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Case report

Illustration of a fatal radiation-induced lung aneurysm: Is central lung stereotactic radiotherapy to be banned?

Illustration d'un anévrysme pulmonaire radio-induit fatal : faut-il bannir la stéréotaxie pulmonaire centrale ?

B. Ledoux[a,*], M. Dupont[b], F. Duplaquet[c], L. Pirard[c], S. Ocak[c,d,e], M. Wanet[f], V. Remouchamps[e,f]

[a] *Department of Radiation Oncology, Cliniques Universitaires Saint-Luc (CUSL), avenue Hippocrate 10, 1200 Wolluwe-Saint-Lambert, Belgium*
[b] *Department of Radiology, CHU UCL Namur, site Godinne, rue Dr-Gaston-Thérasse 1, 5530 Yvoir, Belgium*
[c] *Department of Pneumology, CHU UCL Namur, site Godinne, rue Dr-Gaston-Thérasse 1, 5530 Yvoir, Belgium*
[d] *Pôle de Pneumologie, ORL et Dermatologie (PNEU), Institut de recherche expérimentale et clinique (Irec), Université Catholique de Louvain (UCL), avenue Hippocrate 10, 1200 Wolluwe-Saint-Lambert, Belgium*
[e] *Namur Research Institute in Life Sciences (Narilis), Namur, Belgium*
[f] *Department of Radiation Oncology, CHU UCL Namur, site Sainte-Élisabeth, place Louise-Godin 15, 5000 Namur, Belgium*

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ABSTRACT

Stereotactic body radiation therapy is still controversial for inoperable patients with central lung lesion. We report the case of a 59-year-old woman with previous history of head and neck squamous cell carcinoma who was treated by lung stereotactic body irradiation for an inoperable lymph node in station 10R. One year after, a fibroscopy showed a necrosis of the right main bronchus mucosae and the CT showed a radio-induced aneurysm protruding into the right inferior lobular bronchus. The patient eventually died a few hours later with a massive haemoptysis. This case highlights the potential toxicity of central lung stereotactic body radiation therapy and raises the question of its legitimacy.

Mots clés :
Lésion pulmonaire
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Tumeur centrale
Toxicité à long terme
Anévrisme
Hémoptysie

RÉSUMÉ

La radiothérapie stéréotaxique pulmonaire reste actuellement une technique controversée chez les patients inopérables atteints d'une lésion pulmonaire centrale. Nous rapportons le cas d'une femme de 59 ans ayant un antécédent de carcinome épidermoïde ORL qui a été prise en charge par radiothérapie stéréotaxique pulmonaire pour un ganglion lymphatique inopérable en station 10R. Un an plus tard, une fibroscopie a révélé une nécrose de la muqueuse de la bronche principale droite et la scanographie a révélé un anévrisme radio-induit faisant protrusion dans la bronche lobulaire inférieure droite. La patiente est finalement décédée quelques heures plus tard d'une hémoptysie massive. Ce cas met en évidence la toxicité potentielle de la radiothérapie stéréotaxique pulmonaire centrale et soulève la question de sa légitimité.

1. Background

The incidence of lung cancer is around 52/100,000 per year in European Union with approximatively 80% of non-small cell

* Corresponding author.
E-mail address: benjamin.ledoux@uclouvain.be (B. Ledoux).

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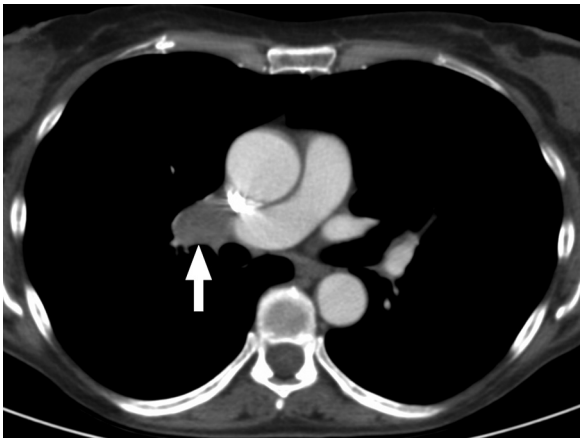

Fig. 1. Axial contrast-enhanced computed tomography at the level of the hilum, in a patient with history of squamous cell carcinoma, showing right enlarged lymph node (large white arrow).

lung cancer. For early stage non-small cell lung cancer, the standard of care remains an anatomic surgical resection (i.e. lobectomy/pneumonectomy and lymphadenectomy). Unfortunately, amongst all patients with stage I non-small cell lung cancer, around 20% are inoperable due to age, other comorbidities such as chronic obstructive pulmonary disease or heart disease. For inoperable patients with small peripheral early stage, lung stereotactic radiation therapy is nowadays a widely accepted alternative. For central lesions (which are by definition located within 2 cm around proximal bronchial tree and immediately adjacent to mediastinal or pericardial pleura), it is still under debate to treat such patients with stereotactic body irradiation due to the risk of high grade toxicity (haemoptysis, bronchi stenosis, fistulae, etc.) [1]. We report here sudden haemoptysis leading to death of a 59-years old woman receiving lung stereotactic radiation therapy at the dose of 8×7.5 Gy for a centrally located tumour. To our knowledge, this is the first description of a lung stereotactic radiation therapy-induced aneurysm described before sudden haemoptysis.

2. Case presentation

The patient had a previous history of squamous cell carcinoma of the neck with unknown primary tumour (pTxN2bM0 according to TNM 7th edition) that initially required a unilateral lymph node dissection followed by concomitant chemoradiotherapy and adjuvant chemotherapy. Eighteen months after the surgery, during the follow-up of her head and neck squamous cell carcinoma, a positron-emission tomography (PET)-computed tomography (CT) was performed (on the basis of weight loss and fatigue without other clinical signs including a negative nasolaryngopharyngeal endoscopy) that showed a pathologic lymph nodes in station 10R (Fig. 1) and no other recurrence in the neck or other distant metastasis. An endobronchial ultrasound was performed and pathology revealed an non-small cell lung cancer with unclear origin. After multidisciplinary oncologic staff review, the patient was considered inoperable (due to her poor lung conditions with forced expiratory volume [FEV_1] at 52% of predicted values, ongoing smoking addiction, history of cancer and arterial hypertension) and decision was taken, after discussion with the patient, to treat the hilar lymph node with stereotactic radiotherapy. The treatment consisted in an irradiation of 60 Gy in eight fractions scheduled three times a week in stereotactic condition with a linear accelerator producing photons of 6 MV. The patient was immobilized with a customized thermoplastic mask, respiratory movement was taken into account with a 4D-CT scan during simulation and positioning corrections were managed by a radiation oncologist on each day of treatment. The tolerance of treatment was excellent with no immediate adverse event. At the beginning the follow-up was good with a regression of the lymph node objected by CT scans and no comorbidities. One year after radiotherapy, she developed cough with expectorations and temperature treated by her general practitioner with cefuroxime. She was hospitalized after one week due to a lack of improvement and an increasing dyspnoea to grade 3. The Eastern Cooperative Oncology Group (ECOG) performance status was 2. Piperacillin and tazobactam were introduced due to persistent high fever. Blood samples and expectorations cultures never showed any pathogen agent. One day after her admission, she started some haemoptysis. A fibroscopy showed a necrosis of the right main bronchus mucosae without active bleeding. Pathology revealed essentially inflammatory tissue without signs of tumoral recurrence. A contrast-enhanced chest multidetector CT was then performed and showed a necrotizing pneumonitis of the right superior lobe, a complete condensation of the right inferior and middle pulmonary lobe, an aneurysm of 10×13 mm of the right descending interlobar artery protruding into the right inferior lobular bronchus, and the necrosis of the right main bronchus (Fig. 2). Vascular stenting was recused because there was suspicion of sepsis. No action could be done, and the patient eventually died a few hours later with a massive haemoptysis.

3. Discussion

Nowadays, stereotactic body radiation therapy with fractionation schemes like three fractions of 15 or 18 Gy, four fractions of 12 Gy or eight fractions of 7.5 Gy is widely used and achieve a local control of around 90% [1]. European Society for Radiotherapy and Oncology (ESTRO) consensus guidelines about stereotactic body radiation therapy for peripherally located tumour were published in 2017 and recommend 3×15 to 18 Gy to peripheral tumour (as recommended also based on the results of study Radiation Therapy Oncology Group [RTOG] 0236) or 4×12 for tumour with broad chest wall contact [2]. Unfortunately, for centrally located tumours, there is still no consensus for stereotactic body radiation therapy despites it is largely used in common practice. Indeed, it still remains unclear if central tumour should be treated with stereotactic body irradiation and if so, which fractionation should be used with which constraints to avoid late high grade toxicity such as massive haemoptysis, oesophageal/bronchi stenosis or fistulae.

In 2013, from the largest retrospective study of 563 central lung tumours treated with stereotactic irradiation with a biological equivalent dose (BED_{10}) at least 100 Gy, an overall treatment-related mortality of 2.7% was reported (16 patients out of 563 amongst which four died of haemoptysis) and 1% if BED_3 was 210 Gy or less (i.e. 8×7.5 Gy). Grade 3 to 4 toxicity occurred in less than 9% [3]. More recently, amongst 80 patients treated with volumetric arctherapy using 8×7.5 Gy for central lung tumours, treatment-related death was considered possible or likely in six patients (7.5%) with 2 fatal haemorrhage [4].

In 2015, dose constraints recommendations were proposed on behalf of the International Association for the Study of Lung Cancer (IASLC) Advanced Radiation Technology Committee, depending on the fractionation scheme (4×12.5 Gy, 5×10 Gy, 5×12 Gy or 10×7 Gy) [5]. They were meant as a guide to help clinicians but prospective clinical trials are still needed to validate these constraints. Central locations were considered as not to be a “no fly zone” as long as the dose – volume constraints are maintained below its thresholds value for each structure to avoid dangerous side effects. However, it is also recommended that irradiation of ultra-central lesion (i.e. hilar and mediastinal lesions) should not be

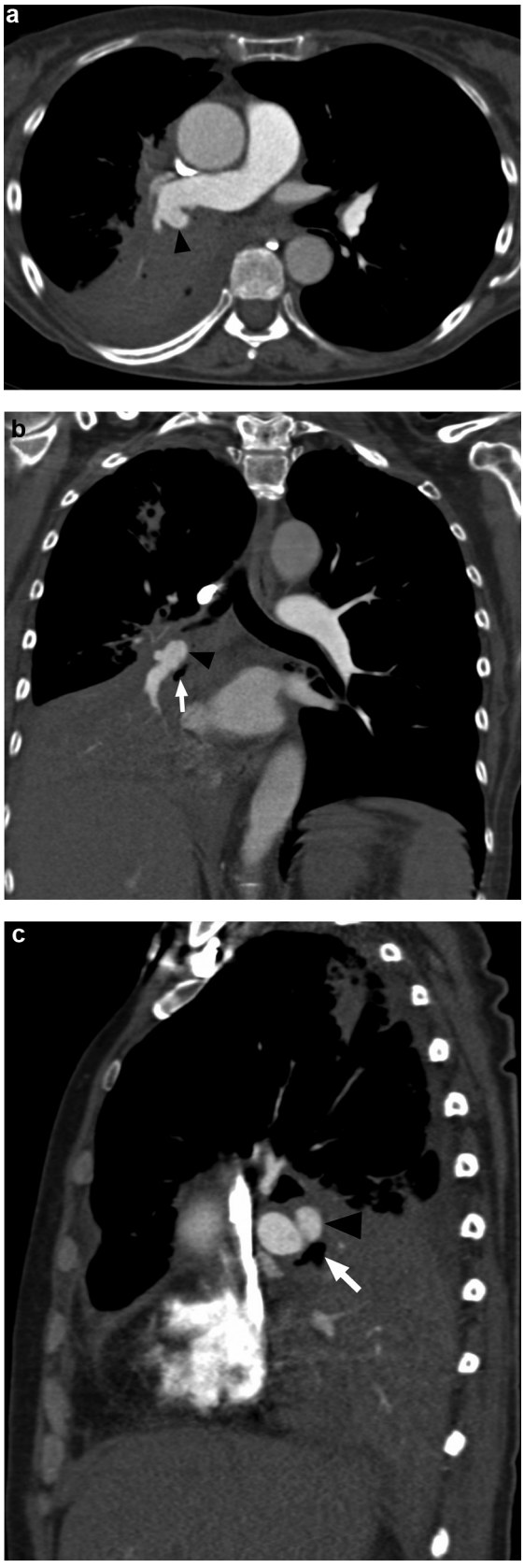

Fig. 2. Contrast-enhanced multidetector computed tomography, depicting a right descending interlobar artery aneurysm (black arrowheads) protruding into the right intermediary bronchus (small white arrow), in a patient with a history of squamous cell carcinoma and hilar lymph node treated with stereotactic irradiation. a: axial view; b: coronal view; c: right sagittal view.

irradiated with biologically equivalent doses (BED_{10}) of more than 100 Gy and to prefer fractionation with more than ten fractions.

Recently, three prospective studies were set up in order to establish robust data on the tolerance of mediastinal structures to high-dose hypofractionated radiation: the EORTC LungTech trial, the RTOG 0813 and the Nordic HILUS-trial. The EORTC LungTech trial (EORTC 22113-08113 – LungTech), with the aim to treat 150 patients with a 8×7.5 Gy scheme, has unfortunately been early closed due to lack of accrual. The phase II RTOG 0813 trial have included 120 patients of which 71 patients were eligible for analyses with either a 5×11.5 Gy or 5×12 Gy scheme. With a median follow-up of 37.9 months, it has shown good results with a 2-year local control of 89.4% and 87.9% respectively, and with four cases (5.6%) of grade 5 toxicity in total (three bronchopulmonary haemorrhage 374, 462 and 1972 days after the start of stereotactic body radiation therapy and one death not otherwise specified that occurred at 439 days) [6]. In the Nordic HILUS-trial, 74 patients were prospectively treated with a 8×7 Gy scheme, amongst which 21 (28.4%) suffered from grade 3 to 5 toxicity, with seven patients (9.5%) with a possible grade 5 toxicity: six cases of haemoptysis and one case of pneumonitis [7]. It is to mention that, in the Nordic HILUS-trial, even if the BED was lower than in RTOG 0813, the higher rate of high toxicity may be explained by the particularity that central tumours were defined as being within 1 cm from the proximal bronchial tree, whereas there were only 13 patients considered as ultra-central in RTOG 0813. Unfortunately, results are still awaited from the Nordic HILUS-trial, especially dosimetric study with dose-volume risk factors in order to better prevent high grade toxicities by using robust organs at risk constraints.

In the meantime, could we prevent these complications? In the prospective or retrospective studies cited above, in cases of fatal haemoptysis, there were no mention of observation of a pre-existing aneurysm or any central airway injuries during the follow-up. ESTRO ACROP consensus guidelines propose to follow the algorithm of Huang and Palmafor follow-up of patients treated with stereotactic body irradiation, i.e. CT scans every 6 months for 3 or 4 year, then annually, plus a physical assessment every 3 to 6 months during the first year, every 6 to 12 months for the next 3 years and then every year [8]. This case suggests that in the case of (ultra-)central lung stereotactic radiation therapy, clinicians should maybe request CT scan every 3 months in the first years. Another case report describing a central airway necrosis after stereotactic body radiation therapy resulting in fatal haemoptysis suggested adding fibroscopy for patient follow-up [9]. Indeed, bronchoscopic monitoring could be of added-value to quickly determine the development of an aneurysm, fistulae and other possible lesions of the central airways before it appears on CT scan, and possibly to treat it more quickly.

In conclusion, central lung stereotactic radiation therapy is certainly not to be banned. Latest prospective studies have shown a 2-year local control up to 89.4% with a risk of lethal toxicity reaching up to 9.5%. Therefore, this treatment should still be reserved for patients for whom no alternative exists. The treatment plan should respect the latest dose constraints recommendations. More dosimetric results are still awaited in order to allow reducing high grade toxicity in the future. Patients should be warned of the risk of possible iatrogenic death and consequently be carefully followed for high grade toxicity: in addition to imaging follow-up recommendation with CT scans, bronchoscopic surveillance could be of added-value to quickly diagnose critical evolution and possibly prevent it. Finally, for ultra-central lesions, a fractionation scheme with more than ten fractions and with a BED_{10} less than 100 Gy should be recommended.

Contribution of author

All authors certify that they have substantially participated in this manuscript, including in its design, writing and revision.

Disclosure of interest

The authors declare that they have no competing interest.

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