Radiation-induced lung disease after complex irradiation techniques

Poster No.: C-1892
Congress: ECR 2017
Type: Educational Exhibit
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Keywords: Toxicity, Radiotherapy techniques, Neoplasia, Radiation therapy / Oncology, Radiation effects, Complications, PET-CT, CT, Radiation physics, Oncology, Lung
DOI: 10.1594/ecr2017/C-1892

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Learning objectives

The purpose of this educational exhibit is to:

1. Illustrate the imaging patterns of radiation-induced lung disease (RILD) produced by complex irradiation techniques such as three-dimensional (3D) conformal radiation therapy (CRT) and stereotactic body radiation therapy (SBRT).

2. Discuss radiologic differentiation of RILD from infection, lymphangitic carcinomatosis and residual or recurrent malignancy.
Background

**Radiation-induced lung disease (RILD)** is frequent after therapeutic irradiation of intrathoracic and chest wall malignancies. Several factors can influence the degree of radiation damage to normal tissue, but irradiated lung volume is probably the most important in symptomatic radiation injury.[1,2]

**Traditional radiation techniques** result in the delivery of therapeutic radiation doses to a broad area, beyond the primary tumor margins, which increases the risk of side effects and therefore the maximum radiation dose that can be used is limited. However, evidence suggests that higher doses of radiation improve local tumor control, which is important to prevent metastatic dissemination and prolong survival.[3]

To reduce the toxic effects and improve the results of radiation therapy, techniques such as **three-dimensional conformal radiation therapy (3D-CRT)** and **stereotactic body radiation therapy (SBRT)** were developed. Instead of conventional radiation therapy, where the daily radiation dose is delivered to the tumor in two parallel beams with opposed orientations (e.g., antero-posterior and postero-anterior beams, with or without oblique angulation), in both SBRT and SBRT, multiple beams are used to generate a dose distribution that conforms tightly to the target volume.[3]

In **3D-CRT**, a 3D image reconstructed from Computed tomography (CT) data is used to determine the target volume to be irradiated. A computer planning system designs beam arrangements with various orientations depending on 3D configuration of the tumor. Multiple coplanar and noncoplanar radiation fields are used (Fig. 1 on page 6). The dose per day (fraction) is usually less than 2 Gy per field combination and the daily dose is conventionally administered over 6 to 7 weeks.[3,4]
Fig. 1: 54-year-old woman with non-small cell lung cancer T4N2M0 of the right upper lobe. a) Chest CT scan shows a central mass (*) with obstruction of the upper lobar bronchus and hilar lymph node involvement (arrow). Axial (b), coronal (c), and sagittal (d) CT images obtained for 3D CRT planning show the the spatial distribution of isodose curves (colored areas) with respect to the target volume. The tumor (pink lesion) and the region immediately surrounding it (red area) will receive the maximum radiation dose (100%), and normal surrounding lung structures will receive radiation doses that decrease with increasing distance from the tumor.

References: Radiology, Portuguese Institute of Oncology - Lisbon/PT

SBRT is a 3D conformal technique in which a stereotactic body frame is used to allow the delivery of high radiation doses given in fewer (usually 1-5) treatments to small, localized tumors (e.g., T1 and T2 non-small cell lung cancer) with great accuracy. In SBRT, a steeper gradient is generated between the periphery of the planned target volume (high-dose areas) and normal adjacent structures (low-dose areas) because the tumors treated with SBRT are smaller than those treated with 3D-CRT and the beam focus is therefore more narrowly circumscribed (Fig. 2 on page 6). In addition, SBRT assumes a hypofractionated scheme delivering the dose typically in 3-5 fractions over a period of 1-2 weeks; thus, a high ablative dose per-fraction is employed, typically 10-20 Gy/fraction, compared to conventional fractionation (2 Gy/fraction).[3,5,6]
Fig. 2: 48-year-old man with locally advanced oral squamous cell carcinoma history submitted to chemoradiation therapy. a) Follow up chest CT scan revealed a solitary cavitated nodule in the right upper lobe that biopsy proven to be a metastasis. b) Axial CT image obtained for planning of SBRT shows the several planar and non-planar beams employed and the dose distribution that conforms tightly to the planning target volume. Coronal (c) and sagittal (d) CT images show the the spatial distribution of isodose curves (colored areas) with respect to the target volume.

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The authors provide a pictorial review of the expected clinical and pathologic features and radiologic findings of lung injury after radiation therapy, particularly with 3D-CRT and SBRT; discuss the signs to suspect from infection, lymphangitic carcinomatosis and residual or recurrent malignancy in post treatment lung injury; and summarize the role of **positron emission tomography (PET)** performed with **fluorine 18 fluorodeoxyglucose (FDG)** in distinguish between RILD and residual or recurrent malignancy.
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Findings and procedure details

CLINICAL AND PATHOLOGIC FEATURES OF RILD:

Two distinct clinical stages are recognized in RILD: [3,7]

1. An early phase of transient radiation pneumonitis that usually occurs within the first 6 months after completion of treatment. Signs and symptoms may include dyspnea, cough, low-grade fever and chest discomfort.

2. A later phase of chronic radiation fibrosis, typically at 6-12 months after completion of treatment and usually becomes stable within 2 years after treatment (Fig. 3 on page 20). Fibrosis is more often asymptomatic but progressive dyspnea and persistent dry cough may be present and may be accompanied by signs and symptoms of cor pulmonale.

In RILD three sequential pathologic phases are distinguished: [3]

1. Acute exudative phase;

2. Organizing or proliferative phase;

3. Chronic fibrotic phase.

(1. and 2. correspond to radiation pneumonitis with more or less organized infiltration of macrophages, and 3. corresponds to radiation fibrosis with progressive collagen deposition and fibrotic changes.)
Fig. 3: 54-year-old woman with non-small cell lung cancer T4N2M0 of the right upper lobe. a) CT image obtained for 3D CRT planning shows the beam configuration needed to delivery the maximum radiation dose to the target volume. b) Chest CT scan obtained 1 month after completion of 3D CRT shows shrinkage of the mass (*) along with subtle ground-glass opacity (arrows). c) Chest CT scan obtained 3 months after completion of radiation therapy shows typical features of radiation pneumonitis with consolidation and ground glass opacities in the right upper lobe as also anterior paramediastinal ground glass opacities outside of the tumor site but still delimited by the radiation portals (arrows) d) 6 months after completion of radiation therapy, chest CT scan shows smaller consolidation with sharply defined margination between normal and irradiated lung parenchyma (arrow), suggestive of radiation fibrosis. Coexists subtle pleural thickening, volumetric loss and ipsilateral mediastinal deviation.

References: Radiology, Portuguese Institute of Oncology - Lisbon/PT

Different variables contribute to the **toxic effects** of radiation on the lungs: [2,3]

A. Patient factors:
- Lung performance status: basal pulmonary function;
- Presence of pre-existing disease, particularly involving irradiated area.

**B. Technical / therapeutic factors:**

- Total dose: correlation between radiation dose and the prevalence of radiation damage is not linear. Radiologic changes are rare after a total dose of less than 30 Gy, variably present after 30-40 Gy and universally seen after more than 40 Gy. As the radiation dose per fraction increases, the probability of late phase injury grows;
- Fractionation and Dose Rate: fractionation reduces the biologic impact of radiation;
- Irradiated lung volume (probably is the most important factor in symptomatic radiation lung injury): increased irradiated area increases radiation damage to normal tissue;
- Portals and beam arrangement: radiologic manifestations of lung injury usually correspond to the margins of the irradiated field;
- Physical characteristics of the irradiation;
- Use of chemotherapeutic agents that can potentiate the effects of radiation (e.g., actinomycin D, adriamycin, bleomycin, and busulfan);
- Steroids: although steroids ameliorate radiation pneumonitis, abrupt termination of administration can unmask latent radiation injury to the lung.

**RADIOLOGIC MANIFESTATIONS OF RILD:**

Radiation-induced lung changes should be classified as either **early** or **late phase** with regard to the time interval after the end of the treatment [5].

Radiologic manifestations of lung injury after conventional radiation therapy (**typical manifestations**) usually correspond to the margins of the irradiated field. Manifestations of RILD after 3D-CRT and SBRT may be similar to those of conventional therapy with regard to the timeline and radiologic findings in early and late phases, but usually have different morphologic characteristics, extent, distribution, and location (**atypical manifestations**) [3,5].

**A) After conventional radiation therapy** [1,7,8]
1. Early phase of radiation pneumonitis

- Ground-glass opacities, consolidation, or both, usually in the irradiated lung;

- Occasionally, an ipsilateral pleural effusion associated with atelectasis of the lung may develop.

2. Late phase of radiation fibrosis

- Well-defined area of volume loss with a linear scar of consolidation, parenchymal distortion, and traction bronchiectasis that conforms to the treatment portals;

- Consolidation usually coalesces and typically has a relatively sharp border that conforms to the treatment portals rather than to anatomic boundaries;

- Shrinkage of the region of fibrotic consolidation or a more sharply defined demarcation between normal and irradiated lung parenchyma may occur;

- Occasionally, an ipsilateral displacement of the mediastinum and adjacent pleural thickening or effusion may be present.

B) After 3D-CRT [2,9,10]

1. Early phase of radiation pneumonitis

- Focal or nodular ground glass opacity, consolidation, or both, usually limited to the area immediately surrounding the treated tumor;

- Findings farther from the tumor site, in both lungs, although still delimitated by the radiation portals (Figs. 3c e 4e).

2. Late phase of radiation fibrosis

CT findings of radiation fibrosis after 3D-CRT have been classified into four patterns:

- Modified conventional pattern: well-defined consolidation with volume loss and traction bronchiectasis, less extensive than conventional radiation fibrosis (Fig. 4f);
Fig. 4: 50-year-old man with right upper lobe adenocarcinoma T4N0Mx. a) Initial evaluation shows a mass (*) in the left upper associated to ground-glass opacities (arrows) and reticular densification. b) CT scan after chemotherapy shows a decrease in the size of the mass (with more spiculated margins). c) CT image obtained for radiation therapy planning shows the target volume of 3D CRT. A total dose of 70 Gy was administered. d) Three months after completion of 3D CRT, chest CT scan shows shrinkage of the tumour with minimal peripheral ground glass opacity (arrow). e) Six months after radiation therapy the lesion maintains the same dimension but is now involved by patchy consolidation (arrowhead) and ground glass opacities within the radiation portals (radiation pneumonitis); coexist a linear ground glass opacity in the right lung with an orientation corresponding to a radiation field (arrow) f) One year after completion of radiation therapy, axial CT scan shows progressive resolution of exudative process and a well defined consolidation with air bronchogram associated with parenchyma distraction, traction bronchiectasis and lung volume loss compatible with a modified conventional pattern of radiation fibrosis (arrow).

References: Radiology, Portuguese Institute of Oncology - Lisbon/PT

- *Scar-like pattern*: Linear opacity less than 1 cm wide that is associated with moderate to severe volume loss and that remains at the tumor site when the primary tumor has completely resolved (Fig. 5 on page 21);
Fig. 5: 62 year-old-man with solitary lung nodule. a) Chest CT scan shows a nodule in the lateral segment of the left inferior lobe that biopsy proven to be lung adenocarcinoma. b) Axial CT image obtained for SBRT planning. c) Chest CT scan obtained 3 months after completion of SBRT shows shrinkage of the tumor and patchy ground glass opacity within the irradiated area. d) Chest CT scan obtained 1 year after completion of SBRT demonstrates resolution of the tumor with a linear opacity distorting the parenchyma, but with no other visible lung abnormalities (scar-like pattern of radiation fibrosis).

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- Mass-like pattern: when consolidation with traction bronchiectasis is focal and confined to a 2 cm margin around the original tumor (the region corresponding to the maximal isodose curve delivered), the CT appearance is that of a mass-like area larger than the original tumor; Unlike of the modified conventional and scar-like patterns, the mass-like
pattern can easily be misinterpreted as malignancy in the absence of a history of 3D conformal irradiation. (Fig. 6 on page 22)

Fig. 6: a) Follow up chest CT scan shows recurrence of lung adenocarcinoma in the left upper lobe after a initial treatment with a right lower lobectomy. b) Axial CT image obtained for planning of SBRT. c) Chest CT scan obtained 3 months after completion of SBRT shows shrinkage of the tumor with no other visible lung abnormalities. d) Chest CT scan obtained 6 months after completion of SBRT shows patchy ground glass opacity within the irradiated area (arrow). e) Chest CT scan obtained 12 months after completion of radiation therapy shows a consolidation with no convex margins and with air bronchogram within the irradiated area (arrow). f) PET image shows low FGD uptake suggesting radiation fibrosis (mass-like pattern).

References: Radiology, Portuguese Institute of Oncology - Lisbon/PT

C) After SBRT [11,12]

The incidence of symptomatic pneumonitis is, in general, low in patients treated with SBRT and that might be related to the fact that only a small volume of lung parenchyma is treated with a dose that would result in pneumonitis. However, radiographic pneumonitis occurs in more than 60% of patients following SBRT.

Lung abnormalities are usually within the high-dose region, which encompasses the tumor and a 3D margin of normal tissue, and are not usually seen at sites remote from the target volume. SBRT in centrally located tumors (< 2 cm around the proximal bronchial tree) seems to have an increased risk of severe toxic effects.
Additionally, lung abnormalities do not usually occur before 2-3 months after completion of therapy, because of the high dose per fraction.

1. Early phase of radiation pneumonitis

CT findings of radiation pneumonites after SBRT have been classified into five patterns:

- Diffuse consolidation;
- Diffuse ground glass-opacities (Fig. 4c);
- Patchy consolidation and ground-glass opacities;
- Patchy ground-glass opacities (Fig. 6d);
- No change.

(The findings are defined diffuse or patchy if lung abnormalities completely fill the high dose region).

2. Late phase of radiation fibrosis

- Similar to 3D-CRT but more circumscribed because a smaller lung volume is exposed to radiation.

DIFFERENTIAL DIAGNOSIS

Patients with thoracic malignancies treated with radiation can develop RILD as well as superimposed lung disease. Additionally, infection and recurrence of underlying malignancy can manifest clinically and radiologically in similar manner as RILD. Careful differential diagnosis is important for determining appropriate therapy. In each case it is relevant to: [5,13]

1. Understand the relationships between CT manifestations and times of initiation and completion of radiation therapy, beam arrangements, and radiation dose delivered;

2. Review chest radiographs and CT scans obtained at the initiation of, during and after therapy.

Infection [3,14,15]

The presence of an infection should be considered if:
1. CT scans show pulmonary opacities before the completion of therapy or outside the radiation portal or if diffuse or bilateral lung abnormalities are present;

2. CT findings respect the anatomic boundaries;

3. Centrilobular nodules with a "tree-in-bud" appearance associated with consolidation or cavitation are more likely due to infection (e.g., tuberculosis) than RILD (;

4. Occurs an abrupt onset of lung abnormalities, since radiation pneumonitis normally follows a more indolent course than infection does.

**Fig. 8**: Pulmonary infection in 74-year-old man with stage IV adenocarcinoma of the right upper lobe. a) Coronal CT image shows a large invasive mass in the right upper lobe (⋆) submitted to palliative radiation therapy. b) CT scan obtained 6 months after completion of radiation therapy shows poorly defined centrilobular nodules in the right lower lobe (arrows) outside the radiation treatment port.

**References**: Radiology, Portuguese Institute of Oncology - Lisbon/PT

*Lymphangitic carcinomatosis* [3,14,15]

The presence of lymphangitic carcinomatosis should be considered if:

1. Dyspnea is out of proportion to the extent of radiologic involvement;

2. Rapid progression of clinical symptoms and radiologic manifestations (nodular septal thickening, outside radiation portal, and non-defined boundaries).

*Tumor recurrence* [14,15]
The presence of tumor recurrence should be suspected if:

1. As RILD stabilizes, there is an alteration in the contour and dimensions of the fibrotic area;

2. Parenchymal consolidation with a straight lateral margin and air bronchogram is typical for radiation fibrosis, whereas a homogeneous opacity without air bronchogram and with a convex border is strongly suggestive of recurrent tumor in the irradiated lung (Fig. 9 on page 24);

3. Filling in of bronchi within radiation fibrosis is abnormal and usually represents local recurrent malignancy or a superimposed infection;

4. Other signs of tumor recurrence appear (e.g., nodules outside the zone of radiation fibrosis, pleural effusion long after treatment completion, bone destruction, or mediastinal involvement).

**Fig. 9:** Recurrent adenocarcinoma in a 63-year-old man. a) Chest CT scan obtained 12 months after completion of 3D CRT shows bilateral findings of radiation fibrosis. (b, c) Axial chest CT scan obtained 18 (c) and 24 (d) months after completion of radiation therapy shows progression of consolidation without air bronchogram and with convex borders in the irradiated lung, suggestive of tumor recurrence (arrow).

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In addition to genetic predisposition and age-related cancer risk, radiation is a well-established carcinogen, particularly with regard to induction of solid tumors. Lung cancer may arise within or at the edge of the irradiated area. The appearance of homogeneous consolidation or increased opacity within pre-existing and stable lung abnormalities in the irradiated areas over a long interval should arouse the suspicion of radiation-induced tumor (Fig. 10 on page 24) [1,16].
Fig. 10: 68-year-old woman with history of breast carcinoma submitted to left mastectomy and radiation therapy. a) Chest CT scan obtained 5 years after radiation therapy shows fibrosis in the left upper lobe (arrow) secondary to radiation therapy. b) Chest CT scan obtained 7 years after radiation therapy shows fibrosis and a small rounded opacity with convex margins and with no air bronchogram (arrowhead) which was not valued. c) Chest CT scan obtained 1 year later reveals progression of the rounded opacity (arrowhead). Biopsy proven to be a new lung adenocarcinoma.

References: Radiology, Portuguese Institute of Oncology - Lisbon/PT

Role of FDG PET [2,15]

FDG PET may have a role in evaluation of patients with RILD, according as:

1. FDG PET allows distinction of metabolically active tumor from inactive fibrosis after radiation therapy;

2. Provides higher accuracy than CT alone for distinguishing residual or recurrent tumor from lung changes after radiation treatment (Fig. 11 on page 25);

3. A normal FDG PET study in patients with RILD has high negative predictive value;

4. Limitation: False-positive uptake of FDG early after completion of radiation therapy (radiation pneumonitis can have increased uptake that mimics recurrent disease) - FDG PET should not be performed until 3 months after the completion of radiation therapy.
Fig. 11: 65-year old woman treated for lung adenocarcinoma with a right lower lobectomy. a) Integrated PET/CT scan image obtained 12 months after surgery shows a nodule in the posterior region of the right upper lobe with high FDG uptake. Bronchoscopy with biopsy proven to be a recurrence. b) Axial CT image obtained for planning of SBRT with a total dose of 48 Gy. c) Axial CT scan obtained 3 months after completion of SBRT shows small patchy consolidation (arrow) and ground glass opacity (arrowhead) in the irradiated area. d) Axial CT scan obtained 6 months after completion of SBRT shows increase of consolidation with some air bronchogram but with convex borders (arrow). e) PET integration shows that the medial component has high FDG uptake representing increased metabolic activity. A biopsy proved malignancy.

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**Fig. 7:** 48-year-old man with right upper lobe metastasis from oral squamous cell carcinoma. a) Axial CT image obtained for planning of SBRT shows the beam configuration needed for delivery a total dose of 60 Gy. c) Chest CT scan obtained 3 months after completion of SBRT, shows shrinkage of the nodule involved by ground-
glass opacity (arrows) confined to the high-dose region, which is indicative of radiation pneumonitis.

Fig. 8: Pulmonary infection in 74-year-old man with stage IV adenocarcinoma of the right upper lobe. a) Coronal CT image shows a large invasive mass in the right upper lobe (*) submitted to palliative radiation therapy. b) CT scan obtained 6 months after completion of radiation therapy shows poorly defined centrilobular nodules in the right lower lobe (arrows) outside the radiation treatment port.

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a total dose of 48 Gy. c) Axial CT scan obtained 3 months after completion of SBRT shows small patchy consolidation (arrow) and ground glass opacity (arrowhead) in the irradiated area. d) Axial CT scan obtained 6 months after completion of SBRT shows increase of consolidation with some air bronchogram but with convex borders (arrow). e) PET integration shows that the medial component has high FDG uptake representing increased metabolic activity. A biopsy proved malignancy.

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Conclusion

Radiologic manifestations in RILD typically have a characteristic temporal relationship to the completion of therapy.

The complex portal configurations in 3D CRT and SBRT result in lung abnormalities that differ from typical manifestations induced by conventional radiation therapy in regard to their morphologic characteristics, extent, distribution, and location.

Understand this temporal relationship and the expected patterns of radiation pneumonitis and fibrosis is critical to suggest a diagnosis of RILD and to differentiate RILD from superimposed infection or recurrent tumour.

FDG-PET may have an important role in differentiate between RILD and residual or recurrent tumor, particularly when performed at least 3 months after the completion of radiation therapy.
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