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Imaging after radiation therapy of thoracic tumors

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Abstract  Radiation-induced lung disease (RILD) is frequent after therapeutic irradiation of thoracic malignancies. Many technique-, treatment-, tumor- and patient-related factors influence the degree of injury sustained by the lung after irradiation. Based on the time interval after the completion of the treatment RILD presents as early and late features characterized by inflammatory and fibrotic changes, respectively. They are usually confined to the radiation port. Though the typical pattern of RILD is easily recognized after conventional two-dimensional radiation therapy (RT), RILD may present with atypical patterns after more recent types of three- or four-dimensional RT treatment. Three atypical patterns are reported: the modified conventional, the mass-like and the scar-like patterns. Knowledge of the various features and patterns of RILD is important for correct diagnosis and appropriate treatment. RILD should be differentiated from recurrent tumoral disease, infection and radiation-induced tumors. Due to RILD, the follow-up after RT may be difficult as response evaluation criteria in solid tumours (RECIST) criteria may be unreliable to assess tumor control particularly after stereotactic ablation RT (SABR). Long-term follow-up should be based on clinical examination and morphological and/or functional investigations including CT, PET-CT, pulmonary functional tests, MRI and PET-MRI. © 2016 Published by Elsevier Masson SAS on behalf of Editions françaises de radiologie.

Surgical resection remains the mainstay of therapy for early non-small cell lung cancer (NSCLC) but only 20\% of those patients are eligible for surgery. Sixty percent of patients with lung cancer will benefit from radiation therapy (RT) at one time during their treatment. Complete response has been reported in 33–61\% after conventional RT but the rate
of success has more recently improved due to refinements in RT techniques [1–3]. The indications of RT in lung cancer are four types:

- **Curative** in patients with medically non-operable stage I or II NSCLC;
- **Adjuvant** in patients with resected or resectable stage IIIa N2 single-station NSCLC;
- **Combined** with chemotherapy in patients with unresectable stage IIIa N2 NSCLC, stage IIIb NSCLC or with limited-stage SCLC;
- **Palliative** in order to decrease some intractable symptoms in locally advanced or metastatic lung cancer [4].

Lung injury is frequent after thoracic RT and features of radiation-induced lung disease (RILD) are important to know for correct diagnosis and appropriate management [5]. CT is more sensitive than chest X-ray for diagnosing RILD and demonstrates the related features earlier. However, interpretation of imaging examinations after RT may be difficult, as the treatment planning, including the beams arrangement and the dose distribution, is individualized for each patient. The aim of the paper is therefore to review the general principles of RT techniques that will aid in the interpretation of images obtained after treatment and to describe the typical and atypical patterns of RILD.

**Basic principles of two-dimensional (2D)-conventional RT**

Although conventional 2D-RT is no longer in use nowadays, the principles of RT treatment and their side effects, including RILD, may be easier to understand when considering this basic technique. 2D-RT uses a single or few beams, usually 2 parallel and opposed beams generating a rectangular-shaped radiation field. The classical treatment delivers 60 Gy to the target volume in 2 Gy per fraction (Fig. 1) [6]. Typically, treatment portals for NSCLC are designed with a 2 cm margin around the tumor and a 1 cm margin around lymph node areas. For extensive mediastinal involvement, the homolateral supraclavicular area is generally included in the irradiated volume [7]. Due to the rough beam orientation, the volume of normal tissue that is irradiated adjacent to the treatment field is relatively large [5].

**Radiation-induced lung disease**

The pattern of RILD evolves depending of the occurrence of events from the day of completion of the RT treatment, which is also termed as the **reference point**. Clinically, pathologically and radiologically, RILD is separated in two successive phases, namely the early or acute phase and the late or chronic fibrosis phase [5,8].

**Pathology and clinical manifestations**

**Early phase**

The early or acute phase is also named as the transient radiation pneumonitis. It appears between 1 and 3 months after the end of the treatment and lasts up to 6 months. The early phase is pathologically characterized by an acute exudative phase with injury to small vessels and capillaries resulting in vascular congestion and increased capillary permeability. Afterwards, interstitial infiltration by mononuclear and other inflammatory cells, and early deposition of collagen fibrils define the organising phase [8,9]. Lesions will gradually resolve without leaving any sequelae when injury to the lung is limited. During this phase, most patients do not present with symptoms although dyspnea, cough, low-grade fever and chest discomfort may be reported in some patients [4]. Noteworthy, symptoms may develop before any radiological change [9]. Symptomatic patients will be treated by steroids in order both to decrease their symptoms and, most of all, to prevent the development of the late phase [5,8].

**Late phase**

The late phase is also named as the chronic radiation fibrosis. It results from an unresolved acute radiation pneumonitis and may last from the 6th to the 12th month after RT or even the 24th month in some conditions. Lesions are usually considered as stable and definite after 2 years [5]. The late phase is pathologically characterized by a marked increase in the deposition of fibrous tissue, fibroblasts proliferation, progressive vascular sclerosis, collapse and obliteration of alveolar air spaces [8,9]. Patients are mostly non-symptomatic but depending on the extent of the lesions may present with progressive dyspnea, dry cough or even cor pulmonale due to pulmonary hypertension [4].

**Imaging of typical pattern or RILD**

The imaging findings of RILD will also change according to the pathological alterations. The typical findings will be
Imaging characteristics and lung tumor.

Early phase
In the early phase, lung injury will manifest on CT as homogeneous, patchy or slightly nodular areas of ground glass infiltration or consolidation (Fig. 2). Infiltration presenting as crazy-paving pattern or reversed halo sign has occasionally been reported [9]. Two major features are characteristics of RILD: first, lung injury is generally confined to the fields of radiation which are therefore important to know for correct interpretation; and second, it does not conform to anatomic boundaries (i.e. the fissures) which may be different from lung infiltration due to other diseases (see Differential diagnosis section). Radiation pneumonitis outside the treatment portals has, however, been occasionally reported [7]. From the exudative to the organising phases, lungs findings tend to move from patchy areas of ground glass infiltration or consolidation to a more homogeneous and discrete consolidation that conforms better to the shape of the portals (Fig. 2) [5]. Pleural effusion may be present and may lead to passive atelectasis depending of volume [7]. RILD usually regresses over 6 months and can resolve without radiologic sequelae.

Late phase
When the injury to the lung is more severe and the late phase develops, parenchymal inflammation may progress to fibrosis. Remaining areas of ground glass parenchymal infiltration turn into consolidation that eventually shrinks and shows a sharper delineation and conformation to the irradiated field. Air bronchogram and traction bronchiectasis are typically seen in consolidated areas (Fig. 2). Shape and location of the abnormalities may change up to the twelfth months towards or away from hilum and then stabilize, although evolution up to the 24th month has been reported. With evolution, demarcation between the normal and irradiated lung parenchyma often becomes more sharply defined. As the late phase is characterized by fibrosis, the involved lung will show volume loss that may result in mediastinal shift and architectural distortion. Small pleural effusion or thickening may be seen [5,7].

Factors affecting RILD
Many factors influence the degree of injury sustained by the lung after irradiation. They include technique-, treatment-, tumor- and patient-related factors [5].

Technique-related
The type of treatment, conventional 2D-RT or recent RT techniques (see Recent RT techniques section), the number of portals and the beam arrangement will influence the volume of tissues submitted to the higher doses. The relation between RILD and the dose delivered is not yet fully understood. Actually lung tissue comprises a number of functional subunits (FSU), i.e. units of cells that can be regenerated from a single surviving clonogenic cell, and the system is organized in parallel. Basically, a critical number of FSU must be damaged before loss of function manifests. Consequently, potential toxicities (as RILD) depend on the dose distribution throughout the whole organ rather than the maximum dose to a small area [10]. The dose-response relationship seems to be non-linear and the risk generally increased according to some thresholds: RILD rarely occurs in tissue receiving less than 20 Gy, it is commonly observed for tissue receiving between 20 and 40 Gy and it develops almost always when a proportion of tissue receives more than 40 Gy [4,7,8]. The V20Gy, namely the proportion of lung volume receiving a radiation dose above 20 Gy seems to be an interesting dosimetric parameter (Fig. 4). The higher the V20Gy, the higher is the risk of RILD [11]. One speculation is that the cells for repair of injured tissue may originate from tissue that receives a low-dose, and the more distant those low-dose areas are from the injured one, the less likely the injured tissue can be repaired [11]. Moreover, fractionation and dose rate are important. A more protracted fractionation schedule reduces the biological effects of radiation [5]. In other words, the ability of the tissues (both tumoral and healthy tissues) to recover from sublethal damage depends on dose rates and time interval between radiation delivery (fraction). Normal tissues tend to repair faster than tumor cells and therefore, fractionation is worthwhile for the repair of healthy tissues [9]. On the other hand, when the radiation dose per fraction increases, the probability of late phase injury grows [12].

Treatment-related
Concomitant radio-chemotherapy may potentiate the lung radiation effects and speed up their onset. RILD manifestations and symptoms may be decreased by the administration of steroids but short duration and abrupt cessation may produce a rebound effect [7,8].

Tumor-related
The location of the tumor is an important factor particularly when considering the vicinity with structures including the mediastinum, proximal bronchi, the heart, the oesophagus or nerves that may result in more debilitating radiation-induced disease [4].

Patient-related
RILD risk increases with age, impairments in lung performance status or pulmonary function tests and pre-existing lung disease [4]. An individual inherent genetic susceptibility to the effect of radiation has also been suggested [8].

Recent RT techniques
Several advances in the field of image data acquisition, computer science and development of new machines and accelerators have led to high precision RT techniques allowing to precisely define the tumor and create shaped dose distribution that closely conform to the target volume while minimizing the dose to critical normal tissue. Local tumor control may therefore be improved without increasing toxicities [9]. This has resulted in a new nomenclature and
many acronyms which are important for the radiologists to be familiar with [13].

**Three dimensional-conformal RT (3D-CRT)**

3D-CRT uses multiple coplanar or non-coplanar beams oriented in various directions resulting in isodoses tightly conformed to the target volume and sparing as much as possible healthy tissues. The dose to critical normal tissue is therefore minimized thanks to computerized treatment planning and 3D CT acquisition of the patient’s anatomy (Fig. 3). The total dose of 60–70 Gy is achieved with a conventional 2 Gy per fraction schedule of 6–7 weeks [6].

**Stereotactic RT**

A major advent for treating small early stage tumors (T1–T2 NO) is stereotactic body RT (SBRT), also called stereotactic ablative therapy (SABR). Using also multiple coplanar or non-coplanar beams, the technique offers the advantage to obtain a steeper gradient between high- and low-dose areas at the periphery of the target (Fig. 4). SABR benefits from a hypo-fractionated scheme of dose of 5–18 Gy per 3 to 5 fractions. A biological equivalent dose of more than 100 Gy (i.e. largely superior to the classical fractionation) is therefore reached over 1 to 2 weeks with local tumor control and 2 year-survival rate estimated at 80–100% and 56–80%, respectively [4,12,14,15].

**Intensity-modulated RT (IMRT)**

Intensity modulated RT (IMRT) refers to a RT technique in which non-uniform fluence is delivered to the patient from some different angles in order to optimize the composite dose distribution. Conformity to the target is therefore further increased compared to 3D-CRT with a sharp dose fall off in the neighbouring tissues. In particular, TomoTherapy, similar to helical CT, delivers intensity-modulated rotational RT using a fan-beam [13].

**Four-dimensional RT (4D-RT)**

4D-CT consists in synchronizing a low-pitch CT data acquisition with the patient respiratory signal. 4D-CT allows a precise and individual quantification of tumor and organ motions. The integration of 4D data into treatment planning allows reducing geometric uncertainties inherent to 3D-CT images, the latter corresponding merely to a snapshot of the patient anatomy. Various approaches to incorporate 4D-CT data in treatment planning have been reported, including respiratory-synchronized techniques (i.e. gating or tracking) or margin-based techniques (i.e. internal target volume or mid-position strategy) [16].

**Boost RT**

One of the more recent refinement consists of delivering a higher dose on some parts of the lesion which are hypermetabolic on PET, considered as more resistant to treatment (‘‘dose painting’’ strategy, 4D-PET-IGRT for four-dimensional-PET-image-guided RT). Research works are intended to dose escalation by delivering up to 125 Gy on selected parts of the tumor, i.e. on metabolically radio-resistant areas (boost dose) (Fig. 5) [13,17].

**Proton-based RT (PT)**

Proton therapy (PT) provides better dose distribution and physical properties compared to photon therapy. Theoretically, PT could lead to an increased therapeutic index, i.e. higher dose to the tumor while keeping isotonic doses to normal tissue. Interestingly, it could be used for tumor located near high risk-structures or critical organs as well as in particular case of re-irradiation. However, additional research should be performed before using PT in clinical routine for lung tumors as the dose distribution obtained with PT is very sensitive to moving target and anatomical changes [9].

**Imaging of atypical pattern of RILD**

The major implications of those technological RT refinements are the multiplication of portals resulting in complex irradiated fields. The shape and distribution of RILD will vary according to the type, location and extension of the tumor and the corresponding beam arrangement to encompass it. The recognition of the radiologic manifestations of such complex portal arrangements is facilitated by dosimetric planning superimposed on the CT scan [9,12]. This may however prove to be difficult to implement on a routine basis. The timeline of RILD after 2D-RT or the various 3D- and 4D-RT treatments is roughly similar. Opposite to the typical pattern described after 2D-RT, RILD are usually described as *atypical or unusual* pattern after 3D- or 4D-RT. Three *atypical* patterns are reported: the modified conventional, the mass-like and the scar-like patterns [4,6,7,12].

**Modified conventional pattern**

As the volume of lung parenchyma receiving a high dose is more limited than with the conventional 2D-technique, the volume of parenchymal infiltration/consolidation and subsequent volume loss of the lung, architectural distortion

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*Figure 2.* Radiation-induced lung disease (RILD) after conventional 2D-RT in a seventy-year-old man presenting with dyspnea, cough and fever: a–b: he had undergone prior combined conventional 2D-RT and chemotherapy for a T3N2 squamous cell lung cancer of the right upper lobe; c–d: axial CT and minimum intensity projection (miniP) images at 2 months after the end of RT show areas of patchy or homogeneous ground-glass infiltration in the right upper lobe and in the anterior segment of the left upper lobe; e–f: axial CT and miniP images at 3 months show a coalescence of the areas of pulmonary ground glass infiltration into sharper areas of consolidation containing an air bronchogram. A small right-sided pleural effusion is seen; g–h: axial CT and miniP images at 8 months demonstrate shrinkage of the consolidated areas, now showing straight margins. The air bronchogram is now containing bronchiectasies; i–j: axial CT and miniP images at 10 months show further shrinkage and migration towards the mediastinum of the radiation fibrosis areas.
Figure 3. 3D-conformal RT (3D-CRT) for a left upper lobe NSCLC: a: 3D-image reconstructed from CT scanning data. A computerized planning system is used to design beam arrangements with a variety of orientations and deliver the dose to the target (coloured in red), while limiting exposure to normal structures; b: four portals are shown on an axial CT image. The planning target volume, i.e. the volume on which the dose is prescribed, is represented in red while the area in green represents the 95% isodose line of prescription, i.e. the area receiving 95% of the dose prescription.

Figure 4. Stereotactic ablative therapy (SABR): a: axial CT image shows a 3 cm T2 NSCLC in the middle lobe; b: axial, c: coronal and d: sagittal views of treatment planning. The planning target volume, i.e. the volume to be treated with the prescribed dose, is contoured in red. This peripherally located tumor received a total dose of 54 Gy (in 3 fractions of 18 Gy). The isodose lines are represented: in green the $V_{54Gy}$, in turquoise the $V_{20Gy}$ and in grey the $V_{5Gy}$, i.e. the volumes receiving 54, 20 and 5 Gy respectively.

Figure 5. ‘‘Dose painting’’ and Boost dose: a: axial PET/CT image shows a right upper lobe NSCLC with metabolically active areas in yellow; b: the contours defined for the treatment planning are shown on the axial CT image. In red, the metabolically active area of the primary tumor is automatically segmented. In yellow, the gross or visible whole primary tumor (GTV of primary tumor) is manually defined on mediastinal window. In green, the involved lymph nodes (GTV of lymph nodes) are manually contoured on mediastinal window. Various margins are defined around the GTV in order to take into account the potential microscopic extension (CTV), the tumor motion (ITV) and the setup uncertainties (PTV). Risk organs including spinal cord and oesophagus are also manually contoured; c: the treatment planning is represented with various isodose lines, i.e. the 40, 50, 60 and 80 Gy isodose lines.
and mediastinal shift will be less extensive. Air-bronchogram may be less frequent or less extensive (Fig. 6).

Mass-like pattern

Due to the multiplicity of portals, the margins of the irradiated field will not manifest as a single opacity with a straight margin and may result in more rounded injury lesion that may simulate tumor (Fig. 7). The resulting lesion may change shape and location away or towards the hilum during the first twelve months due to retraction of the lung [12,14]. A transient increase in size of the tumoral target after SABR has also been reported [18].

Scar-like pattern

With disappearance of the tumor an elongated radiation pneumonitis may in some cases progressively lead to a linear scar less than 1 cm wide simulating a platelike atelectasis (Fig. 8).

Figure 6. Modified conventional pattern. A 70-year-old woman presenting with a stage 3B right upper lobe adenocarcinoma was treated by concomitant radio-chemotherapy. 57.5 Gy in 25 fractions of 2.3 Gy were delivered using the IMRT helical technique: a–b: axial CT and minimum intensity projection (minIP) images at 6 months show minimal patchy areas of ground glass infiltration and consolidation containing a small air-bronchogram in the right upper and middle lobes; c–d: axial CT and minIP images at 9 months show the coalescence of the previous findings into a more uniform consolidation containing dilated bronchi in the anterior part. No straight margin is demonstrated; e–f: axial CT and minIP images at 3 years show a chronic radiation fibrosis presenting as an oval shaped consolidation that has migrated away from the mediastinum compared to (c–d). Margins are sharper and the dilated air bronchogram is demonstrated throughout the whole consolidation.
Figure 7. Tumor-like pattern. A 72-year-old patient presented with two lung metastases from prostate cancer; a: the 15-mm lesion in the right upper lobe was treated by SABR using IMRT helical technique. An amount of 48 Gy were delivered by 8 fractions of 6 Gy; b: control CT at 2 months shows a decrease in size of the lesion that measures 8 mm. No acute radiation pneumonitis is seen; c: follow-up CT at 6 months shows a 3 cm rounded consolidation containing an air-bronchogram and surrounded by ground-glass infiltration. The residual tumor if any cannot be depicted anymore in the radiation pneumonitis area; d: follow-up CT at 9 months shows a 25-mm mass-like pattern of the radiation pneumonitis containing dilated bronchi. The margins are sharper and the ground-glass has decreased compared to (c).

Figure 8. Scar-like pattern: a: 62-year-old patient presented with a 13 mm squamous cell lung carcinoma in the left upper lobe. He was medically inoperable due to severe pulmonary insufficiency. The lesion was treated by SABR using IMRT helical technique with 54 Gy delivered in 3 fractions of 18 Gy; b–d: axial CT images at 10 months show a poorly defined consolidation without air bronchogram and surrounded by a ground glass pattern. Coronal and sagittal reformat better demonstrate the scar-like pattern of the limited radiation fibrosis area.
Differential diagnosis

Diagnosis of RILD requires a high index of suspicion because infection and tumor recurrence may manifest clinically and radiologically in a similar manner. Differentiation from RILD may be difficult and is important in determining the appropriate management and therapy [7].

Infection

Infections are usually easy to differentiate from RILD due to their both clinical and radiological more abrupt onset; an exception would be a recent discontinuation of steroids therapy. Infection should be suspected when pulmonary opacities appear before completion of the RT or outside radiation portals (Fig. 9). Contrary to RILD, infections respect the anatomic boundaries (i.e. fissures) and may be diffuse or bilateral. Centrilobular or tree-in-bud opacities are highly suggestive of bronchiolar infection. Cavitation and filling-in of bronchi may be seen but are not specific of infection [7,9].

Tumor recurrence

Locally recurrent tumor can be difficult to diagnose particularly in patients presenting RILD. It usually occurs within two years after treatment. Any increase in size of the radiation fibrosis area presenting as homogeneous consolidation with convex or lobulated contour and without air bronchogram should raise the possibility of local recurrence (Fig. 10) [4,9].

Figure 9. Pulmonary infection. A 71-year-old male presenting with orthopnea, chest pain, hypoxemia, light fever, cough. He was treated for a squamous cell lung carcinoma of the middle lobe by neo-adjuvant chemotherapy (Cisplatin, Gemcitabin) 2 months ago and underwent completion of 3D-Boost-RT two weeks ago. An infectious pulmonary consolidation (arrowheads) occurring early after RT is demonstrated outside the radiation field at the periphery of the right lower lobe.

The filling-in of bronchi that corresponds to disappearance of a previously seen air-bronchogram may be the first sign of recurrence in up to 30% of recurrence (Fig. 11) [19]. Recurrence may be more difficult to diagnose after SABR as RILD.

Figure 10. Recurrent tumor. A 59-year-old patient was treated for squamous cell lung carcinoma of the right upper lobe with neo-adjuvant chemotherapy (Cisplatin, Gemcitabin) 11 months ago and completion of 3D-Boost-RT 9 months ago. The patient presented with increasing cough, light dyspnea but stayed in good general condition; a–b: Axial CT and PET at 5 months after completion of RT. CT shows a consolidation with concave margins and no air bronchogram. A definite recurrence cannot be confirmed on CT whereas PET already shows a small focus of increased FDG uptake with $SUV_{\text{max}} = 9.2$; c–d: axial CT and PET at 4 months later. CT shows bulging margins and stenosis of proximal right upper lobe bronchi suggestive of tumor recurrence whereas the area of FDG uptake on PET has considerably increased in size with $SUV_{\text{max}} = 18.5$. 

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may present with rounded contours, less air bronchogram and continue to evolve as long as two years after treatment, and there may be a transient increase in size of the tumor target [14,18]. Other findings as lymphangitic carcinomatosis, enlarging lymph nodes or late pleural effusion may also help in diagnosing tumor recurrence. PET should be performed in any case of suspicion of recurrence as it has a higher sensitivity than CT (100% vs 71%) for a close specificity (92 vs 95%) [20]. However, PET is not recommended within 3 to 6 months after treatment and tracer uptake has even occasionally been reported at up to 24 months. The main interest of PET is its excellent negative predictive value and a pathological proof of recurrence is nevertheless usually required before any additional treatment is considered [7,9,21].

Radiation-induced tumor

Radiation-induced tumor is a rarer differential with a risk of 2.4 per 100 patients-years. The risk increases with time and a median time of 9.6 years has been reported. The lungs, oesophagus and stomach are the most susceptible organs after thoracic irradiation. The appearance of a consolidation or an increased opacity inside or at the edge of a long-lasting and stable area of radiation-induced lung fibrosis should raise the suspicion of a radiation-induced lung tumor (Fig. 12) [4,22].

Follow-up: special focus after SABR

SABR is gaining a widespread adoption as the first choice technique in case of inoperable small primitive or secondary lung tumors or in patients refusing surgery. Therefore radiologists need to be aware of the spectrum of CT changes occurring with this technique. Even more than with other RT techniques, one of the main difficulties is to assess tumor response during follow-up, and differentiate RILD from a local tumor progression. Severe clinical toxicity is rare and occurs most commonly in centrally located tumors [12]. RILD

Figure 11. Recurrent tumor: a: spot view of an axial CT image showing an area of radiation fibrosis as a well-defined consolidation containing a dilated air bronchogram in a patient that underwent 3D-CRT for a NSCLC 2 years earlier; b: follow-up CT shows an enlargement with filling-in of bronchi (arrowheads) in the anterior part of the radiation fibrosis area as an early sign of recurrence.

Figure 12. Radiation-induced tumor; a—b: a 68-year-old woman with a past history of left breast cancer treated by RT 15 years earlier presented with a NSCLC (arrow) located in the radiation fibrosis area (arrowhead) of the supraclavicular radiation field. She had no other risk factor for lung cancer.
typically occurs after a longer delay than for other RT techniques, usually not before 3 months at CT, while clinical symptoms develop within 3 to 6 months after SABR. Severe acute RILD may lead to radiation fibrosis beginning within 6 to 15 months. Fibrosis may also develop even in patients without prior acute findings [23]. The sequelae are usually stable after 1 to 2 years [11,12]. Both morphological and functional imaging techniques are not specific in differentiating tumor from scar of the pulmonary parenchyma induced by high doses of radiation. It is therefore necessary to standardize and simplify the evaluation criteria in order to assess more precisely the effectiveness and long-term consequences of SABR. An excellent review has been published recently on the follow-up of patients after SABR [15].

CT

Response evaluation criteria in solid tumours (RECIST) criteria may be unreliable to assess tumor control after SABR for multiple reasons [11,14,15,18,23,24]:
- acute radiation pneumonitis is found in 60% of patients and is mainly represented by lung consolidations (40—60%);
- chronic radiation pneumonitis is frequent (80—100% at up to 3 years);
- the mass-like pattern is the most frequent late manifestation of RILD and appears between 6 months and 2 years of follow-up;
- volume pseudo-progression of the target may be seen in successful treatment and thus does not necessarily indicate recurrence;
- tumor shrinkage is variable and may last 2—15 months (median 6 months).

Therefore, although SABR has demonstrated over 90% local control rate at 3 years most of the studies failed to define precise local control criteria [24—26]. Although derived from a study on a limited number of patients and not yet widely validated, the following features are often considered for detection of tumor recurrence [27,28]:
- increase in size of the lesion;
- continuous increase in size of the lesion over several successive CT;
- increase of the size of the lesion 12 months after completion of RT;
- bulging of lesion margins;
- filling-in of air-bronchogram;
- disappearance of the linear pattern of lesion contours;
- increase in size of the lesion in the crano-caudal axis.

When considered separately, each sign was reported to have a high sensitivity and a low specificity for local recurrence. The best predictive factor was an increase of the size of the lesion 12 months after completion of RT (sensitivity of 100% and specificity of 83%) [27,28]. When at least three criteria are present, the sensitivity and specificity are over 90% for tumor recurrence [28]. The appariation of a homolateral pleural effusion and lymph node enlargement have also been reported as suggestive of tumor recurrence [27]. Other researchers have proposed to use density measurements or texture analysis of the lesion and reported better results than with volumetric or RECIST assessment [29].

FDG—PET

The predictive value of FDG—PET in terms of local or distant recurrence has also been investigated. The initial SUV\textsubscript{max} was reported to be predictive of local control at 2 years (93% for SUV\textsubscript{max} < 6 vs 42% for SUV\textsubscript{max} > 6) [30]. Unfortunately, even if a high SUV\textsubscript{max} is correlated with the metabolic tumor activity, it can also be related to lung inflammation. A persistent low residual metabolic activity (SUV\textsubscript{max} < 5) due to inflammation can therefore be observed despite a partial response according to RECIST criteria, particularly during the first 6 months [15,31]. Indeed, a moderate hypermetabolic PET activity without evidence of treatment failure may persist for up to 2 years after SABR [32,33]. However, beyond six months after SABR, when tumor recurrence is suspected on CT progression, PET—CT is usually recommended to differentiate tumor recurrence from RILD [15]. In one study, a value of SUV\textsubscript{max} > 5 beyond 6 months after SABR had a sensitivity of 100%, a specificity 91%, a positive predictive value of 50% and a negative predictive value of 100% for a local recurrence [34]. Due to the limited positive predictive value and the low-rate of tumor recurrence after SABR, FDG—PET is currently mainly recommended in case of suspicion of recurrence. Potential improvements using respiratory-gated (4D) FDG—PET, PERCIST criteria and other radiotracers that are less susceptible to inflammation than FDG, such as the 18F fluoro-L-thymidine (FLT), are currently under investigation [35,36].

MRI

MRI is an emerging technique that is not yet routinely used in the assessment of lung cancer [37]. The combination of T2-weighted (STIR and T2 SAT) and diffusion sequences (DW-MR) are probably of great interest in tumor assessment. A decrease of tumor signal on those sequences associated with an increase in apparent diffusion coefficient (ADC) value may be a predictor factor for tumor response. A preliminary study evaluated the use of DW-MR and FDG—PET—CT for predicting disease progression among 15 patients after SABR. A low ADC value on pretreatment DW-MR associated with a high SUV\textsubscript{max} may predict disease progression [38]. The hybrid PET—MR may probably prove to be a better predictor.

Follow-up recommendations

Long-term follow-up (5 years) should be based on clinical examination and morphological and/or functional investigations (CT, PET—CT, pulmonary functional tests, MR and PET—MR) [15].

The following algorithm of imaging follow-up after SABR is currently recommended (Fig. 13) [15,27,28]:
- CT every 3 to 6 months during the first year and every 6 months thereafter;
- if less than two of the above 7 high-risk CT features are present, the probability of recurrence is low and a FDG—PET—CT may be justified. A high SUV\textsubscript{max} ≥ 5 or > pre-treatment value at 6 months or more after SABR is strongly suggestive of recurrence;
- if at least three of the previous high-risk CT features are present, the probability of recurrence is high and further
therapeutic options (percutaneous ablation, surgery, re-irradiation) should be considered if applicable. Although usually recommended before any further therapeutic change, the confirmation of cyto/histologic tumor recurrence by percutaneous biopsy remains controversial in literature for some authors [15].

Unusual thoracic findings after RT

Any thoracic tissue exposed to radiations can show radiological features of radiation injury (Table 1) [39]. In addition to the above-described findings, lung parenchyma can present with organizing pneumonia (or BOOP) and necrosis.

Organizing pneumonia

Bronchiolitis obliterans with organizing pneumonia (BOOP) can present with symptoms close to RILD, including dyspnea, fever, fatigue and cough. BOOP has been more frequently reported after RT for breast cancer (1.2–2.9%) [40,41]. In the latter, organising pneumonia is considered to begin close to the radiation pneumonitis area, and then migrate away, sometimes in the opposite lung (Fig. 14) [40,41]. The cause remains largely unknown and due to the presence of a bilateral lymphocytic alveolitis, some kind of lymphocyte-mediated hypersensitivity reaction or immune disorder has been suggested to be involved [40]. In a recent study of 210 lung tumors treated with SABR, BOOP has been reported in 4.8% and occurred 6–16 months after the RT treatment.

Figure 13.   Follow-up algorithm after SABR.

Figure 14.   Organizing pneumonia: a—b: chest X-ray and axial CT image show an organizing pneumonia (arrow) in a patient presenting with fever, mild dyspnea, fatigue and non-productive cough. He had a past history of a NSCLC of the right hilum treated by RT. A radiation fibrosis area is demonstrated in a right posterior paramediastinal location (arrowhead). Case courtesy of Gilbert Ferretti, Grenoble, France.
and 2–7 months after radiation pneumonitis. Interestingly, 8 of those 9 patients presented with a symptomatic radiation pneumonitis (HR: 62; 95%CI: 4–928, P = .003), 5 were treated with steroids for 3 months and 4 relapsed after steroids cessation [42].

**Necrosis**

Pulmonary or bronchial necrosis is a rare complication of RT. One study reported an incidence of 0.6% in patients who underwent surgery followed by chemotherapy and adjuvant RT [39]. Cavitation in the treatment volume may be secondary to post-RT lung necrosis, infection, ischemia and recurrent tumor [9].

**Others**

Though the oesophagus is one of the most radiosensitive organs in the chest, symptomatic radiation esophagitis is reported in less than 1% of patients after thoracic irradiation and usually worsening towards the end of RT. CT may show a circumferential oesophageal wall thickening and 18FDG–PET may show a diffuse activity without focal abnormality (Fig. 15) [9,43]. Among the late complications of RT,

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**Table 1** Unusual thoracic findings after radiation therapy.

<table>
<thead>
<tr>
<th>Target organs</th>
<th>Complications</th>
<th>Target tumor</th>
<th>Risk frequency</th>
<th>Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung–bronchi</td>
<td>Necrosis/cavitation</td>
<td>Breast &gt; lung</td>
<td>0.6%</td>
<td>1–7 y</td>
</tr>
<tr>
<td></td>
<td>BOOP</td>
<td></td>
<td></td>
<td>6–16 m</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Dysmotility</td>
<td>Related to treatment planning</td>
<td>4–12 w</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stricture</td>
<td>2% at 50 Gy and 15% at 60 Gy</td>
<td>Median 6 m (3–18)</td>
<td></td>
</tr>
<tr>
<td>Pleural</td>
<td>Pneumothorax</td>
<td>Hodgkin &gt; breast</td>
<td>Mean 16 m (1–31)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mesothelioma</td>
<td></td>
<td>Median 13.5 y (5–41)</td>
<td></td>
</tr>
<tr>
<td>Mediastinum</td>
<td>Thymic cyst</td>
<td>Hodgkin &gt; breast</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Fibrosing mediastinitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Calcifications</td>
<td>Lymphoma</td>
<td>&gt; 1 y</td>
<td></td>
</tr>
<tr>
<td>Vessels</td>
<td>Stenosis, occlusion or pseudoaneurysm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcifications</td>
<td></td>
<td>&gt; 10 y</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>Coronary artery disease</td>
<td>Hodgkin Risk ↑ factor of 3</td>
<td>10–15 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pericarditis</td>
<td></td>
<td>subacute (12–18 m)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Valvular disease</td>
<td></td>
<td>or chronic (4 y)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conduction abnormalities</td>
<td></td>
<td>10 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sarcoma</td>
<td>Breast</td>
<td>&lt;0.1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rib, clavicle, sternal fractures</td>
<td>1.8%</td>
<td>3–30 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 1 y</td>
<td></td>
</tr>
</tbody>
</table>

Modified from [39].

BOOP: bronchiolitis obliterans with organising pneumonia; m: month; w: week; y: year.

a If different from lung cancer.

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Figure 15. Radiation esophagitis. A 58-year-old patient treated by concomitant radio-chemotherapy for a SCLC and presenting with a severe dysphagia since the end of the treatment: a: severe mid-oesophageal thickening (arrow) two months after completion of the RT; b: three months later, the oesophagus is normal. Note an acute radiation pneumonitis on the right side.
cardiovascular injuries are reported to contribute significantly to morbidity and mortality in long-term RT survivors, i.e. in young patients treated for lymphoma. Stenosis and occlusion from RT are typically limited to the radiation field and a three-fold higher risk of coronary artery disease has been reported among survivors of Hodgkin’s disease (Fig. 16) [39,44,45]. The risk of post-RT sarcoma of the chest wall (less than 0.1%) is very low compared to the benefit effect from RT. Osteosarcoma and malignant fibrous histiocytoma are the most common cell types and occur 3 to 30 years after the treatment. They should be differentiated from rib, sternal or clavicular fractures that are frequently multiple, spontaneous and may show non-union, osseous resorption or an abnormal callus and from large benign dystrophic calcifications (Fig. 17) [39,46].

Take-home points
- Any thoracic tissue exposed to radiations can show radiological features of radiation injury; in particular lung injury is frequent after thoracic radiation therapy (RT) and features of radiation-induced lung disease (RILD) are important to know.
- Two major features are characteristics of RILD: confinement to the fields of radiation and non-conformity to anatomic boundaries (i.e. the fissures). Knowledge of the treatment planning, including the beams arrangement and the dose distribution, may aid in the interpretation.
- RILD presents as early and late features based on the time interval after the completion of the treatment.
- The inflammatory early phase appears between 1 and 3 months after the end of the treatment and lasts up to 6 months. With stereotactic ablation RT (SABR), it may appear around the 4th month after completion of RT.
- The fibrosing late phase results from an unresolved early phase and may last for 6 to 12 months or even 24 months in some conditions. Lesions are usually considered as stable and definite after 2 years.
- Technique-, treatment-, tumor- and patient-related factors influence the degree of injury sustained by the lung after irradiation.
- Advances in RT techniques allow to precisely create shaped dose distribution closely conforming to the target volume while minimizing the dose to critical normal tissue, and therefore changing the pattern of RILD, named as modified conventional, mass-like and scar-like patterns.
- Long-term follow-up up to 5 years after RT should be based on morphological and/or functional investigations (CT, PET-CT, pulmonary functional tests, MRI and PET-MRI).
- RILD should be differentiated from recurrent tumoral disease, infection and radiation-induced tumors.

Figure 16. Radiation cardiovascular injuries. A 50-year-old woman with past-history of Hodgkin disease treated with RT 30 years earlier. She had no other risk factors for cardiovascular disease. She had a long history for 20 years of mitral valvular dysfunction (treated by prosthesis), coronary artery disease and pericarditis, all attributed to late radiation disease. Note also severe calcification of the ascending aorta.

Figure 17. Radiation bone lesion. A sixty-two-year-old patient with a past history of right breast cancer treated by RT 11 years earlier: a: spontaneous rib fracture showing non-union, abnormal callus and soft tissue calcifications that should not be confused with a sarcoma; b: 3D reformat showing the typical location of such radiation fractures in the 5th and 6th anterior segments of the ribs.
Disclosure of interest

The authors declare that they have no competing interest.

References


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