PET-based analysis of tumor glucose metabolism and tumor hypoxia before and during anti-neoplastic treatment
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Residual FDG-PET uptake twelve weeks after stereotactic ablative radiotherapy (SABR) for stage I non-small cell lung cancer predicts local control

V. R. Bollineni, J. Widder, J. Pruim, J. A. Langendijk and E. M. Wiegman

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ABSTRACT

Purpose: To investigate the prognostic value of fluorodeoxyglucose positron emission tomography (FDG-PET) uptake at 12 weeks after stereotactic ablative radiotherapy (SABR) for stage I non-small-cell-lung cancer (NSCLC).

Materials and Methods: From November 2006 to February 2010, 132 medically inoperable patients with proven stage I NSCLC or FDG-PET-positive primary lung tumors were analyzed retrospectively. SABR consisted of 60 Gy delivered in 3-8 fractions. The maximum standardized uptake value (SUVmax) of the treated lesion was assessed 12 weeks after SABR using FDG-PET. Patients were subsequently followed at regular intervals using CT-scans. The association of post-SABR SUVmax with local control (LC), mediastinal failure (MF), distant failure (DF), overall survival (OS), and disease specific survival (DSS) was examined.

Results: The median follow-up time was 17 months (range: 3-40 months). The median lesion size was 25 mm (range: 9-70 mm). There were 6 local failures, 15 mediastinal failures, 15 distant failures, 13 disease-related deaths, and 16 deaths from inter-current diseases. The glucose corrected post-SABR median SUVmax was 3.0 (range: 0.55-14.50). Using SUVmax 5.0 as a cut-off, the 2-year LC was 80% versus 97.7% for high versus low SUVmax, yielding an adjusted sub-hazard ratio (SHR) for high post-SABR SUVmax of 7.3 (95% CI: 1.4-38.5; p=0.019). The 2-year DSS rates were 74% versus 91% for high and low SUVmax (SHR 2.2; 95% CI: 0.8-6.3; p= 0.113). Two-year OS was 62% versus 81% (HR 1.6; 95% CI: 0.7-3.7; p= 0.268).

Conclusion(s): Residual FDG uptake (SUVmax ≥5.0) 12 weeks after SABR signifies increased risk of local failure. A single FDG-PET scan at 12 weeks could be used to tailor further follow-up according to the risk of failure, especially in patients potentially eligible for salvage surgery.
INTRODUCTION

The current standard for stage I non-small-cell lung cancer (NSCLC) is surgical resection resulting in a 60-80% 5-year overall survival (OS) rate [1]. However, many patients with stage I NSCLC have extensive cardiovascular and pulmonary co-morbidity and are considered medically inoperable. Stereotactic ablative radiotherapy (SABR) is emerging as a new standard for this group of patients. SABR enables the accurate delivery of an ablative radiation dose while sufficiently sparing normal tissues in an overall treatment of one to two weeks. Recent publications have shown that SABR is a well-tolerated and efficient treatment approach in medically inoperable patients, with local control rates well above 80% at 3 years [2].

Response assessment in NSCLC is usually performed according to the Response Evaluation Criteria in Solid Tumors (RECIST), using CT-scans of the thorax [3]. However, the reduction in tumor size can take several months, and radiation induced changes such as inflammation and fibrosis may hamper adequate evaluation of tumor response and local control [4]. Therefore, radiological response assessment may not always be reliable for differentiating between local failure and SABR-induced local lung changes. Adding metabolic imaging, using FDG-PET to CT imaging has shown to improve the differentiation between radiation induced inflammation and tumor in lung cancer [5]. In addition, it has been observed that changes in tumor metabolism are more significant than anatomical changes in lung cancer patients 12 weeks after SABR [6], suggesting the utility of FDG-PET as an early response parameter. However, the prognostic value of residual FDG uptake in lung tumors treated with SABR has not been established. Therefore, in the present study, we examined the prognostic value of post-SABR FDG uptake at 12 weeks with respect to local control (LC), mediastinal failure (MF), distant failure (DF), overall survival (OS), and disease specific survival (DSS) in medically inoperable patients with stage I NSCLC or FDG-PET positive primary lung tumors.
MATERIALS AND METHODS

Patients

The study population was composed of 132 medically inoperable patients with a solitary FDG-PET positive lesion in the lung, considered stage I lung NSCLC, who underwent standardized post-SABR FDG-PET-scans at our institution. Work-up minimally included bronchoscopy with biopsy, contrast-enhanced CT and FDG-PET, and lung-function testing including a flow-volume curve at baseline. Patient characteristics are shown in Table 1. All patients were treated with SABR between November 2006 and February 2010 at the UMCG after being discussed in a multidisciplinary team consisting of thoracic surgeons, pulmonologists, radiation oncologists, nuclear medicine specialists, radiologists, and pathologists. Due to relative contraindications to perform a biopsy, pathological confirmation was obtained only in 40/132 (30%) of the patients; the remaining 92 patients were treated based on medical history [smokers at advanced age with COPD], appearance of the [often growing] tumor on CT, and the probability of malignancy of the lesions [7]. Follow-up consisted of a FDG-PET at 3 months, followed by CT-scans at regular intervals.

### TABLE 1. Baseline Patient and Tumor Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, number [%]</td>
<td></td>
</tr>
<tr>
<td>Male; Female</td>
<td>95 (72); 37 (28)</td>
</tr>
<tr>
<td>WHO PS [0-1 vs. 2-3]</td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>106 (80)</td>
</tr>
<tr>
<td>2-3</td>
<td>26 (20)</td>
</tr>
<tr>
<td>Probability of malignancy</td>
<td></td>
</tr>
<tr>
<td>Median [Range]</td>
<td>0.95 (0.80-0.97)</td>
</tr>
<tr>
<td>CCI</td>
<td></td>
</tr>
<tr>
<td>Median [Range]</td>
<td>4 [2-12]</td>
</tr>
<tr>
<td>Pre-SABR SUVmax</td>
<td></td>
</tr>
<tr>
<td>Median [Range]</td>
<td>7.65 (1.90-58.40)</td>
</tr>
<tr>
<td>Post-SABR SUVmax</td>
<td></td>
</tr>
<tr>
<td>Median [Range]</td>
<td>3.0 (0.55-14.50)</td>
</tr>
<tr>
<td>Staging FDG-PET interval</td>
<td></td>
</tr>
<tr>
<td>Median [Range]</td>
<td>45.5 (9-157)</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td></td>
</tr>
<tr>
<td>Median [Range]</td>
<td>75 (46-90)</td>
</tr>
</tbody>
</table>

Abbreviations: CCI = Charlson Co-morbidity Index; WHO PS = World Health Organization performance status; Pre-SABR SUVmax = baseline maximum standardized uptake value; Post-SABR SUVmax = maximum standardized uptake value 12 weeks after SABR; FDG-PET = Fluorodeoxyglucose Positron Emission Tomography.
Stereotactic Ablative Radiotherapy (SABR)

SABR was delivered using the Novalis system [BrainLAB AG, Feldkirchen, Germany], according to the protocol of the Department of Radiation Oncology at the UMCG. In summary, after acquisition of a planning 4D CT-scan incorporating breathing motions, the target volume was delineated. Patients received 60 Gy prescribed to the margin of the planning target volume (PTV), which corresponded to 80% of the dose at the isocenter. Based on the tumor location – peripheral; adjacent to the thoracic wall; central – three, five, or eight fractions were administered as previously described [8].

Positron Emission Tomography (PET)

Out of 132 patients, 70 patients had undergone a staging FDG-PET in referring centers, with varying injection and scanning procedures, which precluded an analysis of pre-treatment SUVmax in these patients. All post-SABR FDG-PET-scans (n=132) were made at the department of Nuclear Medicine and Molecular imaging of the UMCG on a Siemens/CTI ECAT EXACT HR+ or Siemens mCT machine using the Dutch Standard Operating Procedures (SOP) for FDG-PET whole–body scans [9]. Blood samples were taken before injection to confirm an acceptable blood sugar level (<11 mmol/l) after fasting for a period of 5 to 6 hours. Patients were injected with 5 MBq/kg FDG. After a waiting period of 60 min, a scan was made from the mid-thigh to the external acoustic meatus. The SUVmax was obtained by delineating the region of interest comprising the entire tumor volume using the Philips Imalytics system, a computer-based workstation for image analysis, quantification and visualization of PET-images. SUVs were corrected for the blood glucose levels (normalization to 5 mmol/l).

Data analysis and statistics

Local control, DSS, MF, and DF were estimated using competing risk survival analysis scoring non-target types of failure as competing risk as appropriate. Overall survival was estimated using the Kaplan-Meier method. Curves were compared with the log-rank test. Multivariate Fine and Gray competing risk regression analysis for LC and DSS yielding adjusted sub hazard ratios (SHR) was carried out with the following factors: post-SABR SUVmax cut-off (<5.0 or ≥5.0), lesion size, Charlson comorbidity index (CCI) (≤3 or >3), FDG-PET staging interval, WHO Performance status (0-1 versus 2-3) and pre-SABR SUVmax cut-off (<5.0 or ≥5.0). The probability of local failure was estimated using the cumulative incidence function (CIF) calculated from the start of radiotherapy. For OS, multivariate Cox-proportional regression analysis using the above mentioned factors was carried out since there is no competing risk. Statistical analyses were performed using STATA statistical software, version 11.0 (STATA Corp, Texas, USA).
RESULTS

Baseline FDG uptake and definition of post-SABR SUVmax cut-off

The median baseline SUVmax for patients with evaluable standardized baseline scans (n=62) were 7.6 [range: 1.9-58.4]. The median interval between PET-staging and initiation of radiation was 45.5 days [range 9-157]. The median SUVmax12 weeks post-SABR was 3.0 [range: 0.6-14.5] for all 132 patients and it was 3.0 [range: 0.6-12.1] for the 62 patients who had undergone standardized pre- and post-SABR PET scans at the UMCG. To determine the most appropriate post-SABR SUVmax cut-off, a series of SUVmax values between 3 and 7 were tested. A SUVmax cut-off 5.0 was most discriminative for LC and DSS. Using this cut-off, receiver operating characteristics (ROC) curve analysis showed an area under the curve of 0.75 [95% CI 0.525-0.975] for local control (Data not shown). Therefore, a post-SABR SUVmax≥ 5 cut-off was applied to distinguish high and low SUVmax groups.

Local control

Median follow-up time was 17 months [range 3-40 months]. Six patients developed local failure yielding a cumulative incidence of local failure of 3.6 % at 2 years. In patients with post-SABR SUVmax< 5.0 the 2-year LC rate was 97.7% compared to 80.0% in patients with post-SABR SUVmax ≥ 5.0. In the univariate analysis, post-SABR SUVmax [SHR 9.5; 95% CI: 1.8-49.0; P=0.007], lesion size [SHR 1.6; 95% CI: 1.0-2.5; P=0.026] and pre-SABR SUVmax [SHR 0.1; 95% CI: 0.36-0.98; P=0.048] were significantly associated with LC (Table 2). The adjusted SHR for post-SABR SUVmax≥5.0 cut-off was 7.3 [95% CI: 1.4-38.5; p=0.02] (Table 3). Using SUVmax 5.0 as cut-off, cumulative incidence of local failure corrected for lesion size was 2.2% versus 15.3% at two years for low versus high post-SABR SUVmax (figure 1).

### Table 2: Univariate [sub]hazard ratios for potential prognostic factors

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Local Control</th>
<th>Disease Specific Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SHR (95% CI)</td>
<td>P-value</td>
<td>SHR (95% CI)</td>
</tr>
<tr>
<td>Post-SABR SUVmax (≥5 vs. &lt;5)</td>
<td>9.5 (1.8-49.0)</td>
<td>0.007</td>
<td>2.9 (0.9-8.9)</td>
</tr>
<tr>
<td>Lesion size (per cm)</td>
<td>1.6 (1.0-2.5)</td>
<td>0.026</td>
<td>1.5 (1.1-2.2)</td>
</tr>
<tr>
<td>Charlson Co-morbidity Index (≤3 vs. &gt;3)</td>
<td>0.88 (0.16-4.8)</td>
<td>0.89</td>
<td>1.6 (0.5-5.6)</td>
</tr>
<tr>
<td>Staging-PET interval (per day)</td>
<td>1.0 (0.98-1.0)</td>
<td>0.993</td>
<td>0.9 (0.9-1.0)</td>
</tr>
<tr>
<td>WHO PS (0-1 vs. 2-3)</td>
<td>2.3 (0.43-12.3)</td>
<td>0.325</td>
<td>1.5 (0.4-5.5)</td>
</tr>
<tr>
<td>Pre-SABR SUVmax (≥5 vs. &lt;5)</td>
<td>0.1 (0.36-0.98)</td>
<td>0.048</td>
<td>1.3 (0.2-7.9)</td>
</tr>
</tbody>
</table>
Abbreviations: SABR = stereotactic ablative radiotherapy; Post-SABR SUVmax = maximum standardized uptake value 12 weeks after SABR; CCI = Charlson Co-morbidity Index; WHO PS = World Health Organization performance status; Pre-SABR SUVmax = baseline maximum standardized uptake value

### TABLE 3: Adjusted (sub)hazard ratios for post-SABR SUV\(_{\text{max}}\) ≥ 5

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)*</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Control</td>
<td>7.3 (1.4-38.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Disease Specific Survival</td>
<td>2.2 (0.8-6.3)</td>
<td>0.113</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>1.6 (0.7-3.7)</td>
<td>0.268</td>
</tr>
</tbody>
</table>

*(Sub)hazard ratios adjusted for lesion size, Charlson comorbidity Index, interval between staging-PET and start of SABR and WHO performance status.

**FIGURE 1.** Cumulative incidence of local failure corrected for lesion size in all patients and for the two groups of interest: SUVmax ≥ 5 and < 5

**Mediastinal failure**

Out of 132 patients, 15 patients developed MF (cumulative incidence, 13.3 %), five of whom in the high SUVmax group. The 2-year MF rates in the high and low post-SABR SUVmax groups were 19 % and 12 % (\(P=0.392\)) respectively. No statistically significant factors for MF could be identified.
In total, 15 patients (cumulative incidence, 13%) developed distant failure, five of whom had a post-SABR SUVmax ≥ 5.0. The two-year DF rates in the high and low SUVmax groups were 24.0% and 11.0% (P=0.127), respectively. No statistically significant factors for DF could be identified.

**Disease specific survival**

The 2-year DSS rates were 74% in the high SUVmax group and 90% in the low SUVmax group. In the univariate analysis, high post-SABR SUVmax (SHR 2.9; 95% CI: 0.9-8.9; P=0.057) and tumor size (SHR 1.5; 95% CI: 1.1-2.2; P=0.013) were associated with DSS (Table 2). The adjusted sub hazard ratio (SHR) for post-SABR SUVmax ≥5.0 cut-off was 2.2 (95% CI: 0.8-6.3; p= 0.113) (Table 3).

**Overall survival**

The 2-year OS rates in the high and low SUVmax groups were 62% and 81%. In addition, lesion size showed borderline significance in univariate analysis (HR 1.3; 95% CI: 1.0-1.8; P=0.051) (Table 2). The adjusted hazard ratio for post-SABR SUVmax ≥5.0 cut-off was 1.6 (95% CI: 0.7-3.7; p= 0.268) (Table 3).

**DISCUSSION**

SABR is an emerging technology for the treatment of stage I medically inoperable NSCLC patients, achieving superior survival rates compared to conventional fractionated radiotherapy, together with favorable quality-of-life results [8]. Therefore, SABR is increasingly considered as the new standard treatment for medically inoperable patients with stage I NSCLC [10].

Substantial effort has been made to identify factors that predict treatment outcome using FDG-PET. Although data indicate that a high baseline FDG uptake (i.e. SUVmax ≥ 5) of the primary tumor was associated with poor local control in stage I to III NSCLC patients [11], these findings remain controversial [12,13]. Recently we published data from a pilot study, investigating metabolic changes during SABR, indicating that assessment of SUVmax during SABR [after the first of three fractions] could not predict treatment outcome [14]. To our knowledge the present study is the first investigating the prognostic value of FDG-PET 12 weeks after completion of SABR in a larger patient population. We showed that a residual SUVmax ≥5.0 was a prognostic factor for treatment outcome with respect to LC.

Still, FDG-PET has its drawbacks. FDG is an unspecific tracer, which also detects inflammation. Radiation pneumonitis (RP) is relatively common in patients after thoracic radiotherapy and appears
as a region of enhanced FDG uptake on FDG-PET after [15], but also during treatment [14,16]. In a situation without radiation pneumonitis, tumor metabolism can be easily assessed. If a tumor exhibits complete metabolic response, the SUVmax for controlled tumors is around 2.0, with a narrow range of values [range, 1.5 to 2.8], representing the uptake of normal lung tissue [17]. However, if localized RP occurs, such as typically seen after SABR, it remains difficult to assess metabolic tumor response since the FDG uptake of RP may be confused with that of the tumor. Together with our finding that SUVmax ≥ 5.0 may represent true tumor metabolism, an intermediate group [SUVmax 2 - 5] still showing FDG enhancement likely represents patients with a complete metabolic response together with signs of RP. These patients may be referred to as having a “blurred complete metabolic response,” meaning that the observed FDG uptake at the location of the stereotactically ablated tumor is due to local pneumonitis or fibrosis rather than due to neoplasia. It is crucial to differentiate these patients from patients with residual tumor uptake. As such, calculating the SUVmax at the approximate location of a treated lesion may be insufficient. Careful examination of the precise location, aspect, and dimension of the lesion on FDG-PET/CT, while taking into account possible translocations of lung tissue after treatment, is needed. Innovative scanning techniques such as dynamic scanning with kinetic analysis [18] or dual time point imaging [19] may be of additional value for the discrimination between tumor activity and radiation-induced inflammation. It should be stressed that the cut-off value found in this study cannot be easily translated to other centers. Due to differences in SUV quantification, fasting duration, blood glucose correction, waiting time between FDG injection and image acquisition, SUVs will vary among different centers. Following the standardization of tumor PET imaging, such as proposed by the European Association of Nuclear Medicine (EANM) [20] as we did, is highly desirable to enable adequate comparison with other studies.

CONCLUSIONS

In conclusion, our results suggest that residual FDG uptake 12 weeks after SABR predicts LC. A trend was found towards better DSS and even OS for post-SABR SUVmax < 5.0. A single FDG-PET scan at 12 weeks could be used to tailor further follow-up, according to the risk of failure. Patients with post-SABR SUVmax ≥ 5.0 should be considered as having an increased risk of local failure and their follow-up should be intensified. These finding are particularly interesting in case SABR is administered to operable patients or patients potentially eligible for sublobar salvage resections. If confirmed in an independent patient population, this strategy might enable early salvage surgery in patients eligible for at least sublobar resections.
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REFERENCES


