of radiation-related toxicity, early detection of recurrent disease and differentiation of recurrence from radiation-induced lung injury.

Methods: This narrative review summarizes issues surrounding follow-up of patients treated with SABR in the context of a multidisciplinary perspective. We summarize treatment-related toxicities including radiation pneumonitis, chest wall pain, rib fracture, and fatal toxicity, and highlight the challenges of early and accurate detection of local recurrence, while avoiding unnecessary biopsy or treatment of benign radiation-induced fibrotic lung damage.

Results: Follow-up recommendations based on the current evidence and available guidelines are summarized. Imaging follow-up recommendations include serial computed tomography (CT) imaging at 3–6 months posttreatment for the initial year, then every 6–12 months for an additional 3 years, and annually thereafter. With suspicion of progressive disease, recommendations include a multidisciplinary team discussion, the use of high-risk CT features for accurate detection of local recurrence, and positron emission tomography/CT SUV_{max} cutoffs to prompt further investigation. Biopsy and/or surgical or nonsurgical salvage therapy can be considered if safe and when investigations are nonreassuring.

Conclusions: The appropriate follow-up of patients after SABR requires collaborative input from nearly all members of the thoracic multidisciplinary team, and evidence is available to guide treatment decisions. Further research is required to develop better predictors of toxicity and recurrence.

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Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiotherapy (SBRT), has become a standard treatment for inoperable, early stage non–small-cell lung cancer (NSCLC). SABR uses highly conformal radiotherapy plans, with rigorous patient setup procedures, to deliver large, ablative doses of radiotherapy in only a few treatment sessions, often between 1 and 8 fractions (Fig. 1). SABR differs from older radiotherapy techniques in several regards: overall treatment time is much shorter (usually 1–2 weeks duration versus 4–6 weeks, respectively); the dose per fraction is much larger (often 18 Gy per day, rather than 2 Gy per day, respectively); and SABR treatment plans allow for large "hot spots" within the tumor, sometimes more than 150% of the prescribed dose.

These differences in treatment planning and delivery are associated with increased biologic potency: local control rates after SABR are often reported as ~90% at 3 years.[1,2] In light of these promising outcomes, and the relative convenience of SABR delivery using only a few fractions in an outpatient setting, the use of SABR in clinical practice for treating primary lung cancers and oligometastatic disease has increased rapidly.[3–5] These high rates of local control have led to suggestions that SABR may be as effective as surgical resection for the primary treatment of T1N0 or T2N0 NSCLC,[6] a suggestion that has led to debate and the launch of randomized comparisons with lobectomy or wedge resection as primary treatment in operable patients.[6,8] Unfortunately, three such randomized trials have closed because of a lack of accrual; as a result, randomized comparisons with surgery will not be available in the near future.

The assessment of patients after SABR is an increasingly common scenario for the multidisciplinary team: not only are increased numbers of inoperable patients receiving SABR for lung cancer or oligometastatic disease but the use of SABR for borderline or potentially operable patients is also increasing.[8] SABR recipients are increasingly fit with longer life expectancies, resulting in increased opportunity for surgical or nonsurgical salvage. For patients with local progression

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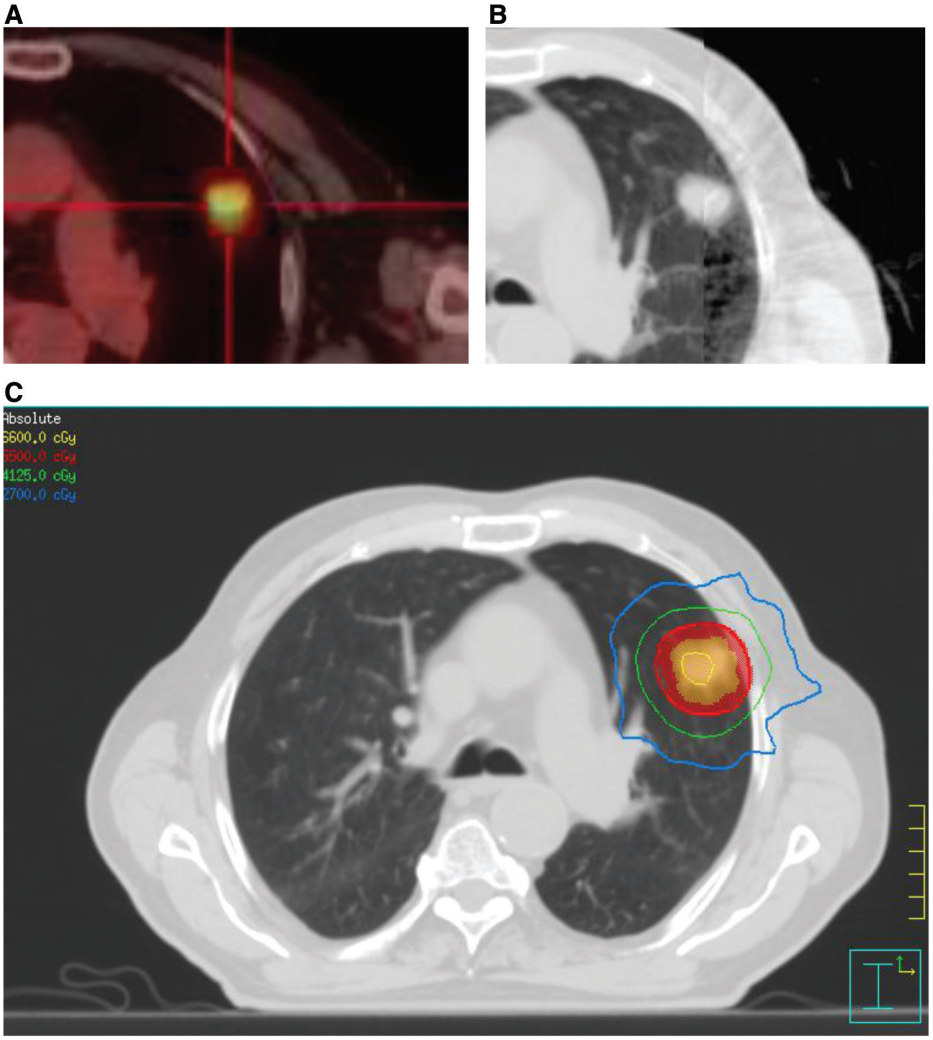

FIGURE 1. 90-year-old man with severe COPD (GOLD III) presents with a biopsy-proven left lung cancer, treated with stereotactic radiotherapy (54 Gy in three fractions). Representative axial images correspond to: *A*, PET/CT. *B*, Patient setup, with ConeBeam CT matched to planning CT to confirm setup accuracy. *C*, SABR treatment plan. COPD, chronic obstructive pulmonary disease; PET, positron emission tomography; CT, computed tomography; SABR, stereotactic ablative radiotherapy.

detected after SABR, several options may be associated with long-term survival, including surgical resection, targeted agents for patients harboring oncogene mutations, or in selected cases, repeat irradiation.[9–11] These posttreatment decisions often require collaboration between members of the thoracic multidisciplinary team, including radiation oncologists, surgeons, radiologists, pulmonologists/respirologists, pathologists, and medical oncologists. This overview will discuss common clinical and radiologic findings after SABR to help guide these multidisciplinary decisions.

Radiation Pneumonitis after SABR

With older conventional radiotherapy techniques for lung cancer, reported rates of radiation pneumonitis (RP) often ranged from 13% to 37%.[12] Symptomatic RP is characterized by cough or dyspnea, often accompanied with fever, chest discomfort and pleuritic pain, sometimes requiring oxygen or hospitalization. Alternative diagnoses include infection, chronic obstructive pulmonary disease (COPD) exacerbation, recurrent tumor, lymphangitic carcinomatosis, among other entities,[13] and in approximately 50% of cases, accurate diagnosis of RP is difficult.[14] The standard first-line treatment of symptomatic RP is oral corticosteroid therapy. Response is usually rapid, and response rates of up to 80% have been reported.[15] Less commonly, intravenous corticosteroids, oxygen support, and hospitalization may also be required. When discontinuing steroid therapy, slow tapering of corticosteroid is important to prevent relapse of symptoms.[16]

Because of the relatively small lung volumes irradiated to high doses during SABR, the development of dyspnea or RP after SABR is uncommon. In a multicenter prospective trial of 55 patients with inoperable stage I NSCLC receiving SABR (RTOG 0236),[17] the rate of grade 3 or 4 pulmonary or respiratory-tract-specific toxicity was 16%, and the rate of protocol-specified hypoxia or pneumonitis was 8%. In a meta-analysis of 11 observational studies of SABR (mostly prospective), the rate of severe (grade ≥ 3) RP following SABR was only 2%, with 0.8% of patients developing irreversible dyspnea.[18]

A recent randomized trial of 102 patients with T1 or T2N0 NSCLC compared stereotactic radiotherapy (66 Gy in three fractions) versus high-dose conventional radiotherapy (70 Gy in 35 fractions over 7 weeks). In the conventional arm,

a 2 cm margin (compared with 0.5 cm for SABR) was added around the tumor to account for targeting uncertainties with the older technique. The trial, reported thus far in abstract form only, demonstrated that with these large margins, conventional RT was able to achieve similar local control as SABR, but with increased toxicity (RP rates 16% in the SABR arm versus 34% in the conventional arm). SABR was favored due to lower toxicity and much shorter treatment duration.[19]

SABR appears to be well tolerated in patients with severe COPD, regardless of oxygen dependence. In a retrospective study of 265 patients treated with SABR, the risk of RP ≥ Grade 1 was lower in patients with severe COPD, defined as a Global Initiative for Chronic Obstructive Lung Disease (GOLD) score of III or IV (odds ratio [OR] of RP 0.37 for GOLD III, compared with patients with GOLD 0, $p < 0.01$).[20] Treatment-related mortality is also low: a systematic review of the literature comparing surgery to SABR in 176 patients with severe COPD (defined as GOLD score III or IV or a predicted postoperative forced expiratory volume in 1 second (FEV_1) of ≤ 40%), showed a 30-day mortality of 10% versus 0% respectively, favoring SABR. Local and locoregional control rates were excellent in all identified studies with either surgery or SABR (≥ 89%).[21]

Certain subgroups of patients may be at higher risk of RP, including patients with large tumors, and those with interstitial lung disease (ILD). In a small study of 18 patients with large tumors (defined as a planning target volume greater than 80 cc) treated with SABR, the crude risk of RP was 26%, and was closely correlated with several factors, particularly the volume of contralateral lung receiving a low-dose bath (≥ 5 Gy) of radiation.[22] In one study, ILD was associated with an increased risk of severe and fatal RP of 26% versus 3% (crude rates, $p < 0.001$).[23] Because many patients with ILD are also at high risk of operative morbidity and mortality, SABR can be reasonably considered with caution after a patient discussion regarding risks and benefits, and attempts to optimize a patient's baseline status before treatment.

Studies reporting on effects of SABR on pulmonary function show only small declines in pulmonary function. A retrospective study of 141 patients treated with SABR who underwent pre- and posttreatment pulmonary function tests (PFTs) detected only small declines in FEV_1 or forced vital capacity (FVC), with statistical significance limited to patients with good baseline pulmonary function (i.e., mild/moderate COPD).[24] Nonsignificant declines in FEV_1 were reported in another study of 92 patients, with declines in FEV_1 of 1.88% predicted and in carbon monoxide diffusion capacity (DLCO) of 2.59% predicted.[25] In RTOG 0236 described above, the mean decline in percent predicted FEV_1 was 5.8% and in DLCO was 6.3% at 2 years, which did not meet statistical significance. Furthermore, baseline PFTs did not predict pulmonary toxicity or overall survival.[26] Patient-reported quality-of-life data also confirms a lack of quality-of-life decline after SABR.[27]

Radiographic Patterns of Lung Injury Following SABR

Although symptomatic RP after SABR is uncommon, radiographic radiation-induced lung injury (RILI) occurs frequently, as a result of the ablative doses of radiotherapy delivered to the peritumoral region. RILI can mimic a local recurrence (Fig. 2) both in morphologic appearance and time course, leading to an important clinical dilemma: how to accurately distinguish recurrence from fibrosis and determine when a biopsy or other intervention is warranted. This distinction is particularly important for an increasingly fit SABR patient population, where salvage options may still be considered, including surgical resection, reirradiation, combined chemoradiotherapy, or palliative local or systemic therapy.

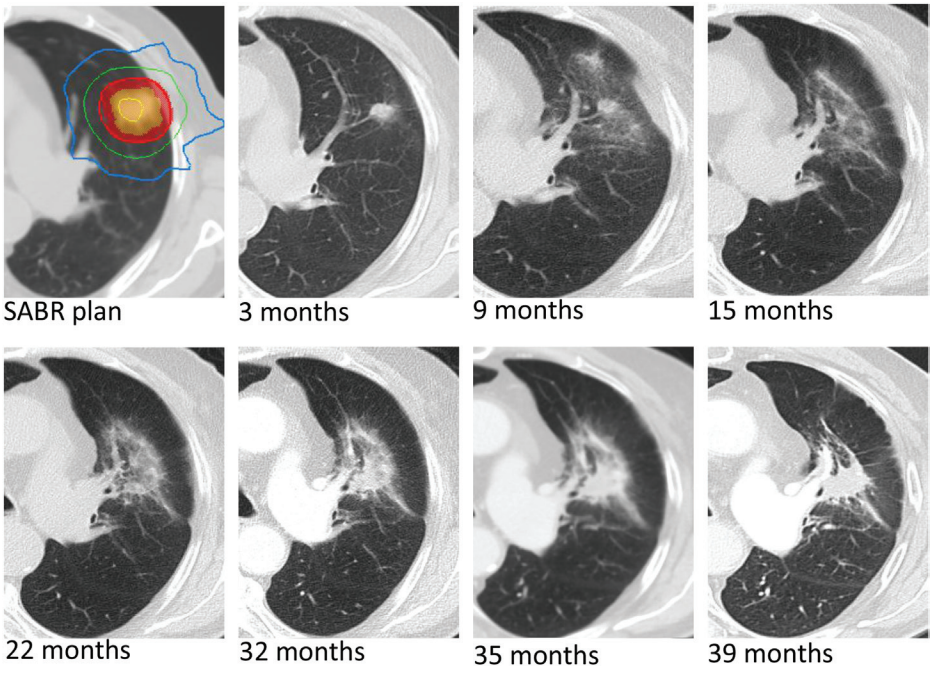

FIGURE 2. SABR plan and follow-up imaging for the patient described in Figure 1. Serial CT chest follow-up were scans obtained at 3, 9, 15, 22, 32, 35, and 39 months after radical treatment. The patient was not a candidate for salvage interventions and thus was monitored throughout without repeat biopsy. There was no change in RECIST measurement beyond 32 months. SABR, stereotactic ablative radiotherapy; CT, computed tomography.

Inaccurate classification as benign radiation lung injury can confound timely detection and delay treatment of disease progression. Alternatively, inaccurate classification of RILI as local recurrence can lead to unnecessary biopsy or even salvage treatment with its associated risk of morbidities; biopsy or resection of pseudoprogression has been reported in several case studies in the literature.[28–30]

RILI can be classified as RP in the acute setting (within 6 months of treatment), and pulmonary fibrosis in the late setting (after 6 months and beyond). The degree of lung injury depends on multiple factors, including total dose and fractionation of irradiation, along with target size.[31] RILI is reported to occur in 62% of patients treated with SABR in the acute setting, and in 91% of patients in the late setting, with the majority of patients remaining clinically asymptomatic.[32] Radiologic signs of fibrosis can potentially evolve even 2 years after treatment or beyond and does not follow a known predictable course.[33]

Common patterns encountered on computed tomography (CT) radiographic imaging have been classified as, in the acute setting: consolidative or ground-glass opacity changes, each subdivided into diffuse (greater than 5 cm) or patchy (≤ 5 cm), and in the late setting: modified conventional, mass-like, or scar-like patterns.[33–35] Despite this distinct range of morphologies, these categories are not generally used to predict recurrence. Furthermore, considerable interphysician variability in assessments can result from the subjective nature of the current image evaluation criteria.[36] However, familiarity with common patterns of RILI may help facilitate diagnosis of local recurrence.

Challenges in Response Assessment

All follow-up imaging modalities have limitations in response assessment in the post-SABR setting. With CT alone, benign changes may appear as an evolving mass-like opacity, easily mistaken for local recurrence.[33,37] The standard evaluation of tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 presents challenges in the post-SABR setting, because these criteria rely on diameter alone to classify response, and increasing areas of fibrosis may meet the criteria for progressive disease. RECIST measurements should be done in the plane of image acquisition (axial for body CT).[38] Positron emission tomography (PET) also has limitations: acute inflammatory reaction within lung parenchyma exposed to ablative doses of radiation can result in falsely elevated metabolic activity suggestive of malignancy.[39,40] PET is more costly than CT and is not often a routine posttreatment investigation at many centers; and standardized uptake value (SUV) measurements are not fully quantitative and are dependent on more complex standardization procedures.[41]

Studies reporting on imaging predictors of response after SABR are limited by the lack of pathologic proof of recurrence for many patients, because of the relative frailty of the SABR patient population and/or the avoidance of biopsy where there is a lack of options for salvage in the event of a positive result. This lack of pathologic proof of recurrence may introduce bias, creating a circular argument whereby imaging is used to define the recurrence endpoint, and then the same imaging modality is investigated as a predictor of recurrence, overestimating the predictive ability of such tests.

A systematic review has identified certain radiographic high-risk features (HRFs) suggestive of recurrence after SABR as per Table 1.[32,43] To reduce the potential bias associated with imaging-defined recurrences, HRFs were validated using CT datasets from known pathology-proven recurrences, who were matched to nonrecurrences, in a blinded study.[43] The best HRFs in terms of both sensitivity and specificity were enlargement after 12 months and cranio-caudal growth of ≥ 5 mm and ≥ 20% (Table 1). The presence of three or more HRFs predicted local recurrence with high sensitivity and specificity (over 90%).

Functional imaging by FDG-PET can complement suspicious CT findings, although FDG avidity can appear transiently following SABR and even persist at a low value for over 12 months.[32] Lung injury following ablative radiotherapy can result in transiently increased metabolically activity resulting in false-positive FDG avidity. Such FDG avidity may lead to unnecessary biopsy of benign inflammatory tissue and has been described as "pseudoprogression" in several case reports.[29,44] Falsely elevated SUV_{max} readings of up to 7.0 has been detected shortly following SABR treatment in patients who ultimately were not classified as having progressive disease.[45] Although the data is highly heterogeneous, a posttreatment $SUV_{max} \geq 5.0$, or greater than the original pretreatment SUV_{max} appears most suggestive of recurrent disease.[32,46–48] In another study with 17 local recurrences, SUV_{max} cutoffs as low as 3.2 and 4.2 have been reported, with sensitivity and specificity of 100% and 96–98%, respectively; however, not all recurrences were pathologically proven.[49]

Other Adverse Effects of SABR

Patients receiving SABR are also at risk of nonpulmonary adverse effects. Approximately one-third of patients will experience fatigue,[50] which is usually self-limiting. Uncommon acute or sub-acute adverse effects can include skin toxicity, chest wall pain (CWP), and nausea, whereas late effects can include ongoing CWP, rib fracture, and rarely, injury to the mediastinal structures when SABR is delivered to centrally located tumors.

The incidence of CWP and rib fracture can be mitigated using a risk-adapted treatment strategy, whereby the risk of toxicity for tumors adjacent to the chest wall can be minimized by giving SABR over more fractions (i.e., using a smaller daily dose). Based on radiobiological modeling,

TABLE 1. High-Risk Features on CT Predictive of Local Recurrence[43]

High-Risk Feature	Sensitivity (%)	Specificity (%)
Enlarging opacity at primary site	92	67
Sequential enlargement	67	100
Enlargement after 12 months	100	83
Bulging margin	83	83
Linear margin disappearance	42	100
Loss of air bronchogram	67	96
Cranio-caudal growth of ≥5 mm and ≥20%	92	83

CT, computed tomography.

smaller daily fraction sizes can substantially decrease the risk of late side effects.[51] In a study cohort of 42 patients treated with stereotactic radiotherapy doses of 54–60 Gy delivered over only three fractions to all patients regardless of tumor location, high rates of chest wall toxicity were observed, with nine patients developing rib fracture.[52] Alternatively, using a risk-adapted radiation treatment scheme as described above and delivering 55 Gy over five fractions (two additional fractions) for tumors abutting the chest wall, lower toxicity rates have been achieved, with reported CWP and rib fracture of only 11.4% and 1.6%, respectively.[53] A separate study of 69 patients used a similar risk-adapted approach, delivering either 54 Gy in three fractions, or 50–60 Gy in five fractions, the latter in patients with significant chest wall dose. The authors report a low incidence of chest wall toxicity at 20 months posttreatment, with chest wall pain in six patients (8.3%; one [1.4%] grade 3, as per CTCAE version 4.0) and rib fracture in five patients (6.9%).[54]

Fatal toxicity has been reported in the treatment of central tumors or tumors located within 2 cm of major structures such as the bronchial tree, trachea, or major vessels—accordingly termed the "no fly zone" in SABR—particularly when such tumors are treated with three-fraction regimens. These excessive toxicities were most notably reported in a prospective phase II trial of medically inoperable early stage lung cancer of 70 patients, where patients were treated with the equivalent of approximately 54 Gy in three fractions, and the 2-year freedom from severe toxicity was 83% for patients with peripheral tumors and only 54% for patients with central tumors.[55] In a 4-year update, severe toxicities occurred in 10.4% of patients with peripheral tumors and 27.3% of patients with central tumors ($p = 0.088$).[56] A case of central airway necrosis following SABR treatment to a central tumor has also been well described.[57] The risk of severe toxicity appears to be closely related to dose and fractionation. In a systematic review of 315 patients with centrally located tumors treated by SABR using various fractionation schemes, overall treatment-related mortality rate was reported at 2.7% and rates of Grade 3 or 4 toxicities were less than 9%.[58] The authors observed a dose–response relationship for toxicity, with a 75% reduction in treatment-related mortality (from 2.7% to 1%) when patients receive a lower biologically effective dose, ≤ 210 Gy[3] (a measure of the biologic effect of radiation on a particular tissue, taking into account radiation dose per fraction and total dose). In a recent study of 100 patients with centrally located tumors, the most common toxicity was chest wall pain (18% grade 1, 13% grade 2) followed by RP (11% grade 2, 1% grade 3) with no grade 4–5 toxicity noted.[59] For a more in-depth review of the issues regarding treatment of central tumors with stereotactic radiation, the reader is referred to the relevant article in this IASLC series.[60]

Toxicities related to SABR in a reirradiation scenario, either as primary or salvage treatment for local recurrence, a secondary lung primary, or metastases, has been described in a limited number of small retrospective studies and in a systematic review. In a study of 39 patients who were treated with salvage SABR following conventional radiotherapy, 23% of patients had grade 2–3 RP, 3% had grade 4 skin toxicity, and no grade 5 toxicity was reported.[61] In a similar larger study of 72 patients, salvage SABR following prior radiotherapy resulted in 20.8% of patients with severe RP (≥ grade 3), with one grade 5 fatality (~1%). Grade 5 toxicity rates, however, vary greatly among studies and fatality has been reported in as high as 12% of patients.[62] In a repeat SABR scenario, Peulen et al. reported on 32 lesions in 29 patients, with 17% grade 4–5 toxicity and 10% ($n = 3$) grade 5 toxicity consisting of massive hemoptysis. Notably, all patients with severe toxicity had centrally located tumors. Overall in the systematic review, of 19 studies involving 466 patients that reported on SABR in various reirradiation scenarios, the rates of grade 1–3 RP, grade 4 toxicity and fatal toxicity was reported in 124 (27%), 2 (less than 1%) and 8 patients (1.7%), respectively.[62] The data suggests that toxicity may be increased in a repeat reirradiation scenario and repeat SABR should be considered with caution. Given most fatal toxicities occurred in patients treated for centrally located tumors, repeat irradiation of such lesions should be avoided or given with caution.

Toxicities following the treatment of multiple primary lung cancers by SABR have also been reported. In one study, synchronous lesions treated to a dose of 54–60 Gy in 3–8 fractions were described in 56 patients, and no Grade 4–5 toxicities were observed after a median follow-up of 44 months.[63] Given a favorable toxicity profile, and 85% lesional control rates, the authors conclude multiple SABR treatments for multiple primary lung cancers without nodal metastasis can be considered as a radical treatment option. Another study where SABR represented the second treatment after an index/dominant tumor was treated by any modality, grade ≥ three RP was also low, reported in 2 of 71 patients (3%).[64]

General Follow-Up Recommendations

Follow-up recommendations, including the frequency and duration of follow-up imaging for lung cancer survivors, are based nonrandomized studies. A retrospective study on the patterns of recurrence following SABR in a large cohort of 124 patients with disease recurrence from the Netherlands showed the vast majority of recurrences occurred within the first 3 years after treatment[1]; a corresponding posttreatment CT imaging follow-up has been proposed at 6-month intervals for the first 3 years, and annually thereafter.

Published consensus guidelines are also available. The American Association for Thoracic Surgery guidelines, applicable to lung cancer survivors eligible for additional therapy, recommend high-resolution surveillance CT scans every 6 months during an initial 4-year surveillance period; in the absence of concerning signs of recurrent disease, the frequency of follow-up imaging can be reduced to an annual low-dose screening CT, to account for the risk for a second lung cancer diagnosis of 3% per year.[65] National Comprehensive Cancer Network guidelines recommend imaging surveillance with a chest CT scan (contrast optional) every 6–12 months for 2 years, then a noncontrast-enhanced chest CT scan annually, in the absence of clinical/radiographic evidence of disease.[66]

Consolidating the various published guidelines as summarized above, a general approach to follow-up of patients following SABR treatment should include physical assessment every 3–6 months during the initial year

following treatment, followed by every 6–12 months for 3 years, then annually thereafter. Exact frequency and duration of follow-up can be left to the discretion of the treating physician's clinical assessment. For example, the presence of CT findings on follow-up imaging may prompt more frequent imaging.

In the setting of suspicious findings on imaging, guidelines for follow-up of patients after SABR are currently lacking. A systematic follow-up imaging algorithm based on HRFs and SUV_{max} thresholds based on current evidence is available for reference and provides literature-based guidelines for management until further evidence becomes available.[43] This algorithm combines high-risk CT features and FDG-PET as tools for the prediction and accurate diagnosis of local recurrence. Patients are categorized as having a low-, intermediate-, or high-risk of recurrence based on the number of high-risk CT features present (no HRFs, 1–2 HRFs, or ≥ 3 HRFs, respectively). Subsequent management is based on this risk stratification: low-risk patients with no HRFs can be imaged every 3–6 months for 1 year, after which an imaging interval of 6–12 months can be considered; intermediate-risk patients with the presence of 1–2 HRFs can benefit from an FDG-PET/CT if available and close follow-up; patients at high-risk of recurrence with the presence of more than three HRFs can be investigated with a biopsy or can proceed directly to salvage treatment. When available, SUV_{max} values that are either greater than five, or exceeding pretreatment SUV_{max} values, trigger additional interventions including biopsy, resection, or nonsurgical salvage. Applicability of this follow-up scheme depends on the specific clinical scenario, and recommendations are expected to change as more data becomes available. More rigorous follow-up and early investigation for any suspicion of disease progression may also be justified in patients with known pretreatment risk factors for local recurrence such as larger lesions (T2), suboptimal radiation dose, and perhaps high pretreatment SUV_{max}.[47,67,68]

Whenever possible, lung cancer patients with suspicious findings on radiographic follow-up scans who are amenable to salvage treatment should be discussed by a multidisciplinary team. Salvage surgery after SABR appears to be safe: at least four small studies have reported on patients who have undergone surgery for salvage of a post-SABR recurrence.[69–72] Across these four studies, such surgery is generally well tolerated with a favorable toxicity profile, with only one patient sustaining a major toxicity (fistula requiring further surgery for correction).[71] Salvage repeat irradiation in the setting of SABR has shown good outcomes in terms of local control, and overall survival, although toxicity is likely higher, as described above. Reirradiation with SABR as either primary or salvage treatment resulted in local control rates ranging from 65.5% to 75% at 1 year.[62]

Future Directions

The results of ongoing research in response assessment will continue to shape the optimal imaging and follow-up guidelines for lung cancer patients in the coming years. Large studies examining patients with pathologic proof of recurrence would be ideal to investigate and test new imaging biomarkers. Given the relative uncommon clinical scenario of local recurrence that is confirmed pathologically, multi-institutional efforts would be required to assemble such data. New quantitative methods such as CT image feature analysis and further characterization of posttreatment FDG-PET SUVs[73] and other biologic markers are emerging.[74,75] Ultimately, further study is needed to help reduce physician uncertainties in imaging response assessment, which is becoming an increasingly critical aspect of survivorship for patients undergoing SABR for NSCLC and their physicians within the multidisciplinary team.

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