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Diagnostic challenges in survivors of early stage lung cancer

Marleen T.A. van Iersel-Vet[a], Erik Thunnissen[b], Femke O.B. Spoelstra[a], Bauke Ylstra[b], Ben J. Slotman[a], Suresh Senan[a,*]

[a] Department of Radiation Oncology, VU University Medical Center, de Boelelaan 1117, 1081 HV Amsterdam, The Netherlands
[b] Department of Pathology, VU University Medical Center, de Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

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ABSTRACT

Objectives: Survivors of early stage non-small cell lung cancer (NSCLC) are at risk of developing disease recurrence, as well as new lung tumors. Distinguishing metastatic disease from a second primary lung tumor (SPLC) is important, but can pose diagnostic challenges in what are often frail patients.
Materials and methods: We highlight three long-term survivors of early stage NSCLC who developed multiple new lung lesions on long-term follow-up after undergoing an initial stereotactic ablative radiotherapy procedure.
Results: New radiological lesions were always evaluated by a multidisciplinary tumor board in order to determine the optimal diagnostic procedure and treatment. When identical histological types were identified, array comparative genomic hybridization (CGH) was used to differentiate between metastases and a second primary tumor. When a tissue diagnosis is not possible, a validated calculator of tumor probability can be used to calculate the likelihood of malignancy. All patients underwent multiple episodes of curative radiotherapy.
Conclusion: These long-term survivors of early stage NSCLC highlight the importance of radiological follow-up, and describe approaches for guiding diagnostic and therapeutic management.

1. Introduction

The survival of patients with an early stage non-small cell lung cancer (NSCLC) has improved in recent years, particularly in less fit patients who undergo stereotactic ablative body radiotherapy (SABR) [1]. The 5-year survival after surgery for early stage NSCLC in a recent phase III trial was 69% [2]. In potentially operable patients who were treated with SABR, a pooled analysis of 2 randomized studies revealed a 3-year overall survival after SABR of 95% [3].

The ESMO Clinical Practice Guidelines recommend 6 monthly CT scans for 3 years, followed by an annual chest CT in order to detect second primary lung tumors (SPLC) [4]. The incidence of SPLC following surgery ranges from 3% to 6% per person-year [5], while an incidence of SPLC following SABR was 16.7% at 5 years [6]. The high risk of developing a second lung cancer was also observed in population studies [7], making long-term follow-up necessary. Up to 10% of survivors may eventually develop a third or fourth primary lung tumor [8].

New lung parenchymal lesions, which are often also detected on routine chest CT scans [9] pose a diagnostic challenge as SPLC must be distinguished from metastatic disease. ESMO guidelines recommend a tissue diagnosis when diagnostic imaging is suspicious, as well as discussion in a multidisciplinary tumor board [4]. In order to highlight the diagnostic challenges inherent in diagnosis and management of lung cancer survivors, we describe these issues in three survivors after SABR for early stage NSCLC.

2. Case reports

Case 1: a 68-year old male, ex-smoker, underwent radiotherapy for laryngeal cancer in 1996. In 2008, an abnormal chest X-ray led to the discovery of a spiculated, intensively ^{18}FDG-PET positive lung lesion in the left lower lobe. Bronchoscopy and lavage showed no evidence for malignancy, and mediastinoscopy revealed reactive lymph nodes (Table 1). The calculated likelihood of malignancy was 95%. After discussion in a multidisciplinary tumor board, patient was included in the ROSEL-study (NCT00687986) comparing surgery versus SABR, in stage IA NSCLC patients fit for resection [3]. The patient was randomized to undergo SABR and received 3 fractions of 18 Gy to the encompassing isodose. On follow-up, a new intensely PET-positive lung lesion was detected in the left

* Corresponding author. Fax: +31 20 4440410.
E-mail address: s.senan@vumc.nl (S. Senan).

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Table 1
Summary of tumor and treatment characteristics for patient 1.

Year of diagnosis	Tumor location	Pathology	Calculated probability of malignancy[a]	Stereotactic radiotherapy scheme[b]
2008	Left lower lobe	No proven malignancy after bronchial brush and mediastinoscopy	95%	3 fractions of 18 Gy
2013	Left upper lobe	Mediastinoscopy: negative. TTNB: SqCC	98%	8 fractions of 7.5 Gy
2013	Right lower lobe	TTNB: SqCC, on array CGH new primary	84%	3 fractions of 18 Gy
2015	Right upper lobe	TTNB: atypical cells	96%	5 fractions of 11 Gy

[a] Herder et al. [12].
[b] To the encompassing isodose. TTNB = transthoracic needle biopsy, SqCC = squamous cell carcinoma, CGH = comparative genomic hybridization.

upper lobe in 2013. Transthoracic needle biopsy (TTNB) showed squamous cell carcinoma (SqCC). Mediastinal nodal biopsy again revealed reactive lymph nodes, and the patient was treated using risk-adapted SABR [10]. Follow-up 6 months later revealed a new growing lesion with moderate ^{18}FDG-PET uptake in the right lower lobe. Again TTNB revealed a squamous cell carcinoma. Array comparative genomic hybridization (CGH) was used to compare copy number aberrations in this lesion with those in the previous squamous cell laryngeal cancer. The CGH patterns showed essential differences of chromosomal gains and losses (Fig. 1). Clonality scoring was performed using a correlation score 0.4 (y-axis) and a loglikelihood ratio −7.5 (x-axis) calculated according to Ostrovnaya et al. [11]. The array confirmed another primary squamous cell carcinoma, which was again treated with SABR. In early 2015, a fourth growing ^{18}FDG-PET-positive lung lesion was discovered in the right upper lobe. TTNB showed atypical cells, and a multidisciplinary tumor board recommended SABR. The patient did not develop any complications following any of his SABR treatments, and is currently free of disease, 7 years after his first SABR.

Case 2: a 60-year old male, ex-smoker, had previously undergone surgery and radiotherapy in 2008 for a recurrent floor of mouth carcinoma. In 2009, two ^{18}FDG-PET-positive lung lesions were discovered (Table 2). A lobectomy performed for a right lower lobe lesion revealed a squamous cell carcinoma (Fig. 2). A second lesion in the left upper lobe was classified by the tumor board as a clinical stage I NSCLC. As the patient declined a second operation, he was treated with SABR using 3 fractions of 18 Gy. In 2013, patient complained of thoracic pain and a CT scan revealed left hilar lymphadenopathy. An open thoracotomy was performed to obtain histological evidence, and pathology showed a small cell lung carcinoma (SCLC). Further staging confirmed a limited disease SCLC, and the patient underwent thoracic chemoradiation, followed by prophylactic cranial irradiation. Follow-up ^{18}FDG-PET-CT scans performed a year later revealed no local recurrence of SCLC. In 2014, a growing peripheral lesion in the left upper lobe was detected during follow-up at another hospital. The lesion showed uptake on ^{18}FDG-PET, but no pathological diagnosis was obtained by the local tumor board, which made a diagnosis of a new primary lung cancer. The tumor board recommended treatment using SABR. Patient is currently alive without evidence of disease, 6 years after the first lung lesion was treated.

Case 3: a 71-year old female, ex-smoker with severe chronic obstructive pulmonary disease (COPD) GOLD stage III, developed a lung nodule in the upper right lobe in 2001. The lesion was spiculated and showed intense ^{18}FDG-PET uptake. Bronchoscopy was negative for malignancy and TTNB was considered to be too risky because of her severe COPD. She was initially observed, but when nodule growth was demonstrated 2 years later, she was referred for SABR. The calculated likelihood of lung tumor malignancy using a model validated for the Dutch population was 92% [12]. The patient underwent SABR in 3 fractions of 20 Gy, based on a clinical diagnosis of stage I NSCLC, a decision consistent with current ESMO guidelines

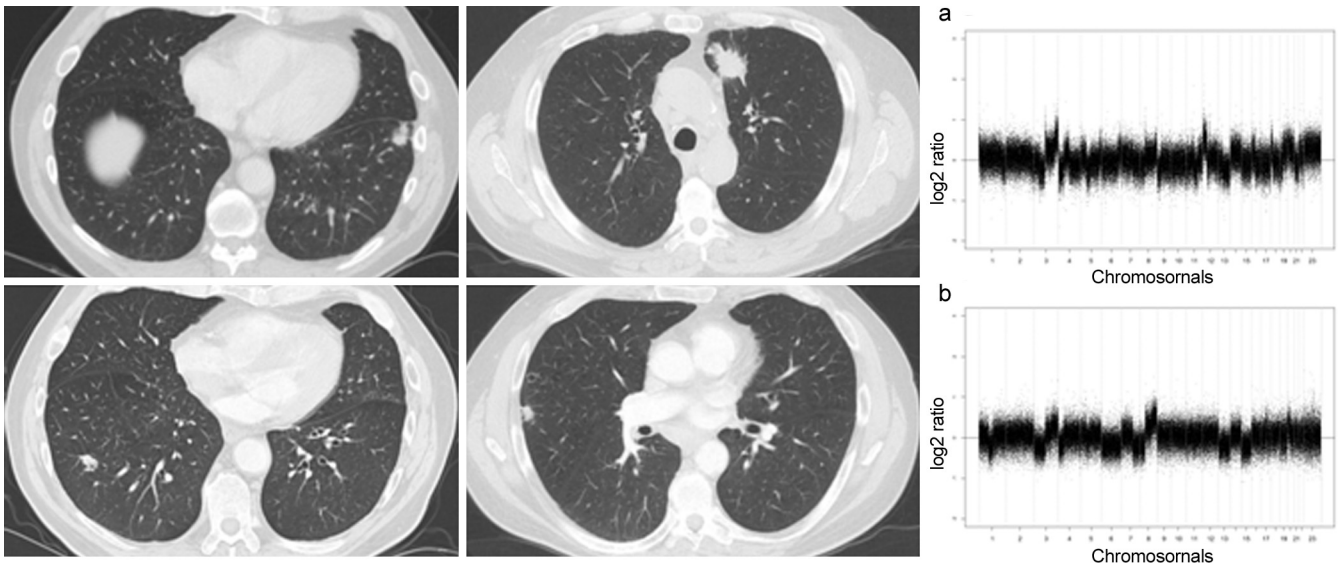

Fig. 1. Panel showing serial CT scans and array CGH in patient 1. Lesion in the upper left panel was treated in 2008, upper middle panel 2013, lower left panel 2013, lower middle panel 2015. Array CGH image of SqCC vocal cord 1996 (a, upper right) and SqCC right lower lobe 2013 (b, lower right) showing differences in patterns of chromosomal gains and losses that were consistent with different tumors. The vertical axis represents normalized log 2 ratios of tumor versus normal and the x-axis represents the ratios ordered by genomic position from chromosome 1 to X. Profiles dewaved using r-script nowaves (van de Wiel et al. [21]).

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