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SHORT COMMUNICATION

^{18}F-FDG PET during stereotactic body radiotherapy for stage I lung tumours cannot predict outcome: a pilot study

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Abstract
Purpose ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG PET) has been used to assess metabolic response several months after stereotactic body radiotherapy (SBRT) for early-stage non-small cell lung cancer. However, whether a metabolic response can be observed already during treatment and thus can be used to predict treatment outcome is undetermined.
Methods Ten medically inoperable patients with FDG PET-positive lung tumours were included. SBRT consisted of three fractions of 20 Gy delivered at the 80% isodose at days 1, 6 and 11. FDG PET was performed before, on day 6 immediately prior to administration of the second fraction of SBRT and 12 weeks after completion of SBRT. Tumour metabolism was assessed semi-quantitatively using the maximum standardized uptake value (SUV_{max}) and $SUV_{70\%}$.
Results After the first fraction, median SUV_{max} increased from 6.7 to 8.1 (p=0.07) and median $SUV_{70\%}$ increased from 5.7 to 7.1 (p=0.05). At 12 weeks, both median SUV_{max} and median $SUV_{70\%}$ decreased by 63% to 3.1 (p=0.008) and to 2.5 (p=0.008), respectively.
Conclusion SUV increased during treatment, possibly due to radiation-induced inflammation. Therefore, it is unlikely that ^{18}F-FDG PET during SBRT will predict treatment success.

Keywords SBRT · Lung tumours · Response monitoring · FDG PET

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Introduction

Lobectomy is considered the treatment of choice for stage I lung tumours [1]. Until recently, conventionally fractionated radiotherapy was offered to medically inoperable patients. Unfortunately, retrospective data suggest poor overall survival rates for stage I disease treated with radiotherapy, even with the use of modern 3-D conformal radiotherapy [2]. Stereotactic body radiotherapy (SBRT) is a relatively new approach in the treatment of lung tumours, utilizing stereotactic targeting and precise radiation delivery. SBRT facilitates hypofractionation with markedly increased biological equivalent doses (>100 Gy) and reduced overall treatment times. Numerous trials have now been published using SBRT for stage I lung tumours. Results are excellent, with local control rates above 80% at 1–5 years [3], comparable to those obtained with surgery. As a consequence, SBRT is gradually replacing conventionally fractionated radiotherapy for non-surgical patients.

^{18}F-Fluorodeoxyglucose positron emission tomography (FDG PET) imaging, visualizing enhanced glucose utilization by tumours, has proven to be useful as a predictive and prognostic test in various treatment settings including response assessment during (chemo-) radiotherapy. Also after

SBRT, a metabolic response is observed weeks to months after treatment [4–6]. Being able to predict the outcome after SBRT in terms of complete tumour response already during treatment would yield two significant advantages: (1) the indication for SBRT could safely be extended to include operable patients, because the few patients who will fail after SBRT could be offered immediate salvage surgery and (2) follow-up after SBRT for all patients could be tailored according to the risk of failure. Both options are very appealing in order to increase the efficiency of early lung cancer treatment as well as follow-up.

We performed this pilot study to explore the potential of FDG PET with regard to early assessment of tumour response during SBRT in patients with FDG PET-positive lung tumours.

Materials and methods

Study design

Medically inoperable patients with an FDG PET-positive lesion in the lung without FDG uptake elsewhere were eligible (stage I lung cancer, according to the UICC TNM Classification of Malignant Tumours, 7th edition, 2009). Diagnostic work-up included bronchoscopy with bronchoalveolar lavage and biopsy, CT scan and lung function testing. Due to the small sizes and peripheral location of the target lesions, cytological and histological confirmation could not be obtained in any of the patients. Only one patient was regarded as having sufficient pulmonary reserve to undergo transthoracic biopsy, which resulted in pneumothorax without histological confirmation of the diagnosis. Patients had to have a WHO performance score of 0–2 and a life expectancy of at least 6 months. SBRT was delivered using a Novalis® system (BrainLAB AG, Feldkirchen, Germany), according to the protocol of the Department of Radiation Oncology at the University Medical Center Groningen. Briefly, after acquisition of a planning 4-D CT scan incorporating breathing motions, the target volume was delineated. Patients received 3 × 20 Gy at the 80% isodose level at days 1, 6 and 11, respectively. All patients underwent a routine ^{18}F-FDG PET scan and CT scan 12 weeks after completion of SBRT for response evaluation. An additional ^{18}F-FDG PET scan to assess early tumour response was performed at day 6, immediately before delivery of the second fraction. The study was approved by the local Medical Ethics Committee and all patients gave written informed consent prior to treatment.

Each ^{18}F-FDG PET scan was made at the Department of Nuclear Medicine and Molecular Imaging on a Siemens/CTI ECAT EXACT HR+ machine, using the Dutch Standard Operating Procedures (SOP) for ^{18}F-FDG PET whole-body scans [7]. In short, patients received FDG at a dose of 5 MBq per kilogram body weight intravenously. After a waiting period of 60 min, a scan was made from the mid-thigh to the external acoustic meatus.

Data analysis and statistics

Data were assessed visually and semi-quantitatively, using the maximum standardized uptake values (SUV_{max}) and the $SUV_{70\%}$ (i.e. the mean SUV in the volume encompassing the isocontour of 70% of maximum activity). For SUV calculation, the tumour was delineated using standard Siemens e.soft analysis and viewing software in order to eliminate inter-observer variability. In order to render the SUVs on the three time points comparable, the waiting time between injection and scanning differed no more than 5 min among the three examinations, as defined in the SOP [7]. SUVs were corrected for the blood glucose levels (normalization to 5.0 mmol/l). SUVs are expressed as medians with range. Comparisons between the ^{18}F-FDG PET scans at different time points were performed using the Wilcoxon signed rank test. The Mann-Whitney U test was used to compare groups of different metabolic responders. Additionally, metabolic response was assessed according to European Organization for Research and Treatment of Cancer (EORTC) criteria [8] (see Table 1). Routine CT thorax 12 weeks after completion of SBRT was used to assess tumour response according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 [9].

Results

Patient characteristics

Ten patients were enrolled between February 2008 and January 2009 as planned. There were nine men and one woman with a median age of 77.5 years and a median Charlson comorbidity index of 4 (range 3–11). Tumour stage according to the 7th edition of the UICC TNM

Table 1 Definition of metabolic response according to EORTC criteria

Response	Definition
CMR	Complete resolution of FDG uptake in tumour, not distinguishable from surrounding tissue
PMR	Reduction of more than 25% in SUV
SMD	Changes of less than 25% in SUV
PMD	Increase of SUV of more than 25% or new (metastatic) lesions

CMR complete metabolic response, *PMR* partial metabolic response, *SMD* stable metabolic disease, *PMD* progressive metabolic disease

Table 2 Patient characteristics

Patient	Sex	Age	Charlson index	cTNM	GTV (cm^3)	SUV_{max} (before)	SUV_{max} (during)	SUV_{max} (12 weeks)	Metabolic response (12 weeks)	Radiological response (12 weeks)
1	M	78	11	T1a N0 M0	5.27	7.1	7.8	3.1	PMR	PR
2	F	88	4	T1b N0 M0	7.10	16.4	13.1	1.4	CMR	PR
3	M	71	4	T1a N0 M0	4.16	4.1	5.3	1.7	CMR	PR
4	M	61	3	T1a N0 M0	2.74	6.3	8.3	1.7	CMR	PR
5	M	81	4	T1a N0 M0	5.87	9.0	14.5	NA	NA	PR
6	M	77	5	T2a N0 M0	16.71	24.8	32.2	3.5	PMR	PR
7	M	81	3	T1b N0 M0	1.32	14.6	15.5	3.5	PMR	SD
8	M	64	4	T1a N0 M0	0.90	4.3	4.3	1.6	CMR	PR
9	M	85	5	T1b N0 M0	9.55	4.3	5.2	3.2	PMR	SD
10	M	61	4	T1a N0 M0	2.89	5.0	5.4	3.2	PMR	PR

GTV gross tumour volume, *CMR* complete metabolic response, *PMR* partial metabolic response, *SMD* stable metabolic disease, *PMD* progressive metabolic disease, *PR* partial response, *SD* stable disease

Classification of Malignant Tumours was T1a (n=6), T1b (n=3) and T2a (n=1). The staging ^{18}F-FDG PET scan was made 5.3 weeks (median; range 3–14 weeks) prior to the start of SBRT. All patients underwent an ^{18}F-FDG PET scan on day 6. Routine ^{18}F-FDG PET and CT scans were performed 12.9 weeks (median; range 11.7–18 weeks) after completion of SBRT for response evaluation. One patient refused the ^{18}F-FDG PET at 12 weeks due to increasing claustrophobia, yielding nine fully evaluable patients. Patient characteristics are shown in Table 2.

Metabolic and radiological response

Prior to SBRT, median SUV_{max} was 6.7 (range 4.1–24.8) and median $SUV_{70\%}$ was 5.7 (range 3.4–20.0). After the first fraction, median SUV_{max} increased to 8.1 (p=0.07) (Fig. 1) and median $SUV_{70\%}$ increased to 7.1 (p=0.05), representing a relative increase of 18 and 21%, respectively.

At 12 weeks, a metabolic response was observed in all evaluable patients (n=9). Four patients showed a complete metabolic response (CMR) (44%) and five patients showed a partial metabolic response (56%). Both SUV_{max} and $SUV_{70\%}$ decreased significantly by 63% (p=0.008) to 3.1 and 2.5, respectively. CMR was not associated with gross tumour volume (GTV) (p=0.29) or SUV_{max} prior to treatment (p=0.34). Routine CT thorax performed 12 weeks after SBRT showed a partial response in eight patients (80%) and stable disease in two patients (20%). Sequential PET/CT images of patient 3 are presented in Fig. 2.

Discussion

SBRT has demonstrated excellent local control rates in medically inoperable patients, establishing an important role for definitive SBRT in the treatment of stage I lung

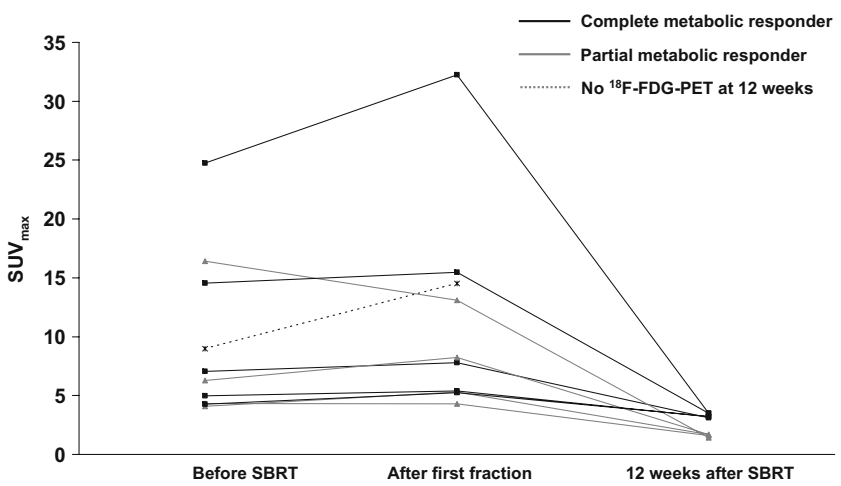

Fig. 1 Absolute SUV_{max} before, after the first fraction and 12 weeks after completion of SBRT. SUV_{max} increased after the first fraction (p=0.07) and decreased significantly 12 weeks after SBRT (p=0.008)

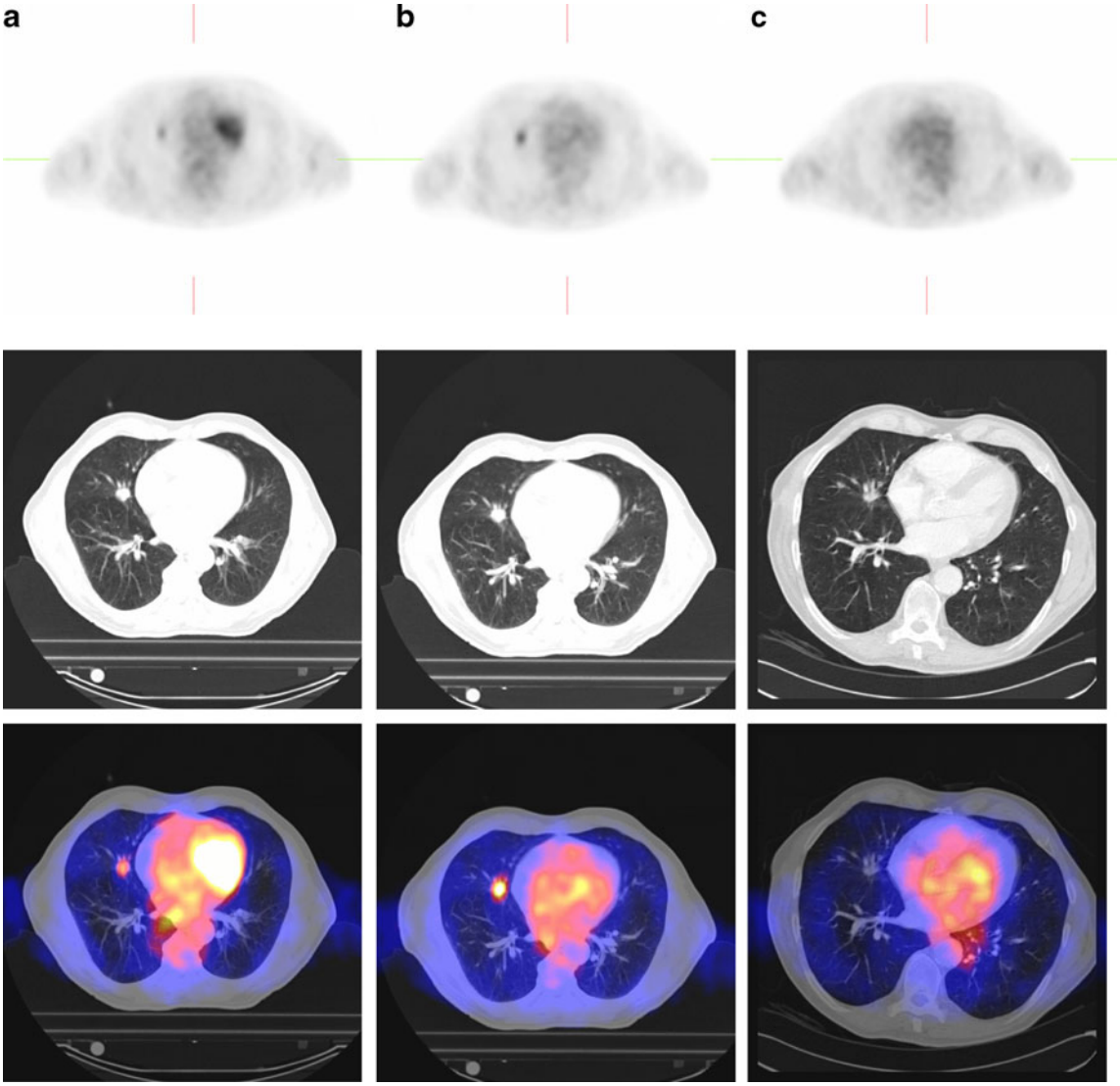

Fig. 2 Sequential axial PET (*upper row*), CT (*middle row*) and fused PET/CT (*lower row*) images of patient 3, before (**a**), after the first fraction (**b**) and 12 weeks after SBRT (**c**). SUV_{max} increased from 6.3 to 8.3 after the first fraction. At 12 weeks SUV_{max} decreased to 1.3 (CMR) and was considered a partial response according to RECIST criteria

tumours. Since local control rates after SBRT are comparable to those obtained with surgery, it could be argued that primary SBRT might also be offered to operable patients as an alternative to lobectomy. This hypothesis is the basis for the phase II RTOG 0618 trial and two randomized phase III trials, i.e. the Dutch ROSEL trial [10] and the STARS trial [11], both comparing SBRT with surgery. As operable patients receiving SBRT would remain eligible for potential salvage surgery in the case of tumour failure, early prediction of local control already during treatment is tempting since salvage surgery could then be performed without the need to complete SBRT and subsequent 3-monthly follow-up response monitoring.

In our study, the ^{18}F-FDG PET scan preceding the second of three fractions of SBRT showed an increased ^{18}F-FDG uptake in the tumour. A number of explanations may exist for this phenomenon. First, the interval between the staging ^{18}F-FDG PET scan and the start of SBRT varied widely. Tumour progression may have occurred in between and may be responsible for the increased uptake. However, no correlation between SUV changes after the first fraction and the interval between the staging FDG PET and start of SBRT was found, suggesting that tumour progression did not play a major role (data not shown). Another explanation may be that ^{18}F-FDG PET also detects inflammation [12]; thus, the elevated FDG uptake may be explained by radiation-induced inflammation with influx of macrophages, which are known to exhibit increased ^{18}F-FDG uptake [13]. Indeed, increased ^{18}F-FDG uptake has been observed during radiotherapy in patients [6, 14, 15] as well

as in a preclinical study [16]. Dynamic scanning with kinetic analysis [17] or dual time point imaging [18, 19] may have been more accurate for the discrimination between tumour activity and radiation-induced inflammation. Also, the use of other tracers capable of discriminating inflammation from tumour activity, such as proliferation markers, may be promising and needs further investigation. Finally, despite inclusion in the Dutch recommendations, the practice of correcting for plasma glucose is controversial and certainly not widely used [7]. If we would have used the uncorrected data, the increase observed after the first fraction would have been 6% for SUV_{max} and 9% for $SUV_{70\%}$. The reduced SUVs at 12 weeks would remain unchanged, i.e. 63%.

In our institution, follow-up of lung cancer patients treated with SBRT consists of an ^{18}F-FDG PET/CT scan at 12 weeks, followed by yearly CT scans of the thorax. It must be kept in mind that the response assessment at 12 weeks is not the standard of care. Its results should be interpreted with caution, especially since a substantial proportion of patients may have persistently elevated SUV up to 1 year after treatment without developing local recurrence [6]. Secondly, 12 weeks is too early to elicit a radiological response and longer intervals are needed to observe tumour shrinkage or disappearance.

In conclusion, given the expectation of at least 80% local control after SBRT, it is unlikely that ^{18}F-FDG PET during SBRT will predict treatment success. Advanced scanning techniques or the use of innovative PET tracers are needed for early response assessment during hypofractionated high-dose radiotherapy techniques such as SBRT.

Conflicts of interest None.

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