Non-small cell lung cancer after surgery and chemoradiotherapy: follow-up and response assessment

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ABSTRACT
The imaging techniques in patients treated for lung cancer may be challenging to interpret. Radiologists are often asked to evaluate computed tomography (CT) scans after surgery, and this interpretation requires an understanding of both the timing and type of the surgical procedure. However, follow-up strategies are still not well defined. The assessment of tumor response to chemoradiotherapy relies on a tight integration of CT and clinical findings. Positron emission tomography-computed tomography (PET-CT) with fluorodeoxyglucose may help to exclude tumor recurrence when the sole CT scan is equivocal. More efforts are needed to validate the tools for volumetric tumor measurement in routine practice and to demonstrate their superiority compared to the Response Evaluation Criteria in Solid Tumors (RECIST). Familiarity with the assessment of lung cancer perfusion is also important because of the increasing use of cytostatic therapy. In this review, we outlined the imaging assessment of tumor recurrence after surgery and the role of CT, magnetic resonance imaging, and PET-CT in the follow-up after chemotherapy, radiotherapy, and radiofrequency ablation.

Lung cancer is the most common cancer in the world and accounts for 12.6% of all new cancers and 17.8% of cancer deaths. An estimated 1.2 million new lung cancer cases and 1.1 million lung cancer-related deaths occurred in 2000; the male:female ratio was 2.7:1 (1). Median survival ranges from 70% for stages I–II to 5% for more advanced stages. In spite of the increasing development of new therapeutic strategies, an increase of only 2% has been reported for the median survival since 1974 (2). In this context, imaging techniques have become a fundamental tool to evaluate lung cancer response to treatment. In this review, the follow-up strategies after surgery and new tools for monitoring response to chemoradiotherapy are discussed.

Treatment strategies

The treatment of choice for non-small cell lung cancer (NSCLC) in the absence of signs of dissemination is surgical resection. Stage I and II tumors are treated by lobectomy or pneumonectomy; cancers that extend along the main bronchi within 2 cm from the carina without involving it, may be resected with bronchoplastic techniques. Intraoperative systematic mediastinal lymph node sampling or dissection is also recommended to provide critical staging information that will influence postoperative adjuvant therapy (3). Completely resected stage II patients with good performance status should routinely receive adjuvant platinum-based chemotherapy; this regimen should also be strongly considered for stage IB patients with tumors >4 cm (4). For patients with stage I or II NSCLC who cannot undergo lung surgery for any reason (i.e., massive functional impairment, severe cardiovascular disease, etc.), fractionated radiotherapy with modern techniques, such as three-dimensional (3D) conformal radiation therapy, stereotactic body radiation therapy, or radiofrequency ablation are options that might be considered (4, 5).

Completion of planned lung resection and mediastinal lymphadenectomy is recommended in patients with N2 NSCLC discovered at surgical resection in whom complete resection of the lymph nodes and primary tumor is technically possible. Subjects with good performance status should also receive platinum-based adjuvant chemotherapy. Although sequential adjuvant radiotherapy has failed to demonstrate a survival increase, it should be considered in selected patients to reduce the risk of local recurrence when multiple nodal stations are involved, extracapsular tumor spread is observed, or close/microscopically positive resection margins are detected (6). The management of patients with preoperatively identified IIIA-N2 disease is very heterogeneous, warranting an intricate multidisciplinary collaboration to determine the most appropriate treat-

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ment for a given patient (6). In these patients, a platinum-based combination chemoradiotherapy is recommended as the primary treatment, whereas surgery in combination with neoadjuvant or adjuvant therapy is considered only for clinical trial after the evaluation of surgical feasibility by a thoracic surgeon (6). Bulky N2 disease prevents any surgical option and is usually treated with a combination of platinum-based chemotherapy and radiotherapy (6).

Surgical options are also considered for patients with stage IIIB tumors without N2 disease only when the carina or superior vena cava is involved. Neoadjuvant chemoradiotherapy demonstrates the same influence on survival both for stage IIIA and stage IIIB. Thus, the final decision about administration of neoadjuvant chemoradiotherapy requires interaction between oncologist opinion and patient preferences. Unresectable stage IIIB patients with good performance status are usually treated by concurrent chemoradiotherapy (7, 8). Radiotherapy alone is an alternative with curative intent when the disease can be contained within a reasonable field. Palliative radiotherapy is also a good alternative for patients suffering from stage IIIB disease with poor performance status and symptoms such as cough, dyspnea, hemoptysis or pain resulting from chest disease (8).

Chemotherapy is the mainstay of treatment for advanced stage IIIB and IV NSCLC (9). Gemcitabine and carboplatinum or cisplatinum are conventionally used as a first-line therapy. The use of pemetrexed instead of gemcitabine was shown to be more efficient for non-squamous NSCLC (10). Furthermore, new molecular targeted agents may be used as a first-line treatment for selected patients. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor, was approved in addition to conventional chemotherapy to treat patients with cancers of nonsquamous histology. Conversely, gefitinib, another monoclonal antibody directed against epidermal growth factor receptor, might be used as the sole treatment of choice in patients affected by adenocarcinoma with epidermal growth factor receptor tyrosine kinase mutations (11, 12). Currently, docetaxel, pemetrexed (for nonsquamous cancers only) and the epidermal growth factor receptor tyrosine kinase inhibitors erlotinib and gefitinib are approved for the second-line treatment of NSCLC. In particular, erlotinib showed increased survival and lowered deterioration of symptoms as a third-line therapy (13). Radiotherapy is an alternative for the palliation of metastases to other normal structures, such as the brain, spine, or bones (8).

Assessment of tumor recurrence after surgery

Lung cancer is associated with a high recurrence rate (30%–70% of cases according to the tumor stage) even after curative intent. More than 80% of recurrences usually occur within the first two years of presentation. Recurrence may be divided into local (bronchial stump, chest wall, or remaining lung parenchyma), regional (mediastinal nodes), and distant (liver, brain, or bony lesions) recurrence. Intrathoracic recurrence occurs in approximately 10%–20% of cases after surgery. These new lesions are treated by radiation, thermoablation, chemotherapy, or combined treatment.

CT findings

An adequate interpretation of follow-up radiologic examinations is based on the understanding of the performed surgical intervention. Because some muscle flaps (taken from the intercostal muscles, latissimus dorsi, or serratus anterior) may be used to strengthen the sites of anastomosis and to reduce the risk of ischemia or bronchial air leaks (particularly following radiation therapy), the normal appearances of such myoplasties must be recognized and not be confused with a recurrent tumor.

Differentiating recurrence on contrast-enhanced computed tomography (CT) scans from postsurgical changes may be challenging. A soft tissue nodule near the surgical clips will show contrast enhancement up to three months after surgery and may represent both an inflammatory reaction and tumor relapse. On follow-up with serial CT scans, the interval growth of an enhancing solid lesion on the resection staple line will be suggestive of recurrence.

Bronchial recurrence following pneumonectomy, lobectomy, or sleeve lobectomy is a potential pitfall for CT because an obstructing soft tissue mass at the bronchial stump on postsurgical CT scans may be interpreted as residual scar tissue. Conversely, a narrowing of the bronchus could be related to extrinsic compression from an adjacent inflammatory node. Again, the interval growth of enhancing tissue on consecutive CT scans may be indicative of recurrence.

Filling defects in the pulmonary artery stump could be misinterpreted as tumor recurrence. Kim et al. (14) demonstrated that in the absence of contrast enhancement or significant growth on serial CT studies, these findings can be considered *in situ* thrombi due to the stasis of blood rather than tumor recurrence.

Usually, enlarged mediastinal nodes with a short axis greater than 1 cm suggest tumor recurrence. Nevertheless, micrometastases can be present in nodes smaller than 1 cm, whereas enlarged nonpathological nodes (i.e., inflammatory nodes) can explain false positive findings. Comparison with previous CT examinations can be useful: evidence of growth in a previously normal node suggests relapse and will need further investigation.

The demonstration of pleural recurrence is difficult on CT scan. Pleural thickening, intrapleural nodules, enhancement of the pleura after contrast media administration, or pleural effusions that persist upon serial examinations suggest recurrence and must be further investigated. Nevertheless, pleural thickenings on a CT scan can be secondary to scarring resulting from a previous surgical procedure. Follow-up studies to discover interval growth could be beneficial.

CT scans showed sensitivity, specificity, positive and negative predictive values of 72%, 95%, 93%, and 79%, respectively, in detecting overall residual or recurrent NSCLC (15). The lack of CT scan sensitivity is primarily due to metastatic nodes with small axes shorter than 1 cm, which are considered nonpathological on CT scans (15).
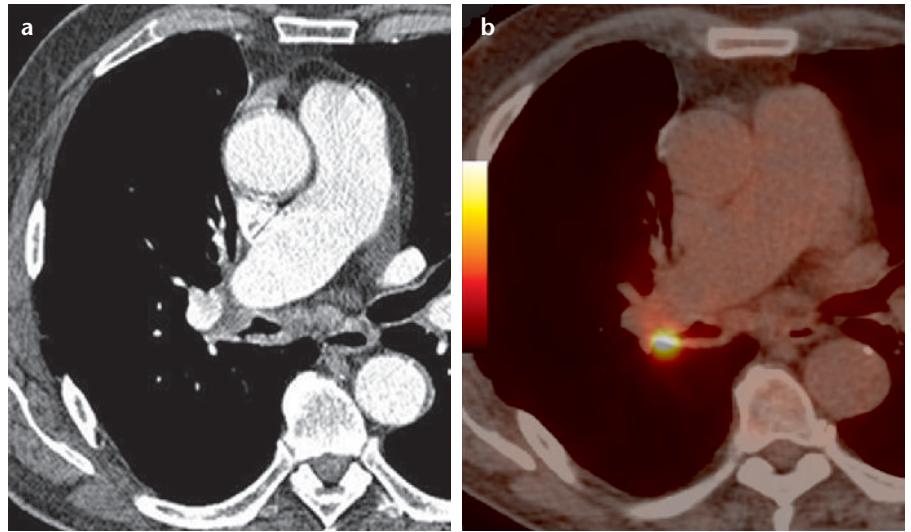
¹⁸F-FDG PET and ¹⁸F-FDG PET-CT

In the last decade, both fluorine-18-fluorodeoxyglucose positron

emission tomography (^{18}F-FDG PET) and ^{18}F-FDG PET-CT have become key tools in the postsurgical setting. In a review of eight studies, including a total of 707 patients treated with curative intent for lung cancer, pooled ^{18}F-FDG PET and ^{18}F-FDG PET-CT showed a sensitivity of 82%–100% and a specificity of 62%–100% in detecting overall recurrences (16). Hellwig et al. (17) reported higher standardized uptake values (SUV) (mean SUV, 10.6±5.1) for recurrent tumors compared to postsurgical inflammatory changes (mean SUV, 2.1±0.6). Another study reported higher diagnostic accuracy of ^{18}F-FDG PET-CT than ^{18}F-FDG PET alone; ^{18}F-FDG PET-CT changed the PET evaluation in 22 patients (52%) by precisely determining the location of lesions that showed uptake and the management of 12 patients (29%) (18). ^{18}F-FDG PET-CT also seems to be more sensitive and specific than sole CT to detect surgical margin relapse (Fig. 1) (19). Dual time point ^{18}F-FDG PET is a new and interesting application of ^{18}F-FDG PET that consists of acquiring PET data at two different time points, namely, 60 min and 90 min after ^{18}F-FDG administration. The rationale of this technique lies in the different ^{18}F-FDG uptake rates of benign and malignant lesions. Specifically, cancers exhibit an increased ^{18}F-FDG uptake over time after its administration, whereas normal tissues (blood pool, liver, spleen) and chronic inflammatory lesions generally show decreased or stable ^{18}F-FDG uptake over time (20). However, ^{18}F-FDG PET-CT shows a high rate of false positive findings, particularly for nodal metastases in both primary staging and follow-up after surgery (16, 21).

MRI

Lee et al. (21) reported that whole body magnetic resonance imaging (MRI) was more accurate than ^{18}F-FDG PET-CT for identifying recurrent malignant lesions in special conditions such as advanced age, brain or liver metastasis, previously repeated radiation exposure, and when a differential diagnosis of infectious diseases is required (21). In addition, diffusion-weighted imaging can potentially differentiate benign from malignant nodes, which

Figure 1. a, b. Disease recurrence in a 75-year-old male patient surgically treated with right upper lobectomy five years earlier. The interpretation of the CT scan **(a)** was equivocal (disease recurrence or postsurgery fibrotic changes). ^{18}F-FDG PET fusion CT axial scan at the same level **(b)** displayed solid tissue on the bronchial stump with intense metabolic activity (SUV, 10.2), which is consistent with lung cancer recurrence.

have increased cellularity and less extracellular space (22, 23). Therefore, the diffusion of water in malignant lesions is restricted, resulting in a decreased apparent diffusion coefficient (22, 24). This technique showed lower false positive findings for NSCLC staging compared to ^{18}F-FDG PET-CT and was highly accurate in distinguishing lymphadenitis from malignant nodes (22). Further studies are needed to test diffusion-weighted imaging accuracy for the detection of lung cancer recurrence after surgery, particularly when ^{18}F-FDG PET-CT findings are equivocal.

Follow-up strategies

Follow-up strategies are generally used to monitor surgically treated patients and to identify recurrent or second primary tumors. There are a number of imaging surveillance guidelines for patients who have undergone surgery for lung cancer. Four guidelines are related to patients with NSCLC following curative intent therapy (Table) (4, 25–27). Some guidelines, such as those from the American Society of Clinical Oncology (ASCO) and the Association of Community Cancer Center (ACCC), suggest not performing routine CT scans during surveillance visits (25, 27). In contrast, the American College of Radiology (ACR) recommended annual baseline CT scans, although the panel disagrees about the added value of

this approach (26). The National Comprehensive Cancer Network (NCCN) suggested contrast CT scans every six months within the first two years and noncontrast CT scan every 12 months in the following period (4).

Two major questions remain unanswered: 1) will close observation detect recurrences or second primary tumors early enough to permit salvage therapy? and 2) will salvage therapy prolong life or reduce morbidity? Three large studies showed that intensive follow-up did not modify the patients' survival (28–30), whereas only one study showed the opposite (31). Of note, it was reported that many physicians did prefer intensive imaging follow-up after curative intent even without evidence of its benefit (32). Furthermore, intensive CT follow-up (i.e., every three months) led to an expenditure increase of 99% compared to annual chest radiographs (€74 107.40 for intensive surveillance versus €697.40 for chest radiograph every year). In other words, expenditure increased approximately 100-fold without any proven clinical benefit (32). Another meta-analysis evaluated several studies using heterogeneous follow-up protocols and did not observe any significant trend suggesting that intensive follow-up improved overall survival (33).

The necessity of ^{18}F-FDG PET-CT for the surveillance of postopera-

tive NSCLC patients is controversial. ACCP guidelines do not recommend ^{18}F-FDG PET-CT for surveillance at this time (34). Conversely, recent studies have demonstrated that asymptomatic patients with recurrences detected by intensive surveillance had a better prognosis than symptomatic patients (35). Toba et al. (36) reported high values of sensitivity (94.4%) and specificity (97.6%) for the detection of recurrences with ^{18}F-FDG PET-CT in asymptomatic NSCLC patients after a potentially curative operation. Considering that most recurrences occurred during the initial two years after surgery, the authors suggested examining the whole body with ^{18}F-FDG PET-CT periodically during this time (36). However, another study reported that the diagnostic capability of integrated ^{18}F-FDG PET-CT for recurrence assessment was not significantly different from those obtained through standard radiologic examinations (combination of brain MRI, chest abdominal multidetector CT, and bone scintigraphy) (19). ^{18}F-FDG PET-CT limitations are well known. In a study by Toba et al. (36), the inflammatory process was the most common cause of false positive results, whereas metastatic foci smaller than 4 mm (particularly pleural or nodal) yielded false negative findings. In addition, both the average radiation exposure and the costs of ^{18}F-FDG PET-CT exceed those of standard radiological examinations. Therefore, further studies regarding ^{18}F-FDG PET-CT effects on survival after curative intent are warranted.

Postradiofrequency ablation evaluation

The period after radiofrequency ablation is divided into an early phase (up to one week after radiofrequency ablation), an intermediate phase (between one week and two months after radiofrequency ablation) and a late phase (more than two months after radiofrequency ablation) (5).

Early phase

The most common findings in the early phase include intralesional bubbles, cone-shaped sectorial hyperemia or a rim of hyperemia characterized by ground glass opacity, which may circumferentially or partially envelop the target lesion (5). Accordingly, the

Table. Specific recommendations for surveillance methods in patients with NSCLC following curative-intent therapy (4, 25–27)

Source	Surveillance methods			
	Baseline	First 2 years	3–5 years	After 5 years
ASCO		Hx, PE every 3 months	Hx, PE every 6 months	Hx, PE every 12 months
ACR	CT scan 3 months after therapy	CXR every 2–4 months; chest CT every 12 months	CXR every 6 months; chest CT every 12 months	CXR every 12 months; chest CT every 12 months
NCCN		Hx, PE, and contrast CT scan every 6 months	Hx, PE, and noncontrast CT scan every 12 months	Hx, PE, and noncontrast CT scan every 12 months
ACCC		Hx, PE, CXR, CBC, and blood chemistry every 3 months	Hx, PE, CXR, CBC, and blood chemistry every 6 months	Hx, PE, CXR, CBC, and blood chemistry every 12 months

ACCC, Association of Community Cancer Center; ACR, American College of Radiology; ASCO, American Society of Clinical Oncology; CBC, complete blood count; CXR, chest radiograph; Hx, history; NCCN, National Comprehensive Cancer Network; PE, physical examination.

ablation zone is larger than the lesion before treatment. Increased rates of recurrence were noted with ground glass opacity margins of 3 mm but were not observed in cases where the ground glass opacity extended more than 5 mm beyond the tumor margins (37). Yamamoto et al. (38) demonstrated that these perilesional ground glass opacities correspond to three distinct layers: an inner layer of preserved architecture, an intermediate layer of alveolar effusion and an outer layer of lung tissue congested with hemorrhages and neutrophil infiltration. Immunohistologic staining with with reduced nicotinamide adenine dinucleotide showed that only the inner and intermediate layers were necrotic and that the outermost layer (with a mean width of 2.6 mm) contained viable lung parenchyma (5). The authors concluded that because the outermost layer may contain viable tumor cells, the ground glass opacities overestimate the area of necrosis, providing a histologic explanation for the observed increased rates of recurrence for tumors with ground glass opacity margins of less than 5 mm (38). CT scans could also identify complications after the procedure, including pneumothorax, which is considered the most frequent complication, occurring in 30%–50% of patients. In addition, contrast-enhanced CT scans typically show a central hypoattenuating area and a thin rim of enhancement because of the physiologic inflammatory response to thermal injury, which may persist for as long as six months after radiofrequency ablation (5).

Intermediate phase

In the intermediate phase, the surrounding ground glass opacities resolve and are accompanied by a consequent reduction in size of the ablation zone. Cavitation is the most common finding with the reparative hyperemic envelope that progressively thins, occurring in approximately 30% of patients (39) (Fig. 2a–2d). Another frequent finding is pleural thickening in the region of the pleura crossed by the radiofrequency needle. Peripheral lesions are at a particular risk for bronchopleural fistulas.

Late phase

The cavities progressively shrink and scar with a minimal architectural distortion of the surrounding parenchyma (Fig. 2e, 2f). Therefore, the size of the ablation zone after six months is equal to or smaller than the tumor before treatment. A growing ablation zone after three months and nodule satellites along the electrode track and tines are both indicators of tumor recurrence. A recovery of circulation in the ablation zone increases the mean contrast enhancement compared to that of the intermediate phase, but a
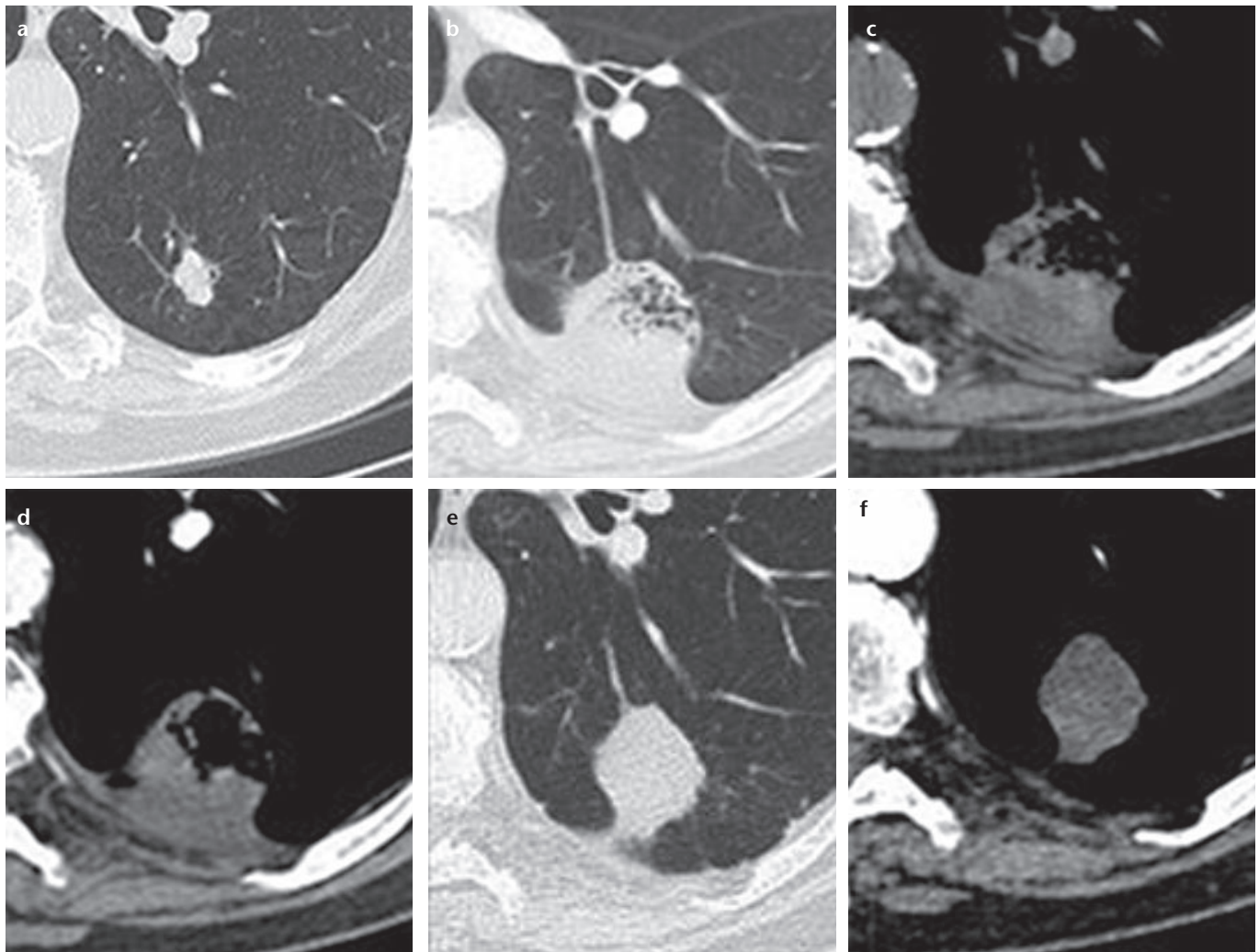
Figure 2. a–f. A 72-year-old man with inoperable lung adenocarcinoma of the left lower treated by radiofrequency ablation. Lung cancer was located at the level of left inferior pulmonary vein **(a)**. CT images without **(b, c)** and with intravenous administration of iodinated contrast material **(d)** obtained one month after treatment show an ablation zone larger than the original tumor with hypoattenuating bubbles in the context. Pleural thickening was present adjacent to the ablation zone. Four months later, CT images with intravenous administration of contrast material **(e, f)** display a reduction in size of the ablation zone and the resolution of bubbles. The lack of contrast enhancement within the ablation zone suggests no tumor recurrence.

central or nodular enhancement of more than 15 Hounsfield unit (HU) or 10 mm in size suggests progression or incompletely ablated disease. Unlike in previous phases, increased metabolic activity on ^{18}F-FDG PET images within the ablation zone, particularly two months after the procedure, is highly suggestive of recurrence (5).

Postradiotherapy evaluation

The newest techniques are 3D conformal radiation therapy and stereotactic body radiation therapy. For high resolution CT, early radiation pneumonitis (occurring within six months after completion of therapy) consists of ground glass opacities, consolidation,

or a combination of the two. An ipsilateral pleural effusion associated with atelectasis of the lung may sometimes develop. Radiation fibrosis (from six to 12 months after completion of therapy) appears as a well-defined area of volume loss with a linear scar or consolidation, parenchymal distortion, and traction bronchiectasis that conforms to the treatment portals. After 3D conformal radiation therapy, radiation pneumonitis abnormalities are primarily limited to the area immediately surrounding the treated tumor, although some may appear distally (40). By contrast, stereotactic body radiation therapy-related radiation pneumonitis abnormalities are usually limited, stri-

ctly conforming to the shape of the tumor (40). Radiologic imaging manifestations of radiation fibrosis after both 3D conformal radiation therapy and stereotactic body radiation therapy have been classified according to one of three patterns: modified conventional, mass-like, or scar-like (41). The modified conventional pattern of radiation fibrosis consists of a well-defined consolidation with volume loss and traction bronchiectasis. This pattern is different from conventional radiation fibrosis, which involves the total irradiated lung tissue from the anterior to the posterior pleural surface, whereas modified conventional radiation fibrosis is less extensive (41). When consoli-
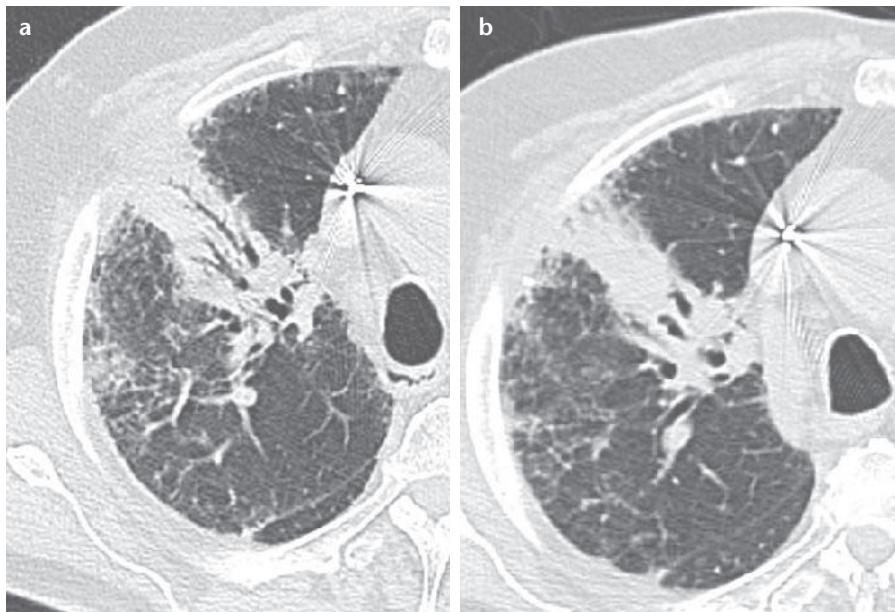
Figure 3. a, b. A 75-year-old male with NSLC in the right upper lobe who received 46 Gy radiotherapy. CT scan at the level of aortic arch eight months after radiation therapy **(a)**, depicting bronchiectasis within the consolidation in the anterior segment of the right upper lobe; note the subpleural area with ground glass appearance close to the consolidation, an expression of fibrosis. CT scan obtained three months later **(b)** shows filling in of the same bronchiectasis supporting endobronchial recurrence.

dation with traction and bronchiectasis is focal and confined to a 2 cm margin around the original tumor, CT shows a mass-like area larger than the original tumor, and this pattern is therefore described as mass-like (41). The scar-like pattern after three dimensional conformal radiation therapy or stereotactic body radiation therapy consists of a linear opacity less than 1 cm wide that is associated with a moderate to severe volume loss and remains at the tumor site when the primary mass has completely or almost completely resolved (41).

Local tumor recurrence usually manifests within two years after treatment, but it may be difficult to identify within a radiation-induced mass-like pattern of fibrosis (41). An increase of the convexity of the borders in the irradiated lung on CT scans or filling of the traction bronchiectasis (Fig. 3) may suggest a recurrent malignancy or superimposed infection (42). ^{18}F-FDG PET scanning may help differentiate a metabolically active tumor from an inactive fibrosis. Importantly, ^{18}F-FDG PET should only be performed 3 months after the completion of radiation therapy to avoid false positive results (40). Because of the high negative predictive value of ^{18}F-FDG PET, a finding of little or no ^{18}F-FDG uptake is considered

a definitive indication that lung cancer has not recurred and that CT follow-up alone is sufficient (40). Furthermore, positive CT changes associated with increased FDG uptake ($SUV_{max} \geq 5$) very likely indicate residual or recurrent lung cancer, and additional diagnostic or interventional procedures (bronchoscopy, percutaneous needle-aspiration biopsy, open lung biopsy, thoracentesis, etc.) are required (43).

Postchemotherapy evaluation
RECIST criteria and their limitations

Response to chemotherapy should be carefully assessed to promptly consider therapy changes and reduce its potential toxicity (44). In 2000, the Response Evaluation Criteria in Solid Tumors (RECIST) criteria were proposed as follows: tumor assessment is obtained by categorizing measurable lesions (one-dimensional evaluation by measuring the longest diameter in the transverse plane of at least 10 mm with spiral CT scan), nonmeasurable lesions (all other lesions, including small lesions of less than 10 mm with spiral CT scan) and truly nonmeasurable lesions (including bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pul-

monis, and cystic lesions) (45). The RECIST criteria were revised in 2009 (46). RECIST 1.1 provided almost perfect agreement for response assessment after therapy compared with RECIST 1.0 (47). However, these criteria tended to overestimate disease progression and are prone to several limitations (48). The assessment of the lung nodules or mass diameters suffers from substantial inter- and intra-observer variation, which might significantly bias the assessment of the patient's outcome or suggest inappropriate changes in therapy (49). Furthermore, RECIST might not take into account the mixed response of multiple lesions, particularly in the case of new ablation therapy, where treated and untreated lesions may coexist (i.e., some lesions decrease while others increase in size).

CT response assessment after molecular targeted therapy

Recent studies on the tumor response to targeted therapies have emphasized the morphologic changes within a tumor. Crabb et al. (50) recorded cases that showed cavitation, which accounts for tumor response, during the treatment of NSCLC with an angiogenic inhibitor, such as gastrointestinal tumors treated with imatinib (51). Lee et al. (52) developed an alternative method to assess the response of NSCLC treated with antiangiogenic agents (cytostatic therapy). In a cavitary lesion, only the soft tissue wall thickness was measured to determine tumor size by subtracting the cavity diameter (zero if no cavity was present) from the longest diameter of the target lesion (52). Both the alternative method and RECIST 1.1 demonstrated significant differences to predict the overall good (complete response, partial response, or stable disease) and poor responders (progressive disease) (52).

NSCLC response to targeted therapy with epidermal growth factor receptor tyrosine kinase inhibitor could be assessed with the New Response Criteria (NRC), which consider both the attenuation values on contrast-enhanced CT scans and tumor size. Like Choi's criteria regarding gastrointestinal tumors' response after targeted therapy, the tumor is categorized as partial response if

a region of interest of the solid portion within a tumor greater than 5 mm^2 shows a decrease in attenuation ≥15% or if the lesion decreases in size ≥10% (53). Furthermore, only the soft tissue wall thickness (except the cavitary area) is measured to determine the tumor size (53). The NRC reclassify approximately half of the cancers sorted as progressive disease by RECIST 1.1 to partial response or stable disease and facilitate the identification of at least an additional 19% of patients with favorable survival among those categorized as progressive disease by RECIST 1.1 (53).

Neoplastic angiogenesis has been regarded as a useful and promising target for new treatments (54). In recent years, CT perfusion has been developed as a noninvasive imaging modality that can provide both qualitative and quantitative information regarding the angiogenic characteristics of tumors (Fig. 4). Technical details about CT perfusion are extensively discussed in a review by Petralia et al. (54). CT perfusion shows encouraging results for prognosis and therapy assessment in advanced NSCLC treated with chemotherapy. Baseline blood flow is significantly higher in responders than in nonresponders, likely because chemotherapy has better access to tumor masses (55). CT perfusion also has a good prognostic value: cancers with decreased permeability surface-area products are associated with a longer median progression-free survival time and longer median overall survival time (55). An increased permeability is linked with microvessel leakage, a precursor of tumor invasion and metastasis (55). Fraioli et al. (56) demonstrated that perfusion CT performed shortly after the initiation of a combined therapy with antiangiogenic drugs may be more helpful for therapeutic planning than the conventional size assessment obtained with RECIST. In some cases, perfusion CT may show a change in tumor perfusion after treatment before observing any significant variations in tumor size (56). Future studies are needed to clarify the utility of CT perfusion as a tool for both prognosis assessment and the evaluation of new drug combinations.

The dual energy CT technique is another promising tool to evaluate NSCLC response after antiangiogenic therapy. To evaluate a tumor's response to treatment when measuring CT attenuation changes, it would be ideal to measure the net enhancement of the tumor and thus evaluate the exact tumor response, even in cases with intratumoral hemorrhage or necrosis. Intratumoral hemorrhage might lead to the overestimation of tumor size and thus the misinterpretation of stable disease or partial response as progressive disease using the traditional tumor response criteria. Moreover, the hemorrhage may be mistakenly regarded as an enhancing solid component when only the enhanced CT images are obtained. Dual energy CT could facilitate tumor response monitoring by allowing the detection of intratumoral hemorrhages and evaluating the tumor net enhancement (measuring the iodine component) without additional unenhanced scanning (57, 58). A previous study has already demonstrated that dual energy CT can correctly measure the enhancement degree of pulmonary nodules (59). Kim et al. (57) detected intratumoral hemorrhages after antiangiogenic treatment on virtual unenhanced images in 14% (4 of 29) of solid target lesions. In 75% of these lesions (3 of 4), the tumor response evaluations based on RECIST 1.1 and Choi's criteria were discordant, with the latter categorizing the response as partial response rather than progressive disease or stable disease (57). The authors concluded that dual energy CT may serve as a useful tool to evaluate the NSCLC response after antiangiogenic treatment by providing information on the extent of tumor nodules and lymph node enhancement, which can be accomplished without obtaining unenhanced images. The virtual unenhanced and iodine-enhanced dual energy CT images may facilitate the identification of intratumoral morphologic changes, such as hemorrhages associated with antiangiogenic therapy, and the differentiation of such changes from true tumor growth (57).

Perspective of volumetric assessment

Recently, volumetric measurements have been proposed as a potentially more accurate method to assess the response to therapy (Fig. 5). Commercially available software can semiautomatically measure both the diameter and volume of lung masses. The seg-
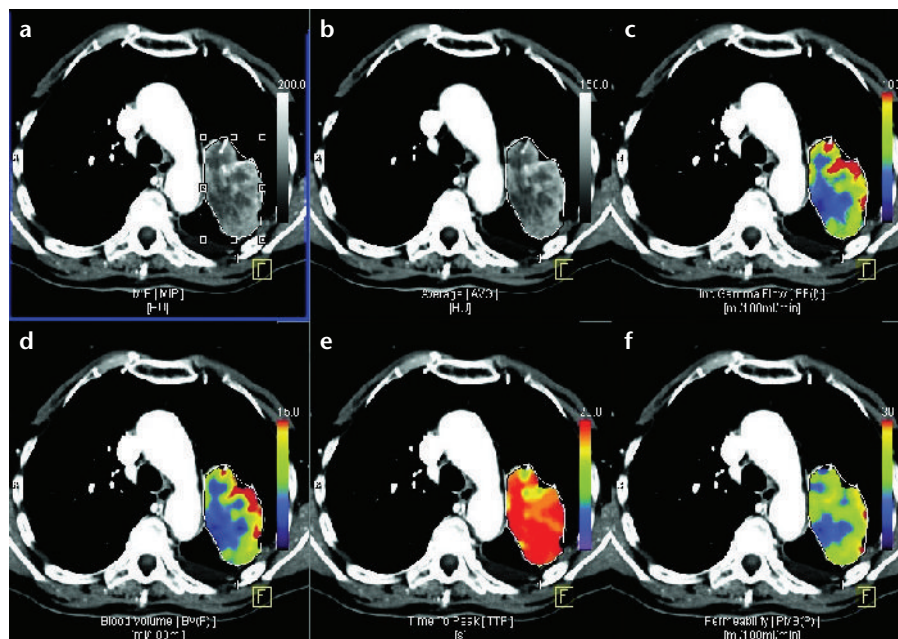
Figure 4. a–f. CT perfusion images of a 75-year-old woman with peripheral lung cancer of the left lung. Morphologic axial images **(a, b)** and color-coded maps of blood flow **(c)**, blood volume **(d)**, time to peak **(e)**, and permeability **(f)** (mean, 65.39 HU; blood flow, 53.47 mL/100 mL/min; blood volume, 7.59 mL/100 mL; time to peak, 19.26 s; permeability, 16 mL/100 mL/min). Courtesy of Dr. Francesco Fraioli, Department of Radiological Sciences, University of Rome, Rome, Italy.

mentation quality can be checked by using multiplanar CT images, allowing manual adjustments. The advantages provided by volumetric measurement over the RECIST method have not yet been fully demonstrated (60). In a previous study that evaluated the tumor response to combined chemotherapy and radiotherapy or radiotherapy alone, the one-dimensional size, a product of the perpendicular dimensions and volume, seemed to be approximately equally accurate (60). Conversely, Levine et al. (61) established that CT volumetric measurement is more reliable than RECIST criteria evaluation in sample objects assessment. A volumetric evaluation on CT scans with a maximum slice thickness of 1.0 mm can distinguish the volumes of objects with diameters of approximately 5 mm to 10 mm dramatically better than RECIST (61). Zhao et al. (48) showed that a computer demonstrated highly reproducible volumetric measurements: volume difference measured on the serial scans outside the range of -12.1% to +13.4% could be considered a true change in tumor volume. In a preliminary study, the RECIST criteria and semiautomatic computer volumetric measurements were discordant in categorizing 10% of patients (62). For example, two volumetric increases of 135% and 90% were initially scored by RECIST as "stable disease". The time of disease progression in RECIST was therefore postponed by nine weeks (62). Therefore, further studies to test volumetric changes as a "radiologic marker" for therapy response in lung cancer are necessary.

18F-FDG PET

The data on the utility of 18F-FDG PET to evaluate chemotherapy response are controversial. Tanvetyanon et al. (63) reported no evidence that the assessment of the tumor response after chemotherapy by 18F-FDG PET scanning was predictive of survival among patients with resectable NSCLC treated with neoadjuvant chemotherapy. By contrast, another study showed that tumor response was highly predictive, with one study reporting one-year survival rates fourfold better for patients affected by advanced NSCLC with SUV

reduction of more than 20% after the first cycle of chemotherapy (64). Furthermore, Vansteenkiste et al. (65) demonstrated that a greater than 50% reduction in the metabolic activity of the tumor or nodal clearance after three cycles of neoadjuvant chemotherapy was associated with longer survival in patients with stage IIIA-N2 NSCLC. Tumor response evaluation using a combined interpretation of 18F-FDG PET and CT was more effective than the interpretation of CT or PET response alone to predict tumor recurrence and pathologic response (66). A large body of evidence supports these results in a wide range of human cancers evaluated with PET, including esophageal, lung, head, neck, and breast cancers as well as lymphoma. Thus, Wahl et al. (67) proposed a new guideline to assess tumor response based on metabolic activity after treatment evaluated by 18F-FDG PET. Complete metabolic response corresponds to the visual disappearance of all metabolically active tumors; partial response is defined as a more than 30% decline in metabolic activity between the most intense lesion before treatment and the most intense lesion after treatment; and an increase of more than a 30% of glucose uptake, the appearance of new lesions or an increase in total lesion glycolysis greater than 75% defines progressive disease. Nevertheless a lack of reproducibility and standardization of response measures, poor harmonization

of response criteria, and uncertainty regarding the optimal timing for response assessment are important issues that still need to be addressed before 18F-FDG PET can be effectively used as an early response biomarker, limiting its use only to clinical trials (68).

MRI

In agreement with previous studies on other types of cancer, Yabuuchi et al. (44) showed that an early response and prognosis after chemotherapy in patients with NSCLC could be detected by evaluating the diffusion-weighted imaging change by contrast-enhanced dynamic and diffusion-weighted MRI. Accordingly, patients could switch anticancer drugs after the first cycle of chemotherapy and avoid unnecessary systemic toxicity if the first-line agents were determined to be ineffective based on the early diffusion-weighted imaging change (44).

Conclusion

Long-term follow-up strategies for patients who have undergone surgery for lung cancer are still controversial. Further data are needed to establish whether CT or 18F-FDG PET-CT scanning can identify earlier tumor recurrence and concurrently increase patient survival. The assessment of NSCLC response to chemoradiotherapy through sole use of the RECIST criteria has several limitations, and radiologists should standardize the use of
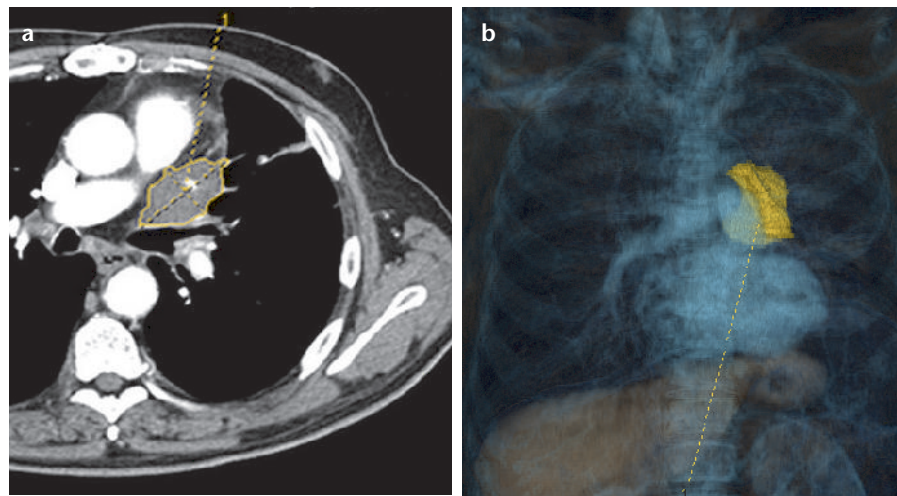
Figure 5. a, b. Volumetric measurement of a central neoplasm with involvement of mediastinal 10 L nodal station in a 63-year-old patient. Computer-generated contours (*yellow lines, superimposed on original images*) **(a)**, two maximal perpendicular diameters (*dotted yellow lines*), and three-dimensional volume rendered view **(b)** (unidimensional, 59.7 mm; volumetric, 45.086 mL).

other parameters, such as attenuation changes and volumetric measurements. Dual energy CT and diffusion-weighted MRI are promising tools to assess NSCLC treatment response.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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