Imaging of Novel Oncologic Treatments in Lung Cancer Part 2
Local Ablative Therapies

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Abstract: Conventional approaches to the treatment of early-stage lung cancer have focused on the use of surgical methods to remove the tumor. Recent progress in radiation therapy techniques and in the field of interventional oncology has seen the development of several novel ablative therapies that have gained widespread acceptance as alternatives to conventional surgical options in appropriately selected patients. Local control rates with stereotactic body radiation therapy for early-stage lung cancer now approach those of surgical resection, while percutaneous ablation is in widespread use for the treatment of lung cancer and oligometastatic disease for selected other malignancies. Tumors treated with targeted medical and ablative therapies can respond to treatment differently when compared with conventional therapies. For example, after stereotactic body radiation therapy, radiologic patterns of posttreatment change can mimic disease progression, and, following percutaneous ablation, the expected initial increase in the size of a treated lesion limits the utility of conventional size-based response assessment criteria. In addition, numerous treatment-related side effects have been described that are important to recognize, both to ensure appropriate treatment and to avoid misclassification as worsening tumor. Imaging plays a vital role in the assessment of patients receiving targeted ablative therapy, and it is essential that thoracic radiologists become familiar with these findings.

Key Words: thoracic malignancy, lung cancer, response assessment, stereotactic body radiation therapy, percutaneous lung ablation

(*J Thorac Imaging* 2020;35:37–48)

LEARNING OBJECTIVES

After completing this CME activity, physicians should be better able to:

1. Assess the role of targeted ablative therapies in lung cancer, namely stereotactic body radiation therapy (SBRT) and percutaneous ablative therapy.
2. Outline the patterns of response and recurrence with novel ablative therapies compared with conventional therapies.
3. Identify imaging finding of thoracic-related adverse events associated with targeted ablative therapies.

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This research was funded in part by the National Institute of Health/National Cancer Institute Cancer Center Support Grant P30 CA008748.

The authors, faculty and all staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial organizations relevant to this educational activity.

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DOI: 10.1097/RTI.0000000000000452

Lung cancer is the leading cause of cancer-related morbidity and mortality.[1] The advent of targeted therapy in oncology has dramatically changed the treatment of thoracic tumors.

In addition to novel targeted medical treatments, developments in the areas of interventional oncology and radiation therapy have led to the routine use of percutaneous ablative therapies and novel forms of radiation therapy, such as stereotactic body radiation therapy (SBRT) (also known as stereotactic ablative radiotherapy), as viable alternative treatment options in medically inoperable patients.[2–5] For example, local control rates when SBRT is used to treat appropriately selected patients with early-stage non–small cell lung cancer (NSCLC) now approach those of surgical resection.[3–5] Both SBRT and percutaneous ablation are also used in the context of oligometastatic or limited metastatic thoracic disease from other malignancies.[6,7]

Imaging findings, when targeted ablative therapies are used, can differ from those seen following the use of conventional radiation and surgical techniques. It is crucial that radiologists become familiar with these novel therapeutic options and are aware of the expected posttherapy imaging findings. We aimed to review the clinical background of SBRT and percutaneous ablative therapies in the treatment of lung cancer, to describe expected posttreatment radiologic findings, and to summarize approaches to radiologic response assessment.

PERCUTANEOUS LUNG ABLATION

Overview of the Therapeutic Approach

The standard of care for early-stage primary lung cancer is surgical resection.[8] In addition to surgery, local therapies available for patients with small malignant nodules include SBRT and percutaneous ablative therapies (thermal and nonthermal).[9] The rationale for percutaneous ablation relates to the fact that, in the lung, there is natural temperature insulation and low electrical conductivity, which results in large ablation volumes requiring less effective energy[10] (Fig. 1).

Traditionally, radiofrequency ablation (RFA) has been used as the thermal ablation modality[9]; however, the effectiveness of the technique can be decreased due to the cooling effect of bronchi/vessels in the proximity of the targeted lesion.[11–13] In order to overcome these limitations, multiple probes can be used, although only one probe can be activated at a time.[14] Because of these technical challenges, other technologies have been developed that attempt to overcome the technical

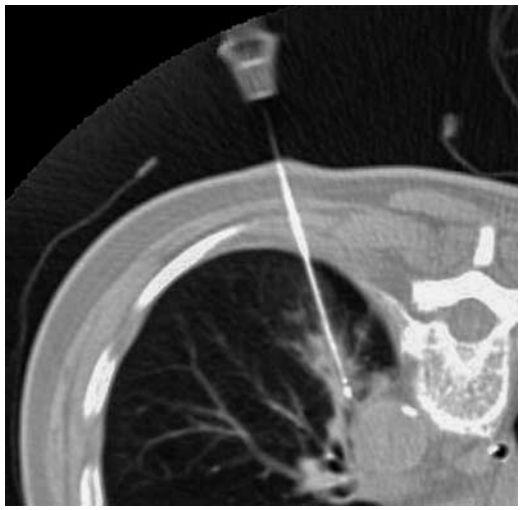

FIGURE 1. Coned CT image during percutaneous ablation of a left lung neoplasm demonstrating the tip of the probe in the treated lesion.

challenges of RFA. Microwave ablation,[15] cryoablation,[16] and irreversible electroporation[17] all allow simultaneous energy delivery through several probes activated at the same time with a synergistic effect.

Microwave ablation, by working at higher temperatures, demonstrates lower convective cooling close to large vessels, although the reproducibility and sphericity of the ablation zone is still a challenge, especially for lesions > 3 cm.[14,15,18] Cryoablation causes ice formation within the extracellular space, resulting in cellular dehydration,[16] cell membrane rupture, and local tissue ischemia. Electroporation is a nonthermal ablation process that causes cell death by irreversibly creating membrane pores due to the transmission of a high-voltage short-duration electric pulse with preservation of adjacent vulnerable structures.[17]

Early reports of the use of percutaneous thermal ablation in primary NSCLC demonstrated a median survival of 30 months for stage IA and 25 months for stage IB,[19] while a recent case series in patients with recurrent NSCLC after surgery demonstrated 1-, 3-, and 5-year overall survival (OS) rates of 97.7%, 72.9%, and 55.7%, respectively.[20] Tumor size, histopathology, and preablation clinical comorbidities are all important predictors of survival following ablation. For example, when lesions are stratified by size, the 1- and 3-year OS rates have been reported as 100%, 79.8%, and 60.5% in patients with tumors measuring <3 cm, compared with 1- and 3-year OS rates of 83.3% and 31.3% in patients with tumors measuring 3 to 4 cm.[15,18,20–23]

Comparative studies of lung RFA and other treatments are rare, with numerous biases and different sample sizes.[22] A case series comparing sublobar resection, RFA, and cryoablation in patients with stage I NSCLC medically unfit for standard resection, showed no difference in 3-year OS, cancer-specific survival, and cancer-free survival,[21] with longer hospital stays in the surgical group. In a matched cohort study of patients with stage I NSCLC comparing surgery and RFA, patients treated surgically had a mean survival of 45.5 months compared with 33.2 months for those treated with RFA; however, log-rank analysis demonstrated no significant difference in OS between the 2 groups.[8]

SBRT typically demonstrates higher locoregional control when compared with percutaneous ablation; however, in the most recent Surveillance, Epidemiology and End Results Program (SEER) database study, thermal ablation for the primary treatment of stage 1 NSCLC was noninferior to SBRT in terms of OS.[22] Overall, good tolerance and lung function preservation have been demonstrated in the ablation literature, which, at the end, allows for retreatment when required.[11,12,23,24] In addition, the ability to repeat treatment in the same location is higher with thermal ablation than with SBRT.[25]

Response Assessment Using Imaging

Immediately following ablation, computed tomography (CT) typically demonstrates an area of ground-glass opacity (GGO) that may also contain air foci surrounding the treated tumor. In addition, there may be several concentric ring-like opacities within the GGO that are felt to demarcate distinct histopathologic zones around the tumor, with the overall opacity on CT representing (from center to periphery) (i) coagulated tumor centrally, (ii) coagulated pulmonary parenchyma; (iii) mixed coagulation necrosis and hemorrhage in pulmonary parenchyma, and (iv) surrounding inflammation.[10,26] The track of the ablation electrode is frequently visible after ablation and can remain visible for several months.[27]

Importantly, the GGO surrounding the treated tumor probably overestimates the area of adequately treated lung, and the outermost region of the GGO may contain viable tumor. It has been suggested that a GGO extending > 5mm from the tumor margin should be obtained to ensure an adequate ablation zone and to minimize the risk of local recurrence.[28] The adequacy of ablation may be affected by clinical factors such as the presence of large adjacent vessels and the size of the tumor. Several authors have reported a larger ablation zone as predictive of a complete response.[12]

With time, the treated area increases in density and becomes more well defined. By 1 month, the area of GGO has typically been replaced by a dense opacity. Cavitation occurs in up to 31% of treated lesions in the first 3 months.[29] Up to 3 months after ablation, the opacity will gradually reduce in size but will generally remain larger than the treated tumor. By 6 months, the opacity will typically be smaller than the treated tumor. Figure 2 demonstrates the typical evolution of post-ablation change. This pattern of gradual reduction is important to document, and any size increase after 3 to 6 months should be treated as suspicious for recurrence.[29] New or increasing peripheral nodularity within the treated lesion, new or increasing lesional enhancement, or new satellite nodularity around the lesion or along the track of the electrode are all suspicious for local recurrence (Fig. 3). Regional nodal enlargement can be seen as a transient reactive phenomenon following ablation, typically within the few months after ablation, and lymphadenopathy at this stage should be interpreted with caution to avoid an incorrect diagnosis of metastatic disease.[30]

Using dynamic CT contrast enhancement is a potential means for assessing the response in ablated lung tumors.[27,31,32] Lesional enhancement markedly decreases in the first 2 months following ablation, probably due to disruption of the perilesional microcirculation. In the initial weeks following ablation, there may be a thin (< 5 mm) rim of periablation enhancement, which is benign and reflects reactive hyperemia and which can persist for several months.[15,33,34] Some authors have described mild enhancement centrally within the ablated lesion at 3 months following ablation, possibly due to recovery of the local microcirculation[32]; however, after 3 months, central enhancement, particularly if it is nodular, progressive over multiple scans, > 15 HU compared with precontrast CT, or greater than enhancement in the preablation tumor, should be treated with suspicion.[35]

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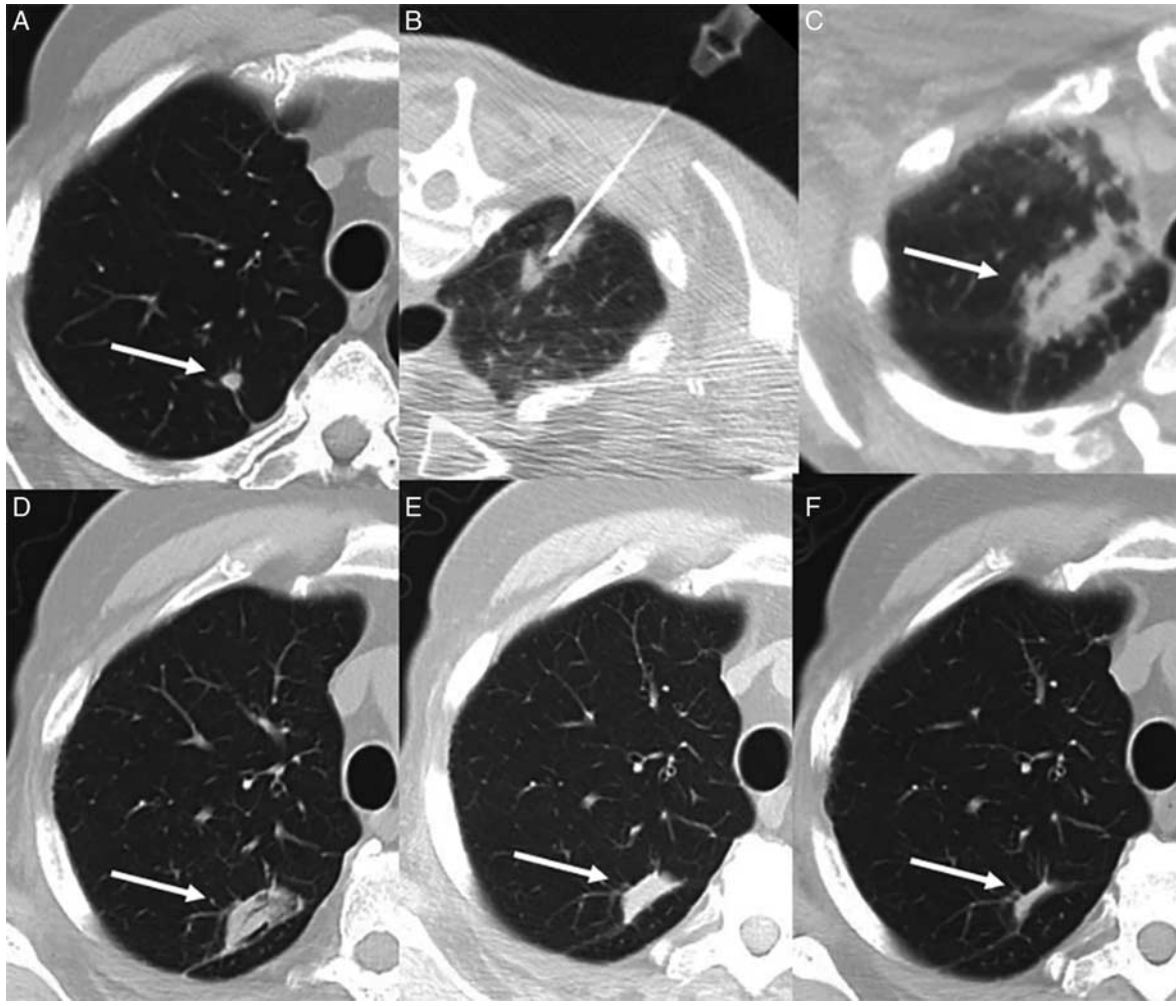

FIGURE 2. Evolution of percutaneous ablation changes on CT. A, Pretreatment CT demonstrating right upper lobe lung adenocarcinoma (arrow). CT during percutaneous radiofrequency ablation (B), and immediate postprocedure CT demonstrating GGO surrounding the tumor (arrow) (C). D, CT, 1 month after treatment, demonstrates dense opacity with early cavitation at the site of previous tumor and larger than the original tumor (arrow). E, CT, 3 months after treatment, demonstrates dense opacity with resolution of cavitation (arrow). F, CT, 12 months after treatment, demonstrates continued reduction in the size of the post-treatment opacity (arrow).

Because a successfully treated lesion is replaced by a posttreatment opacity that is initially larger than the original tumor, traditional size-based assessments of tumor response, such as Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1), which measure a lesion in its maximum diameter, are inadequate for characterizing tumor response. This is particularly true in the early posttreatment phase when a RECIST-based assessment would likely incorrectly characterize a treated lesion as progressive disease.[36]

A modified version of the RECIST criteria has been proposed as an alternative response assessment tool following lung ablation, and it takes into account lesion size (as per RECIST 1.1), lesion morphologic characteristics, and positron emission tomography (PET) uptake.[37] Using this system, for progressive disease to occur, a lesion must demonstrate at least 2 of the following characteristics: size—increase $>20\%$ in longest diameter; morphology—solid mass with invasion of adjacent structures; PET characteristics—increased standardized uptake value (SUV) or larger area of ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) uptake.[37]

The Society of Interventional Radiology (SIR) states that the optimal strategy for imaging follow-up after ablation remains to be defined, but suggests than an initial CT scan be performed early after ablation (within the first 1 to 3 mo), which should act as a new baseline for follow-up. Subsequent CT imaging should be performed at regular intervals, and SIR suggests every 3 to 4 months; these follow-up CT studies should be compared with the "new baseline" CT rather than the preablation CT.[38] SIR also recommends that imaging studies following lung ablation be reported according to the reporting guidelines suggested by the SIR Technology Assessment Committee and the International Working Group on Image Guided Tumor Ablation.[39,40]

No standardized protocol exists with regard to the use of PET/CT after ablation; however, it is a potentially useful imaging technique in this context. PET/CT may be alternated with CT during sequential follow-up[35] or alternatively used as a problem-solving tool when there are suspicious or equivocal CT findings.[34] PET/CT performed immediately after ablation is of limited value, as inflammatory FDG uptake will frequently obscure the treated tumor, with the degree of FDG uptake gradually decreasing after 2 weeks. Attempts have been made to identify suspicious patterns of FDG uptake on later scans. For example, Singnurkar and colleagues identified several patterns of FDG uptake on the

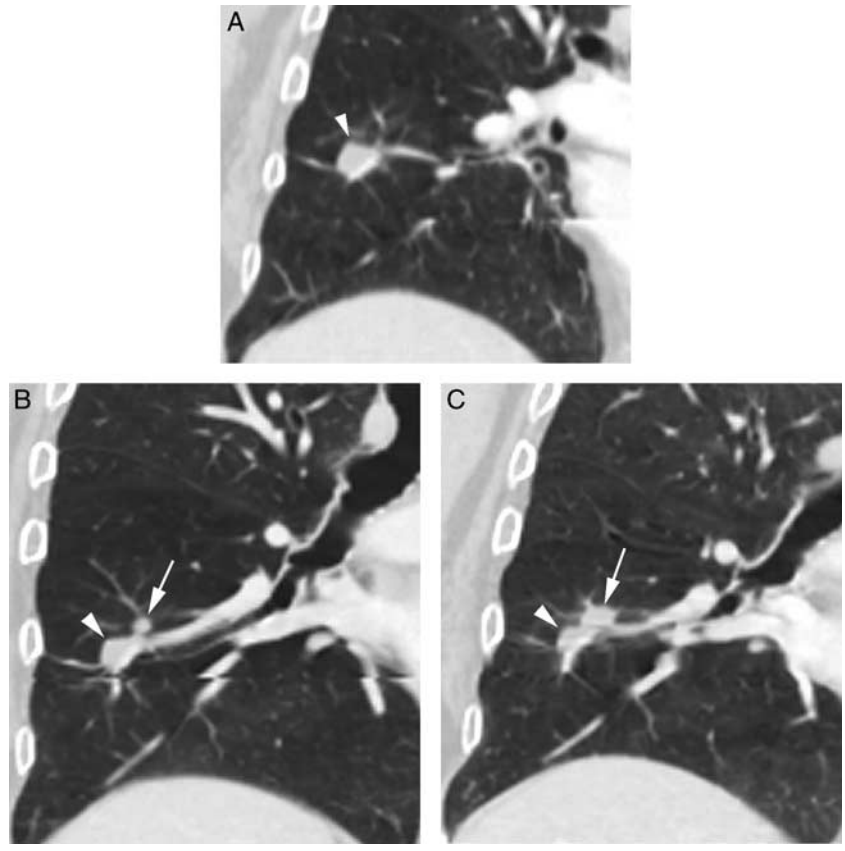

FIGURE 3. Local recurrence following percutaneous ablation. A, Coronal CT image obtained 1 year following percutaneous ablation of a right lung neoplasm demonstrating an opacity (arrowhead) at the treatment site, which is smaller than the treated lesion, consistent with an adequately treated lesion. B, CT obtained 1.5 years following ablation shows a new small nodule (arrow) immediately superior to the posttreatment opacity (arrowhead), suspicious for local recurrence. C, CT obtained 8 weeks after (B) showing further growth in the new nodule (arrow), immediately superior to the posttreatment opacity (arrowhead), consistent with local recurrence.

first postablation PET/CT (performed 1 to 4 mo after ablation): (i) diffuse, (ii) focal, (iii) heterogenous, (iv) rim, (v) rim plus focal uptake corresponding to the site of the original lesion, and (vi) rim plus focal uptake at a different location not corresponding to the site of the original lesion.[41] Uptake patterns deemed suspicious were (a) focal uptake, and (b) rim uptake with focal uptake corresponding to the original tumor nodule (Fig. 4). Of 12 patients with these patterns of uptake, 10 had a local recurrence. Lesions with recurrence also had a significantly higher SUV value than those without recurrence.[41] Other proposed suspicious findings on PET/CT include a reduction of <60% in SUV compared at 2 months with baseline SUV and increasing SUV values in the treated lesion after 2 months.[42] Similar to its recommendations for postablation CT imaging, SIR suggests that if PET/CT is to be performed as part of imaging follow-up, an early "new baseline" PET/CT study should be obtained, followed by PET/CT every 6 months.[38]

Imaging of Complications

Image-guided ablation of lung tumors is a generally safe procedure, with mortality rates of <1% in most large case series.[43–45] Reporting of major and minor complication rates has in many cases lacked standardization; however, when the Common Terminology Criteria for Adverse Events[46] was applied to a recent large retrospective cohort from Japan, minor complications (classified as grade 1 or 2 adverse events) were seen in up to 60% of patients, and major complications (classified as grade 3 or 4 adverse events) were seen in 10%.[44] In that series, the frequency of complications was significantly associated with the center's experience of performing ablation procedures. Major complications occurred in 19% of the first 100 cases and 9% of the remaining 900.[44]

Pneumothorax is the most common complication, encountered between 38% and 46% of cases[43,44] (Fig. 5). Most cases of pneumothorax can be managed conservatively with between 6% and 29% of cases requiring chest tube placement.[47] The large majority of pneumothoraces resolve following chest tube placement. The development of a persistent air leak/bronchopleural fistula is very rare and is probably associated with tumors that abut the visceral pleura.[44] Other complications include development of postprocedural pneumonia (2% to 6%), pleural effusion (4% to 13%), hemoptysis (4% to 9%), subcutaneous emphysema (9% to 16%), lung abscess (2%), aseptic pleuritis (2%), and empyema (0.3%).[43,44,48] Tumor seeding is a very rare phenomenon, seen in 0.1% of cases in a series of 1000 patients reported by Kashima et al.[44] Pain during ablation is common and is more frequent in patients with peripheral tumors, presumably due to the direct thermal effect on the chest wall tissues. Deliberate introduction of air or fluid into the pleural space can be used to minimize the thermal effect of ablation on the chest wall in patients with peripheral tumors.[27]

Risk factors associated with developing a pneumothorax include emphysema, ablation of multiple tumors at

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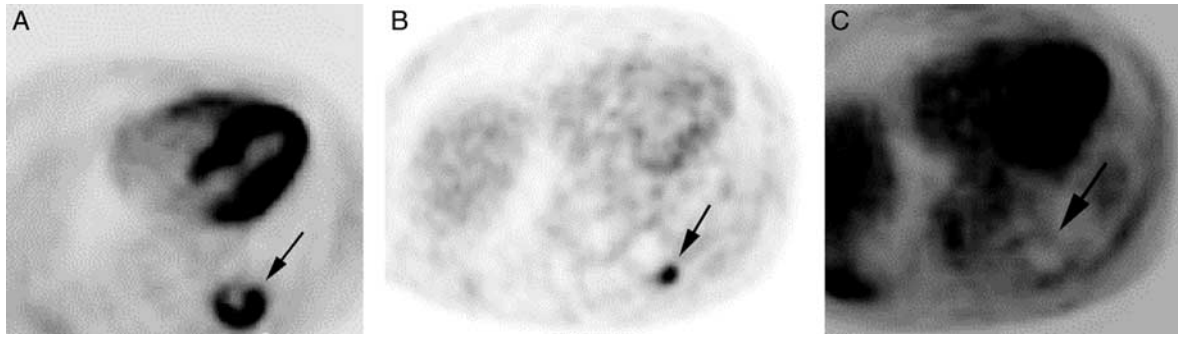

FIGURE 4. Suspicious PET findings following percutaneous ablation. A, Baseline axial attenuated corrected PET image preradiofrequency ablation for left-sided lung cancer shows an FDG-avid partially necrotic mass with SUV 10.9 (arrow). B, Axial attenuated corrected PET, 2 months after RFA, shows rim uptake but with focal uptake corresponding to the original tumor nodule (arrow), a pattern previously found to be suspicious for recurrence. C, Subsequent RFA of the mass was performed. PET image, 9 months after the salvage procedure, demonstrates rim uptake without focal uptake corresponding to the original tumor nodule, indicating response to treatment (arrow).

the same session, ablation of centrally located tumors, and ablation of tumors in the middle lobe or lower lobes.[44,45,47] Large tumor size and low platelet count have been identified as risk factors for hemorrhagic complications.[44] In a large retrospective study analyzing nationwide trends, neither pneumothorax nor the need for chest drain placement was associated with increased mortality.[43] Factors associated with increased postablation mortality include a Charlson comorbidity index score ≥ 4 (odds ratio [OR], 2.84), post-ablation respiratory failure/arrest (OR, 22.58), effusion (OR, 6.78), pneumonia (OR, 35.09), and empyema (OR, 53.25).[43]

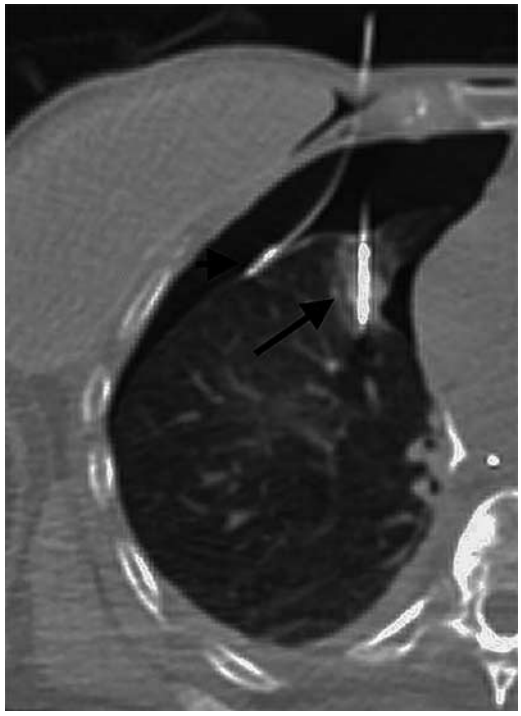

FIGURE 5. CT image obtained during percutaneous ablation of a right lung neoplasm demonstrating a right-sided pneumothorax. A percutaneous pleural drain has been inserted (small arrow). The ablation probe can be partially seen (large arrow).

SBRT

Overview of the Therapeutic Approach

The standard of care for operable, early-stage NSCLC remains lobectomy with mediastinal lymph node evaluation. For the treatment of medically inoperable patients, SBRT has been established as a highly effective and well-tolerated treatment. Advances in radiation treatment planning, motion management techniques, and on-board imaging over the last several decades have allowed for the development of SBRT. Radiation Therapy Oncology Group (RTOG) 0236 was the first North American multicenter prospective study of SBRT in early-stage NSCLC. RTOG 0236 helped increase the utilization of SBRT and established the high rates of disease control attributed to SBRT, with the initial publication finding the 3-year primary tumor and involved lobe control rate to be over 90%.[49]

By definition, SBRT requires the delivery of highly conformal ablative radiation doses in 3 to 5 fractions with exacting image guidance. Multiple arcs of radiation that converge at the target are utilized to allow for a sharp dose fall-off beyond the tumor that spares adjacent organs (Fig. 6). This contrasts to conventional radiation therapy that delivers 20 to 33 daily fractions of radiation with a larger treatment margin. Recent data from Trans-Tasman Radiation Oncology Group (TROG) 09.02 provide level 1 evidence on the superiority of

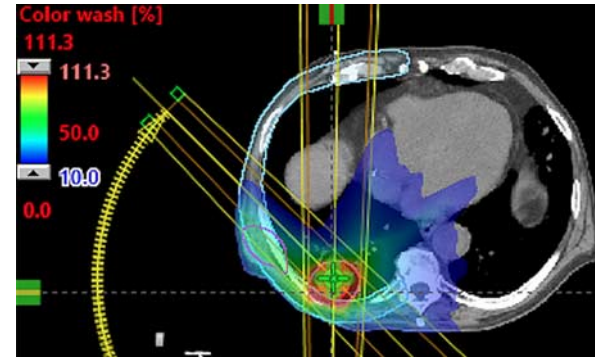

FIGURE 6. SBRT treatment plan: axial images demonstrating complex beam arrangement and steep radiation gradient of SBRT, which ensures a high dose to the tumor and minimizes exposure to normal tissue. full color online

SBRT versus conventionally fractionated radiation for early-stage NSCLC. TROG 09.02 found patients with T1-T2a N0M0 NSCLC randomized to SBRT to have significantly higher local control and a longer OS versus patients treated with conventionally fractioned radiation.[50]

Future clinical directions with SBRT in the management of NSCLC include evaluation of the role of SBRT in medically operable patients and in combination with new systemic agents. While prior phase III randomized studies comparing SBRT to surgery in early-stage NSCLC closed due to poor accrual, pooled data from these trials and propensity-matched analyses have suggested similar outcomes between SBRT and surgery.[51,52] Currently, 3 ongoing multicenter randomized trials (STABLE-MATES, VALOR, and POSTILV) are underway comparing SBRT to surgery in early-stage disease. An area of development with particular interest is that of the multiple ongoing studies combining SBRT with checkpoint-inhibitor immunotherapy in patients with early-stage NSCLC. There is growing evidence that SBRT enhances antitumor immunity, and that these responses may contribute to the favorable outcomes seen with treatment.[53,54] While high rates of primary tumor control are found with SBRT, the concern for distant failures remains. Therefore, future treatment approaches combining SBRT with checkpoint inhibition may allow for a synergistic approach that increases cure rates.

Response Assessment Using Imaging

CT findings following SBRT differ from the well-defined linear opacities seen after conventional radiation therapy. Post-SBRT CT findings can be divided into early and late phases,[55] which both differ fundamentally from those seen with conventional radiation therapy. Specifically, they are typically localized only to the area around the treated tumor, in distinction to conventional postradiation changes, which have straight, linear borders, occupying most of the lung from anterior to posterior within the treated field (Fig. 7). The atypical pattern of opacities that are seen on CT following SBRT can lead to challenges in assessing treatment response.

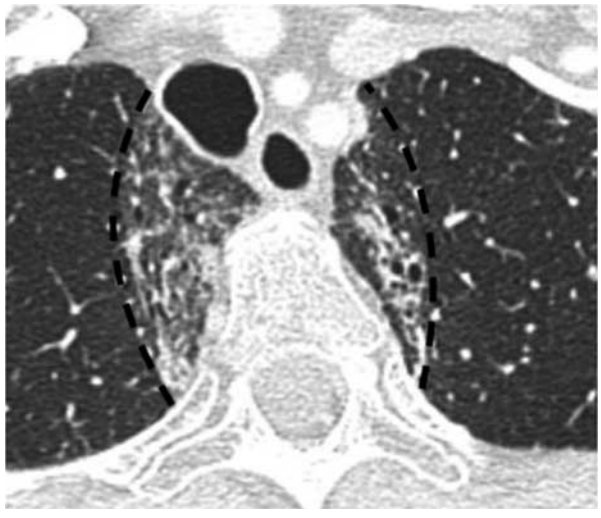

FIGURE 7. Classic radiation fibrosis pattern: contrast-enhanced axial CT image shows classic well-demarcated linear opacities (dashed lines) corresponding to radiation field in a patient who received conventional external beam radiation to treat head and neck cancer.

Early CT changes occur within the first 6 months following treatment. Although early post-SBRT CT changes are common, occurring in 62% of patients by 6 months,[56] they are frequently asymptomatic and do not necessarily herald the onset of symptomatic radiation pneumonitis. High-grade clinically significant radiation pneumonitis does occur, for example, the incidence was 3.6% in the RTOG 0236 population,[49] but is much less common than radiographic changes. In general, little impact has been noted in pulmonary function testing post-SBRT, and poor baseline pulmonary function has not been found to impact post-treatment pneumonitis.[57,58] The median time to development of acute post-SBRT findings on CT is 4 months,[55] but, in a subset of patients, it can take up to 1 year for any postradiation opacity to develop,[55] which contrasts with conventional radiation therapy after which changes are visible on CT in the majority of patients after 4 weeks.[59]

The most common acute post-SBRT CT findings are either "diffuse consolidation" or "patchy consolidation," which occur in up to 45% of patients.[56] Although termed "diffuse," diffuse opacities are typically localized to the region of lung around the treated tumor that received the highest dose, but are defined as being >5 cm and with more than 50% of the abnormal lung involved by consolidation (Figs. 8A–C). "Patchy" opacities are less extensive. The less common patterns of acute post-SBRT opacity are a diffuse ground-glass pattern, a patchy ground-glass pattern, or a combination of the 2.[55]

Late CT changes correspond to the clinicopathologic entity of radiation fibrosis and are defined as those changes that develop after 6 months. The most common pattern of post-SBRT fibrosis is termed "a modified conventional pattern" and occurs in the majority of patients.[56] It is characterized by sharply marginated consolidation with volume loss, air bronchograms, and traction bronchiectasis, similar in appearance to conventional radiation fibrosis, but less extensive and typically localized to the area around the treated tumor.

Less common patterns are scar-like fibrosis characterized by an area of linear fibrosis replacing the treated tumor, and mass-like fibrosis in which the posttreatment opacity becomes larger than the treated tumor, but has a mass-like appearance without the reassuring imaging features of conventional fibrosis (ie, volume loss, air bronchograms, straight borders) (Figs. 8D–F). Mass-like fibrosis can present a diagnostic dilemma for radiologists, particularly as it can evolve on a background of an already established conventional pattern[60] and can be misinterpreted as recurrence. Late post-SBRT changes typically stabilize between 1 and 2 years following treatment. At this point, they most commonly either maintain stability or slowly decrease, although continued evolution of late CT fibrosis has been reported beyond 2 years.[55]

The local recurrence rate is low following SBRT; however, detecting local recurrence is vital, as options for salvage therapy such as ablation or surgery can be considered.[60] Size-based CT assessment of tumor response following SBRT results in an overestimation of tumor recurrence. For example, in 88 patients with lung cancer treated with SBRT, 35 were determined to have PD using RECIST 1.1-based assessments; however, 25 of these cases were ultimately deemed false positives.[61] This lack of specificity has led to attempts to identify additional CT imaging features that may be predictive of local recurrence. CT findings that have been proposed as high-risk features include loss of a linear margin of the opacity, a new convex bulging margin of the opacity, a loss of air bronchograms, a sequentially enlarging opacity,

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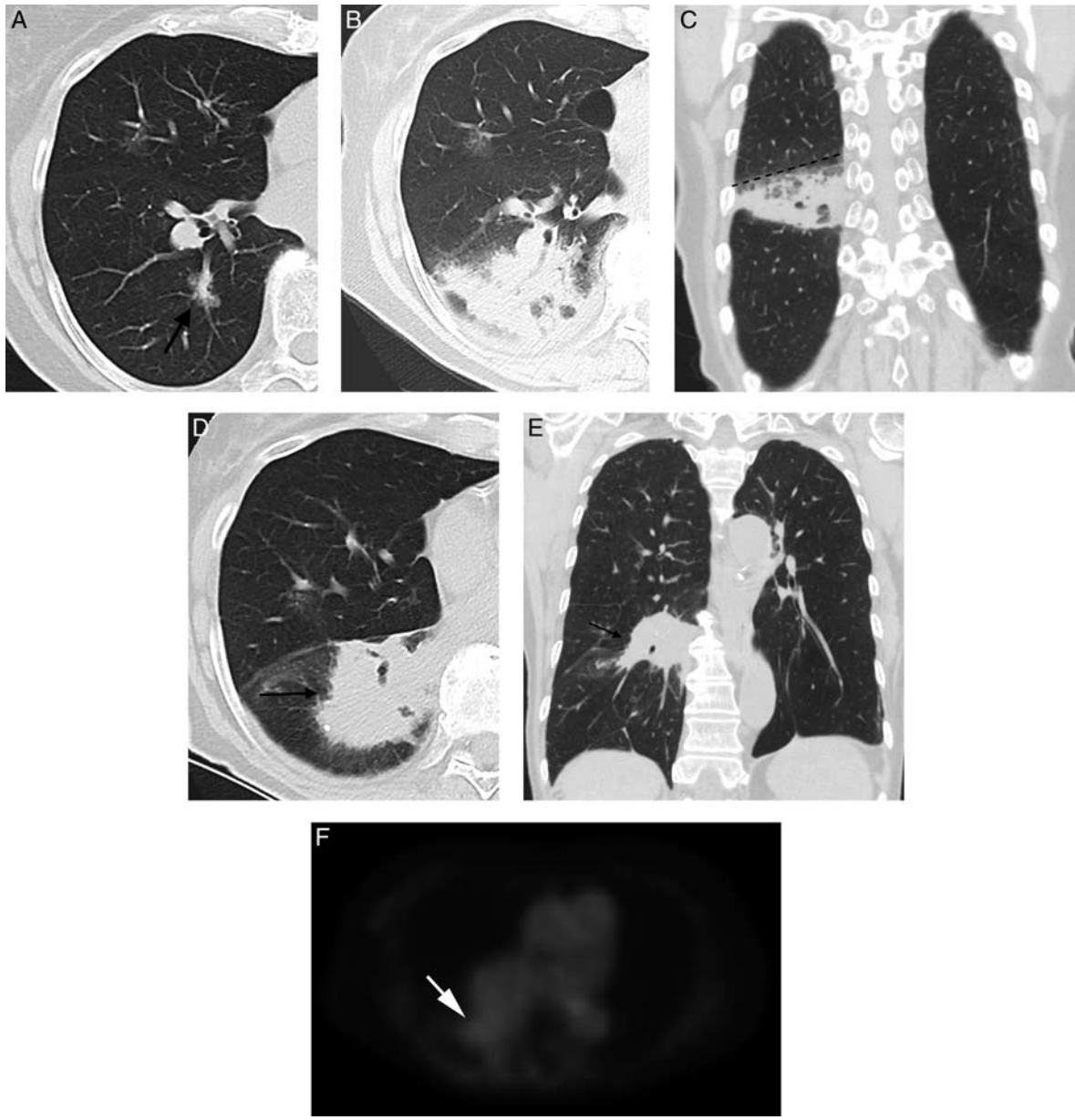

FIGURE 8. Post-SBRT CT changes. A, Baseline contrast-enhanced axial CT image shows left lower lobe part-solid lung neoplasm (arrow), before treatment with SBRT. B, Contrast-enhanced axial CT image, 3 months post-SBRT, shows diffuse consolidation pattern of acute post-SBRT change. C, Corresponding contrast-enhanced coronal CT image shows linear border (dashed line) of consolidation relating to radiation field. D, Contrast-enhanced axial CT image 2 years post-SBRT demonstrating late mass-like SBRT change with loss of linear border (arrow). E, Corresponding coronal CT image of late mass-like SBRT change (arrow). F, Axial PET image 2 years post-SBRT demonstrates uptake in the right lung opacity similar to mediastinal blood pool, a finding consistent with mass-like fibrosis (arrow).

craniocaudal growth $\geq$5 mm, and overall increase $\geq$20% [56,62] (Fig. 9).

There have been varied results in studies attempting to validate these features as predictors of recurrence. Halpenny et al[62] demonstrated that a bulging margin was the only feature significantly associated with local recurrence, while Peulen et al[63] found the features with the best diagnostic performance to be bulging margin, linear margin disappearance, and craniocaudal growth. It is likely that the more high-risk features present in a given patient, the higher the diagnostic accuracy for detecting recurrence, with the presence of 3 or more high-risk features at a given timepoint conferring a sensitivity and specificity of 90%.[64] Interpretation of these studies is difficult, as there is overlap in CT findings between those with and without recurrence. For example, a new bulging margin can be seen in up to 10% of patients without recurrence,[62] and up to half of the patients without recurrence will develop at least 1 high-risk feature.[65]

Although PET/CT is not currently recommended for routine surveillance of patients following SBRT,[5] it has a role in the evaluation of suspicious CT findings. The treated lung typically remains FDG avid for the first 3 to 6 months

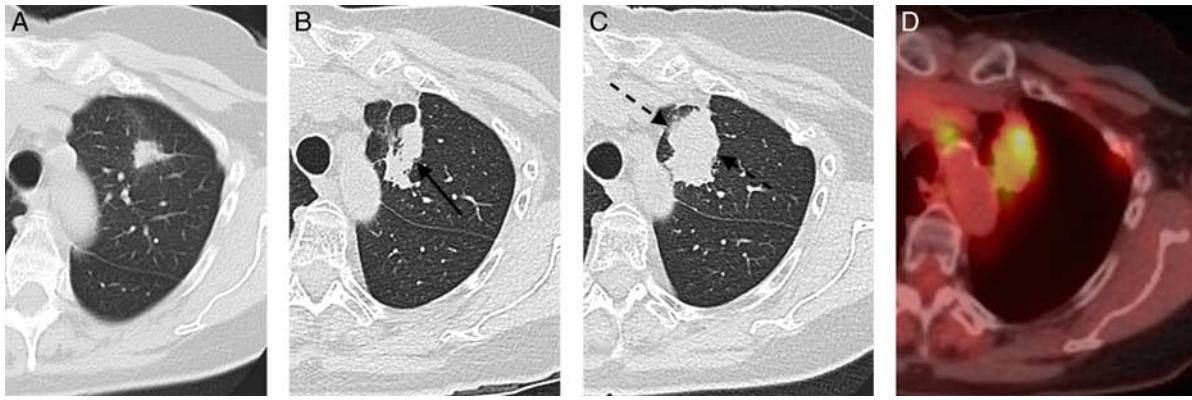

FIGURE 9. SBRT recurrence. A, Baseline contrast-enhanced axial CT shows left upper lobe adenocarcinoma, which was subsequently treated with SBRT. B, Follow-up contrast-enhanced axial CT, 2 years post-SBRT, shows opacity at the site of treated tumor larger than original tumor, but with a non–mass-like appearance (black arrow). C, Follow-up contrast-enhanced axial CT at 2.5 years post-SBRT shows increase in overall size with loss of air bronchograms and new bulging margins (black dashed arrows), suspicious for recurrence. D, Fused axial PET/CT at 2.5 years shows corresponding FDG avidity, raising further suspicion for recurrence. full color online

following SBRT, although, in some cases, inflammatory ^{18}F-FDG uptake can persist for >12 months,[66] and differentiating ^{18}F-FDG-avid tumor from ^{18}F-FDG-avid posttreatment inflammation can be challenging.[66] Some studies have suggested that early PET evaluation can predict the efficacy of treatment, for example, Bollineni et al[67] found that, in patients with inoperable stage 1 NSCLC, a PET/CT performed at 3 months demonstrating a treated lesion with an SUVmax of >5 was significantly associated with lower local control rates (80% local control vs. 98% local control, hazard ratio 7.3). However, because of the possibility of false positives in the early posttreatment phase, if PET is performed, the results should be interpreted with caution.[68] After 6 months, PET/CT is a more reliable imaging tool and is particularity useful in patients who have high-risk CT features. In this context, a combination of moderate to intense ^{18}F-FDG uptake with a mass-like pattern should raise suspicion for local recurrence.[69] Additional suspicious PET features include quantitatively assessed SUV >5, or SUV greater than that of the tumor on pretreatment PET/CT.[69]

Imaging of Complications

In general, SBRT is a well-tolerated treatment in the appropriately selected patient with a low incidence of clinically significant toxicity.[70] This is particularly true for peripheral lesions, which represent the large majority of treated tumors. In RTOG 0236, assessing the use of SBRT for inoperable early-stage lung cancer, the incidence of grade 3 or 4 adverse events was 16%.[49]

Central tumors are associated with a higher complication risk.[71] Timmerman and colleagues defined a central location as being within 2 cm of the proximal tracheobronchial tree, and, in a series of patients with stage 1 NSCLC treated with SBRT, demonstrated that a hilar or pericentral location was a strong predictor of toxicity. When compared with peripheral lesions, patients with central tumors had an 11-fold higher incidence of severe toxicity.[71] Some subsequent studies have demonstrated that, in medically inoperable patients, SBRT can be delivered safely to central tumors[72]; however, the role of SBRT in central lesions has remained controversial.[73] The current American Society for Radiation Oncology guidelines acknowledge that SBRT to central lesions carries unique and significant risks and state that, if SBRT is being considered for a central lesion, a higher number of fractions should be used, or, if the risk is considered too high, then hypofractionated radiation therapy should be used.[3]

The most common complications encountered when central lesions are treated are pulmonary/pleural toxicities including pneumonitis, airway stricture, postobstructive pneumonia, pleural effusion, and respiratory failure.[71,74,75] Less common but potentially serious complications that have been encountered with central lesions include airway necrosis, tracheoesophageal fistula, esophagitis, and hemoptysis.[71,76–78]

Song et al[75] demonstrated bronchial strictures in 89% of patients with central tumors following treatment with SBRT. In the acute phase following treatment, airway wall thickening is common, and, on CT, it will typically present as diffuse, smooth, and circumferential thickening. Later, if airway stricture develops, it will typically appear on CT as an area of smooth narrowing. Nodularity or increased soft tissue associated with the airway should be treated with suspicion for recurrent tumor. Although rare, SBRT-associated fatal hemoptysis has been reported following the treatment of central tumors.[76,79] Esophagitis is well described in the context of central tumors, for example, $\geq$ grade 2 esophagitis was seen in 12% of patients with central lesions reported by Wu and colleagues. In patients with esophagitis, CT will typically demonstrate esophageal thickening, submucosal edema, and mucosal enhancement.[80] Fatal hemoptysis associated with SBRT-related tracheoesophageal fistula has also been reported.[81] Esophageal fistulation may be difficult to demonstrate on CT; however, it should be suspected if a linear tract is visualized between the esophagus and adjacent mediastinal viscus (most commonly the central airways), containing air or contrast material.[82] If there has been frank perforation, periesophageal pneumomediastinum and fluid will typically be seen on CT.

The reported rate of rib fracture following SBRT varies considerably. A recent meta-analysis reported an incidence of 6%[83]; however, there are several studies that suggest that, if a dedicated review of CT images is performed, assessing specifically for fracture, the incidence is considerably higher. For example, when a retrospective CT review was performed, Pettersson et al[84] and Nambu et al[85,86] reported a fracture

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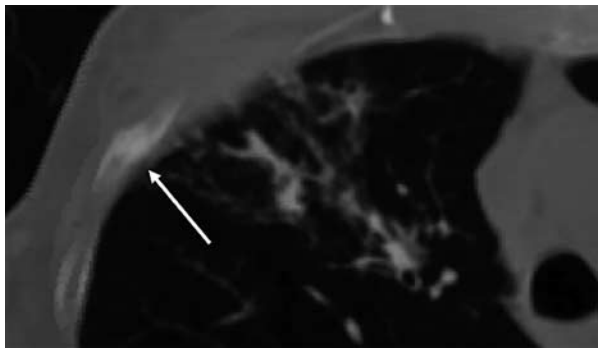

FIGURE 10. Rib fracture post-SBRT. Osteosclerosis and cortical discontinuity in the right third rib indicating an SBRT-associated fracture. Adjacent postradiation changes are visible in the anterior segment right upper lobe (arrow).

incidence of 21% and 23%, respectively. The median time to diagnosis of rib fracture is 21 months.[83] Rib fractures are frequently asymptomatic, for example, in their series, Nambu et al[85] demonstrated that 34% of patients had fracture-related symptoms, while Stam et al[87] found that 9% of patients with a fracture had pain that required intervention. Post-SBRT chest pain, in general, has an incidence of between 11% and 22% [83,85]; however, pain often occurs in the absence of demonstrable rib fracture. Fractures are strongly associated with radiation dose to the rib, and, consequently, patients with peripheral tumors are at higher risk.[86,87] Female sex also confers increased fracture risk,[85,86] while obesity and diabetes mellitus are associated with an increased incidence of chest wall pain, but not necessarily fracture.[88]

On CT, cortical thinning and osteosclerosis frequently precede the development of a fracture. Fractures present as an area of linear sclerosis or as an area of mixed lucency and sclerosis with associated cortical irregularity/disruption (Fig. 10).[86] Some displacement of the fracture fragments and infiltrative change in the adjacent soft tissues frequently occurs. A radiologic grading system for post-SBRT rib fractures has been proposed: grade 1 fractures are represented by either a healed fracture line or fracture-dislocation of <50% of the rib diameter; grade 2 fractures demonstrate dislocation of >50% of the rib diameter; and grade 3 fractures are similar to grade 2 fractures, but with chest wall edema/infiltration.[89]

CONCLUSIONS

The role that novel ablative therapies play in the treatment of thoracic malignancy continues to expand. The after treatment imaging findings associated with these treatments can complicate response assessment, and it is essential that thoracic radiologists become familiar with these treatments, the expected posttherapy findings, the impact on response assessment, and therapy-related complications.

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SA-CME EXAMINATION QUESTIONS

[*] 1. Which of the following is ***true*** regarding the role of novel ablative therapies in Non-Small Cell Lung Cancer (NSCLC)?
- A. Novel ablative therapies offer a viable alternative to surgery in all patients with Stage 1 NSCLC.
- B. The standard of care for operable, early-stage NSCLC is either SBRT or thermal ablation.
- C. The 3-year primary tumor and involved lobe control rate is over 90% in patients treated with SBRT.
- D. Ability to repeat treatment in the same location is higher with SBRT than with thermal ablation.

[*]2. With regards to percutaneous ablation, which feature is associated with recurrence?
- A. Decreased lesional enhancement.
- B. New peripheral nodularity within the treated lesion.
- C. Regional nodal lymphadenopathy within first 3 months post ablation.
- D. Central cavitation.

[*]3. Which of the following statements is ***true*** regarding response patterns in SBRT?
- A. Acute SBRT changes are similar to conventional radiotherapy changes.
- B. Acute SBRT changes are seen earlier on CT than conventional radiotherapy changes.
- C. The most common acute SBRT CT finding is scar-like fibrosis.
- D. Evolution of late SBRT CT changes can occur up to 2 years post treatment.

[*]4. Which CT feature is associated with recurrence post SBRT?
- A. Filling in of air bronchograms in the treated lung.
- B. Concave peripheral margin of the treated lesion.
- C. Decreased size of treated tumor.
- D. SUV >5 on PET/CT 3 months post treatment.

[*]5. Which of the following statements is ***true*** regarding post SBRT complications?
- A. Serious adverse events are common following SBRT.
- B. Central tumors are defined as being located within 2 cm of the proximal tracheobronchial tree.
- C. Peripheral tumors are associated with higher complication rates.
- D. Post SBRT chest pain is almost always associated with demonstrable rib fracture.