CT appearance of pulmonary carcinomas after stereotactic radiation therapy

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**Abstract** Stereotactic radiation therapy (SRT) is becoming more and more important in the treatment of inoperable patients with early stages of pulmonary carcinomas (T1-T2 N0M0). In certain cases, evaluation of the response is still problematical and it can be difficult to differentiate response from progression. The aim of this paper is to set out these various changes and to produce a protocol for optimal monitoring. By comparing our clinical experience with data from the literature, the main visual aspects on a CT scan are set out and illustrated for each clinical situation: radiation pneumonitis, radiation fibrosis, therapeutic response and progression. The literature was reviewed by querying the main databases and selecting papers concerning pulmonary SRT and post-therapeutic radiological appearance. CT appearance induced by SRT differs significantly from images after classic conformal radiation therapy, both morphologically and chronologically. In particular, the modifications induced by stereotactic radiation therapy are only seen in a limited volume surrounding the volume treated. Knowledge of the radiological criteria necessary to differentiate between a therapeutic response and recurrence is of major importance in the present context of increase in use of this technique.

**Context**

Stereotactic radiation therapy (SRT) is used for the management of early stage pulmonary carcinomas in inoperable patients [1—4]. Owing to its great accuracy, it opens the way to radiation ablation treatments with very high doses per fraction and a biological equivalent in the order of 110 to 180 Gy [5].

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A report published by the French National Authority for Health (Haute Autorité en santé – HAS) in 2006 considered the benefits expected from extracranial stereotactic radiation treatment for primary bronchopulmonary tumours and slow-growing pulmonary metastases with a controlled primary tumour as being sufficient [6]. Since then, many studies, most of them retrospective and with limited numbers, have been published and have confirmed the usefulness of this type of technique [2–4,7–10]. In the years to come therefore, it may well be used more and more and possibly be considered for the treatment of operable patients [11], if the results of prospective studies currently underway are convincing (STARS and ROSEL trials). Although the radiological appearance after fractionated three-dimensional conformal radiation therapy has been described in the literature [12], the CT changes following treatment with pulmonary stereotactic radiation therapy differ significantly and have still not been greatly described and are little known. Indeed, the irradiation technique, dose distribution, biological effect of high doses per fraction and the total time of treatment suggest that the radiological results will not be comparable with those found after conventional external beam radiation therapy. Radiologists and radiotherapists consequently need to be aware of the radiological appearance following such treatment in order to determine its efficacy. The aim of this review is to describe and illustrate the early and late CT characteristics found after SRT, to set out the risk factors for toxicity, and to propose an optimal post-SRT radiological monitoring protocol.

Methods

We searched for all the papers concerning SRT, early stage lung cancer and radiological appearance after treatment in the Medline (Pubmed), Google Scholar and ScienceDirect electronic databases. Only papers in French and English published between 1990 and 2011 were included. The keywords used were: stereotactic body radiation therapy (SBRT), lung cancer, radiological findings, toxicity, radiation pneumonitis, and radiation fibrosis.

There were two stages to the process: firstly, we selected all the papers concerning extracranial stereotactic radiation therapy applied to treatment of early stage pulmonary carcinomas. Secondly, we selected all the papers devoted to the radiographic appearance found after SRT and other factors predicting toxicity.

Our centre has been treating patients by stereotactic radiation therapy since 2008 [13]. Three hundred and twenty-four patients have been treated in our department for pulmonary tumours with levels of local control of 100% at 6 months [3], 92% after a year and 86% after 2 years for the patients treated with real time monitoring of the target (results not published). Post-therapeutic CT scans performed as part of monitoring patients treated by robotic CyberKnife® stereotactic radiation therapy, with real time monitoring of the target without fiducial marker, have provided illustrations of the main eventualities. All the patients whose CT scans are presented were treated with the protocol most generally used at present (three sessions of 20 Gy).

Results

The search found 222 papers concerning stereotactic radiation therapy for the treatment of early stage pulmonary carcinoma. Of these, 21 papers dealt specifically with the use of imaging for evaluating the response and factors predicting toxicity after stereotactic radiation therapy.

Stereotactic radiation therapy for pulmonary carcinoma

Stereotactic radiation therapy is at present playing an increasing part in the treatment of pulmonary tumours. The principle of stereotactic radiation therapy differs from that of conformal radiation therapy in the very great accuracy it provides. The conformity of the therapy is greatly improved by multiplying the number of treatment beams (up to 150 in certain treatment plans) which are often non-coplanar and non-isocentric [14]. It is possible to increase the dose per fraction, the total dose, and thus the biological equivalent dose, allowing ablative doses to be reached and access to the area of extracranial radiosurgery. This treatment, for inoperable patients with pulmonary carcinoma, is reserved for early stages, T1 or T2, of less than 6 cm, with no lymph node or distant metastases.

Differences from conformal EBRT

For conventional radiation therapy, the lung injuries induced are usually described as early or late reactions [13,15].

Early reactions occur between 1 and 6 months after treatment. Fibrosis appears on pulmonary parenchyma having had radiation pneumonitis and becomes apparent between 12 and 24 months after the radiotherapy. Most of these occurrences are asymptomatic and do not require specific treatment. CT modifications affect the field of treatment and do not keep to anatomical limits. Condensations, ground glass opacities and an infiltrate in the treated area, with or without disappearance of the vascular or bronchial contours, are characteristic of the initial phase, in which nodules or focal condensations may also appear. Pleural effusion may sometimes be found. These aspects can gradually regress or lead to pulmonary fibrosis in the severest cases.

Pulmonary fibrosis appears as a well-defined area of loss of volume, linear scarring, septal thickening, opacity and bronchiectasis producing a picture of interstitial pneumonia. Mediastinal deviation may also be found. The characteristic SRT dose distribution is radically different from that of treatment using standard conformal radiation therapy [16]. Consequently, lung injuries induced by SRT are not presented in the same way: the linear shape of lung injuries caused by conformal radiation therapy, clearly delineated between the irradiated and non-irradiated tissue, is not found here. In SRT, the low dose regions are larger and irregular, since there are more treatment beams and more angles. In contrast, the high dose area is uniform and smaller in size. The shape of SRT-induced lesions thus more precisely matches the initial PTV and is not linear. A spherical shape is often found which is perhaps explained by the great conformity and homogeneity of the dose. Secondly, the chronology of the appearance of abnormalities is different: most changes
appear less than 3 months after treatment. This latency period is not found with conformal radiation therapy since the majority of modifications occur in the first weeks after treatment [17,18]. This difference may be explained by the radiobiology of high doses per fraction [5,19,20].

Radiofrequency as treatment of early stage bronchial carcinoma

Radiofrequency ablation (RFA) is a minimally invasive technique initially used as a palliative treatment for pulmonary carcinomas which has gradually become a curative option for inoperable patients, in the same way as stereotactic radiation therapy. Studies report levels of local control of between 57% and 100%, depending on the stage treated [21–26]. This technique has the advantages of being able to be offered to inoperable patients and of being performed in one session. It can also treat several pulmonary lesions. Its drawbacks are related to the transthoracic puncture needed for the procedure, particularly haemorrhage or pneumothorax. However, these complications are not common, ranging between 10% and 34% [22,24] if patients are correctly selected. When patients are considered to be too greatly at risk, particularly for the puncture, a stereotactic radiation technique with non-invasive monitoring of the target can be suggested. Finally, RFA carries no risk of radiation pneumonitis or pulmonary fibrosis, which can sometimes be encountered after stereotactic radiation therapy.

Main radiological visual aspects after stereotactic radiation therapy

The radiologist who has to assess the changes in a patient’s pulmonary carcinoma treated by SRT faces many difficulties. Differentiating progression of the disease from a response can often prove difficult given the specific radiological characteristics explained above. However, knowledge of some clearly described radiological signs will help answer the majority of questions. We will now first set out the signs related to toxicity of the treatment, then those connected with progression of the disease, and finally the signs suggesting a therapeutic response.

Radiological signs related to toxicity of the treatment

Early toxicity

The principle of stereotaxy consists of increasing the number of incidences of photon beams converging on the target, thus creating a strong dose gradient between the adjacent organs at risk and the tumour to be treated. This particular feature, which distinguishes it from standard conformal radiation therapy, creates unique radiographic changes.

The changes induced by SRT have been classed into five categories [27,28]:

- diffuse condensation (Fig. 1): diffuse, uniform increase in the attenuation of the pulmonary parenchyma which masks the vessels and the bronchial walls and totally fills the field of irradiation. An air bronchogram may be seen in the treated area;
- diffuse ground glass opacity (Fig. 2): increase in the density of the parenchyma, this time retaining the vascular and bronchial contours present in the treated area;
- patchy heterogeneous condensation with ground glass opacity: heterogeneous mosaic areas of increased density which no longer totally fills the area treated;
- mosaic of ground glass opacity: patchy areas of increased attenuation and normal tissue density found around the tumour, not totally filling the area treated;
- no reaction: no increase in the density of the parenchyma in the area treated.

Late toxicity

The appearance of pulmonary fibrosis induced by SRT has been classified into four categories [27,29]:

- modified conventional images (Fig. 3): condensation, loss of volume, bronchiectasis similar but less extensive than in conventional conformal radiation therapy;
- mass type image (Fig. 4): limited focal condensation around the tumour;

Figure 1. A 84-year-old female patient treated for a right upper lobe lesion: a: CT scan before treatment; b: CT scan 4 months after treatment showing radiation pneumonitis extending to the area which had received the maximum dose, shown by irregular condensation with persistence of an air bronchogram.
• scarring image (Fig. 5): linear opacity located in the region of the tumour associated with loss of pulmonary volume;
• no radiological interpretation: no increase in density in the field of treatment.

In a study by Trovo et al. [16], 74 to 76% of the patients treated had images compatible with pulmonary fibrosis. In most cases, these images stabilised after 12 months.

Differential diagnosis between recurrence and radiological changes induced by SRT

The main signs of recurrence described in three-dimensional conformal radiation therapy — filling of the bronchiectases induced by the radiotherapy and the appearance of a convexity at the limits of the mass [30,31] — cannot always be used when an SRT has been performed [32,33]. Similarly, the RECIST criteria are sometimes no longer usable because an increase in condensation of the pulmonary parenchyma is not always correlated with progression when SRT has been undertaken. The signs need therefore to be described which make it possible to differentiate between continued progression and expected recurrence of toxicity due to the SRT.

Two studies have taken an interest in changes in images after SRT and in the signs which ought to indicate recurrence. Matsuo et al. followed 40 pulmonary tumours (30 primary and 10 metastases) treated by SRT [33]. For the 43% patients in partial response, the median minimal diameter was found after 8 months of treatment. The complete response rate (disappearance of the tumour) was 20%. Up to 57% of the patients presented radiation pneumonitis reactions which were impossible to evaluate. Only the increase in condensation after 12 months was found to be a statistically significant factor for recurrence (P = 0.001). The other, non-significant factors explored were the disappearance of bronchiectasis in the volume treated, the degree of radiation pneumonitis, modifications before 12 months and dose conformality. However, a second study by Kato et al. [34] in 27 patients treated by SRT for early stage pulmonary

Figure 2. A 74-year-old male patient, treated for a left upper lobe lesion: a: CT scan before treatment; b: CT scan 3 months after treatment with poorly demarcated ground glass appearance.

Figure 3. A 83-year-old male patient, treated for a right upper lobe lesion: a: CT scan before treatment; b: CT scan 15 months after treatment, showing widespread radiation fibrosis which could be interpreted as recurrence.
carcinoma found five recurrences and showed the importance of the disappearance of bronchiectasis as a sign of recurrence. Of the patients who developed recurrence, three had had an air bronchogram following the SRT all of which disappeared (100%). In addition, the patients with recurrence all presented pleural effusion and an increase in diameter of the condensation 12 months or more after the SRT.

The main signs which should therefore suggest recurrence rather than radiation pneumonitis are:

- location: continuity with the treated tumour lesion;
- distribution: modification of the contours of the fibrosis;
- radiological signs:
  - disappearance of bronchiectasis initially found,
  - appearance of pleural effusion;
- chronology:
  - modifications are possible between 6 and 9 months,
  - after 12 months, an increase in size or a modification of the contours should no longer be found.

**Relationship between CT scan modifications and pulmonary emphysema**

Stereotactic radiation therapy for pulmonary lesions is currently indicated for inoperable patients. The majority of these patients are elderly [35,36] or have considerable pulmonary comorbidities such as an advanced stage of emphysema. It is therefore important to know the type of parenchymal reactions induced by SRT in this type of patient so as to be able to determine the response and select patients who can benefit from the treatment without needing to anticipate increased toxicity. The role of pulmonary emphysema in the reaction of lung tissue to SRT has been explored by Kimura et al. [28]. In their study, 18 of the 47 patients (52 lesions) treated had emphysema (almost exclusively men, n = 17). Expiratory volume was lower in patients with emphysema (FEV greater than 70% in 19 patients without emphysema but in only six patients with emphysema). The percentage of patients with
Figure 6. A 63-year-old female patient with a history of right upper and middle lobectomy in 2005 for a hilar neuro-endocrine tumour and adjuvant radiotherapy for capsular rupture of a lymph node in station 7r. A CT scan in July 2008 found a PET fixing right lower lobe node. Treated by CyberKnife® (3 × 20 Gy) in November 2008: a: CT scan before treatment; b: treatment dosimetry produced by CyberKnife® — coronal slice; c: treatment dosimetry produced by CyberKnife® — sagittal slice; d: CT scan 6 months after treatment — transverse slice with dosimetry; e: CT scan 6 months after treatment — sagittal slice with dosimetry: the area of peritumoral radiation pneumonitis corresponds to the crossing of the treatment beams.

Modification of respiratory functions after pulmonary stereotactic radiation therapy

Stereotactic radiation therapy does not seem to have any impact on the pulmonary functions of patients treated.

emphysema was lower among those showing diffuse condensation ($P=0.0108$) or modified conventional images ($P=0.0288$). In addition, the patients with emphysema presented more scar type reactions ($P=0.00038$) or showed no increase in density ($P=0.00044$).
Stephans et al. have published a study on 134 patients evaluating the modifications to respiratory function tests after pulmonary stereotactic therapy [37]. The forced expiratory volume in 1 second (FEV1) decreased non-significantly by 0.05 L (from −0.98 to +1.29, *P* = 0.22). The mean diffusion capacity of the lungs for CO (DLCO) similarly decreased non-significantly by 2.59% (from −37% to +33%, *P* = 0.27). There was no significant difference in variation of the FEV1 between patients treated for central or peripheral tumours (*P* = 0.55).

**Proposals for a monitoring protocol**

Radiation pneumonitis reactions are common at 3 and 6 months and even if, in the majority of cases, they have no clinical consequences, they make evaluation of the response difficult. These reactions resolve spontaneously and often require no treatment. Corticosteroids are however sometimes necessary for the most serious cases. Up to 10% of patients present radiation pneumonitis after SRT [38], so that it is therefore essential to monitor these patients early on and in the long term, firstly to detect the most severe cases needing treatment and secondly in order to distinguish between a response, radiation pneumonitis and progression.

At present, there are two recommendations which can be applied to patients treated by SRT. The first, published by the American College of Chest Physicians (ACCP) in 2007 [39], concerns monitoring patients with non-small cell lung cancer undergoing curative treatment. For this population, the ACCP recommends monitoring for complications due to the treatment for 3 to 6 months and CT or chest X-ray screening for recurrence every 6 months for 2 years, then annually. The European Society for Medical Oncology (ESMO) also published recommendations in 2009 [40], pointing out that monitoring treated patients is still controversial and proposing an Imaging examination every 3 to 6 months for 2 years, then every 6 to 12 months afterwards. This follow-up protocol could be adapted for patients treated by SRT. Appropriate close monitoring could consist of a thoracic-abdominal-pelvic CT scan at 1, 3, 6, 9 and 12 months, then every 6 months. Several centres also use FDG-PET to detect recurrence, although to date the level of evidence is not sufficient for its use in monitoring. For this approach to be considered valid, an FDG-PET would have to be performed before the treatment, then at 6 months and then every 6 months, alternating with a CT scan for 2 years, the annually after that. Performing an FDG-PET before 6 months could find abnormal FDG uptake in the area treated without it being possible to decide between progression and radiation pneumonitis. It could also be interesting to merge the re-evaluation CT scan and the dosimetry of the treatment given (Fig. 6) to determine whether the areas affected by the attenuation modifications correspond to the field treated.

**Conclusion**

The radiological changes induced by pulmonary stereotactic radiation therapy are specific to this technique and differ from the visual aspects known for conformal radiation therapy, in terms of topography and chronology. Evaluation of the response is therefore based on criteria which radiologists and radiotherapists need to know. Dose distribution is an essential element which helps understand the biological phenomena induced by the treatment and should therefore be used to interpret the results.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

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