ORIGINAL ARTICLE

# Stereotactic Ablative Radiation Therapy for Lung Oligometastases: Predictive Parameters of Early Response by $^{18}$FDG-PET/CT

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**ABSTRACT**

**Objectives:** The objective of this study was to investigate fludeoxyglucose F 18 positron emission tomography/computed tomography ($^{18}$FDG-PET/CT) parameters as predictive of response after stereotactic ablative radiotherapy (SABR) for lung oligometastases.

**Methods:** The inclusion criteria of the current retrospective study were as follows: (1) lung oligometastases treated by SABR, (2) presence of $^{18}$FDG-PET/CT before and after SABR for at least two subsequent evaluations, (3) Karnofsky performance status higher than 80, and (4) life expectancy longer than 6 months. All patients were treated with a biologically equivalent dose of at least 100 Gy with an alpha/beta ratio of 10. The following metabolic parameters were semiquantitatively defined: maximum standardized uptake value ($SUV_{max}$), mean standardized uptake value ($SUV_{mean}$), metabolic tumor volume, and total lesion glycolysis.

**Results:** A total of 50 patients met the inclusion criteria, for a total of 70 lung metastases. The pre-SABR median $SUV_{max}$ was 6.5 (range 4–17), the median $SUV_{mean}$ was 3.7 (range 2.5–6.5), and the median metabolic tumor volume was 2.3 $cm^3$ (0.2–31 $cm^3$). The following metabolic parameters were significantly related to complete response at 6 months: $SUV_{max}$ less than 5 ($p < 0.001$) and $SUV_{mean}$ less than 3.5 ($p = 0.03$). $\Delta SUV_{max}$ at 3 to 6 months was +126% for lesions with in-field progression versus −26% for the remaining lesions ($p = 0.002$). $\Delta SUV_{mean}$ at 3 to 6 months was +15% for lesions with in-field progression versus −26% for the remaining metastases ($p = 0.008$).

**Conclusions:** In the current analysis, complete response from lung metastasis at 6 months after stereotactic body radiation therapy was significantly associated with both the maximum and mean values of pre-SABR $^{18}$FDG-PET/CT SUV. Longer-term trials are strongly advocated to improve the personalization of the monitoring of tumor response in patients with lung oligometastases and, consequently, monitoring of the cost-effectiveness of the health care.



*Keywords:* SABR; Lung malignancies; Predictive factors; $^{18}$FDG-PET/CT

## Introduction

Stereotactic ablative radiotherapy (SABR) is an emerging therapeutic approach that involves the use of focused ablative radiation doses with a higher biological effect compared with conventional radiotherapy (RT). During the past few years, the efficacy and safety of SABR has been documented in several settings, including in a subset of selected patients with metastases, usually with one to five lesions, designated with the term

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*oligometastases*.[1–4] In lung oligometastases, SABR guarantees excellent local control (LC) rates with negligible toxicity.[5–8] Unacceptably increased levels of grade 3 to 5 pulmonary toxicity for centrally located lesions (i.e., tumors within 2 cm of the large bronchial tree) were initially reported for the stereotactic body radiation therapy (SBRT) schedule of 60 Gy in three fractions[9] and confirmed for schedules with 40 to 60 Gy given in three or four fractions.[10] Thus, the use of more fractionated schedules has been developed as an adequate approach to SBRT for centrally located tumors,[11–13] although caution according to patient's specificity is still necessary.[14]

Tumor control seems to be strictly related to a biologically equivalent dose (BED) of at least 100 Gy with an alpha/beta ratio of 10 (100 $Gy_{10,}$)[15] resulting in a high rate of cell killing owing to several biological effects (direct tumor cell death, vascular damage, indirect tumor cell death, and imunomodulation).[16] Fludeoxyglucose F 18 positron emission tomography integrated with computed tomography ($^{18}$FDG-PET/CT) is often adopted in the setting of lung metastases as an effective tool in staging and to monitor the response after systemic therapies. Additionally, disease assessment by means of $^{18}$FDG-PET/CT could affect the management of patients with lung metastases who are candidates for local treatment with curative intent (lung metastasectomy), especially in metastatic colorectal cancer.[17] The evaluation of tumor response after SABR for lung malignancies by $^{18}$FDG-PET/CT needs further validation; however, the metabolic features could be utilized as a surrogate for tumor response.[18]

Apart from a BED of at least 100 $Gy_{10}$, in lung SABR for oligometastases no factors to predict the efficacy of the treatment are available as yet. Thus, the radiation oncology community is wondering whether other parameters could be helpful to predict response to SABR or to select the subset of patients with oligometastases appropriate for SABR.[19] The metabolic profile of lung oligometastases, defined by means of $^{18}$FDG-PET/CT, could represent a *piece of this puzzle* concerning the issue of predictive factors to customize SABR for this subset of patients.

The aim of the study was to assess $^{18}$FDG-PET/CT results during the follow-up period and the difference from functional imaging before SABR.

## Materials and Methods

### *Patients and SABR*

Lung SABR for oligometastases was performed when the following criteria were satisfied: (1) controlled primary tumor, (2) absence of progressive disease for longer than 6 months, and (3) no more than five metastatic lesions.

Planning and treatment for all patients was performed while they were in a supine position with a Posirest (CIVCO Medical Solutions, Orange City, Iowa) and a Vac-Lok cushion (CIVCO Medical Solutions). A four-dimensional CT scan in the treatment position was acquired for all patients, and for each patient, 10 phases were reconstructed with 3 mm of slice thickness and interslice distance. Gross tumor volume was equal to clinical target volume. It consisted of the radiological lung lesion, as identified by optimizing the Hounsfield units (HU) window for lungs and by repeating the delineation on each four-dimensional CT phase. Internal target volume was defined as the Boolean envelope of the gross tumor volumes from each respiratory phase. Planning target volume (PTV) was defined as the internal target volume plus an isotropic margin of 5 mm in all directions. The conceived organs at risk (OAR) were the homolateral and contralateral lung, heart, spinal cord, esophagus, and chest wall.

The prescribed total dose of SABR was varied according to the tumor site (central or peripheral) and maximum diameter of the lesions by using a strategy of risk-adapted dose prescription. We used schedules of three to five fractions for peripheral lesions versus schedules of eight to 10 fractions for central lesions. Furthermore, schedules of four fractions of 12 Gy or five fractions of 11 Gy, instead of three fractions of 18 Gy, were selected for peripheral lesions of patients with larger tumors (>2 cm) and/or a higher risk profile. Similarly, 10 fractions of 7 Gy, instead of eight fractions of 7.5 Gy, were considered for centrally located lesions according to the potential presence of overlap between PTV and critical OAR (e.g., bronchial tree or esophagus). In the case of overlap, the sparing of the OAR was privileged with respect to the target dose coverage: 95% of the prescribed dose (Dp) was then optimized to at least 95% of the target volume, which was usually defined as PTV minus OAR, unless a further crop was necessary to ensure a within-tolerance maximum dose to the overlapping OAR. The dose prescription was at the median PTV dose with assurance from optimization to 95% of the Dp to at least 95% of the PTV and a near-maximum target dose not larger than 107% of the Dp.

By neglecting tumor repopulation, given the reduced number of fractions in SBRT schedules, BED was calculated by the formula $D \times [1 + d/(\alpha/\beta)]$,[20] where d is the dose per fraction, and D is the total dose. All adopted schedules satisfied a $BED_{10}$ of a least 100 Gy at the isocenter, where $\alpha/\beta$ equal to 10 Gy was assumed for all metastatic lesions.

The constraints for OAR were a $D_{0.1cc}$ value of less than 20 Gy on the spinal cord planning risk volume (isotropically expanded by 4 mm from spinal cord) and

a $D_{1cc}$ value less than 30 Gy for the heart and esophagus. For the total lungs minus PTV, the dose constraints were $V_5$ less than 30%, $V_{10}$ less than 20%, and $V_{20}$ less than 10% and mean lung dose less than 4 Gy. All plans were performed by RapidArc, version 10.0.28 (Varian Inc., Palo Alto, CA) volumetric modulated arc therapy by typically using two coplanar arcs of approximately 200 degrees with a single isocenter per metastatic lesion. Jaw tracking was used to minimize residual leaf transmission. The final dose distributions were computed with the analytical anisotropic algorithm (version 10.0.28), as implemented in the Eclipse treatment planning system, version 10.0.28 (Varian Inc.). Patients were typically treated with 6-MV flattening filter–free photon beams by means of a TrueBeam linac (Varian Inc.) equipped with a Millennium multileaf collimator (Varian Inc.) with a leaf dimension at the isocenter of 5 mm. A maximum dose rate of 1400 MU/min for the 6-MV flattening filter–free photon beam was used. Before each fraction, image-guided RT was performed by means of kV cone beam CT. Evaluation of tumor response was assessed by means of $^{18}$FDG-PET/CT and according to the PET Response Criteria in Solid Tumors[21] within 3 months after SABR and every 3 months thereafter.

### Study Design and Definition of the Metabolic Parameters

The inclusion criteria of the current retrospective study were as follows: (1) one to five lung oligometastases treated with SABR for each patient, (2) presence of $^{18}$FDG-PET/CT before and after SABR for at least two subsequent evaluations, (3) Karnofsky performance status higher than 80, and (4) life expectancy longer than 6 months.

Pre-SBRT $^{18}$FDG-PET/CT three-dimensional (3D) scans (i.e., without gating) were performed with the patient within the same fixation devices to be used for treatment, whereas in the post-SBRT PET/CT 3D-scans no fixation device was adopted. The scans were performed with a Siemens Biograph mCT-S(64) system (Siemens Knoxville, TN). Tomographic images were reconstructed by using the TrueX point spread function plus time of flight iterative reconstruction algorithm (three iterations, 21 subsets, and a 5-mm full-width at half-maximum Gaussian filter) and analyzed with the Siemens Syngo TrueD 3D VOI isocontour tool (Siemens). PET acquisitions were started 60 minutes after administration of 2.96 MBq/kg of $^{18}$FDG; patients were enrolled if their blood glucose level was lower than 140 mg/dL. When lesions in the lower lung segment were detected, patients underwent a 30-second breath-hold acquisition to avoid or minimize movement issues.

For the intent of the analysis, the following $^{18}$FDG metabolic parameters were retrospectively defined: (1) $SUV_{max}$ (i.e., the highest uptake value over all pixels within the region of interest [ROI]), (2) $SUV_{mean}$ (i.e., the mean uptake value within the ROI), (3) metabolic tumor volume (MTV) (i.e., the total volume with an SUV of 2.5 or greater), and (4) total lesion glycolysis (TLG) as an estimate of tumor metabolic rate (i.e., the product of $SUV_{mean}$ and MTV). Both pre- and post-SBRT $^{18}$F-FDG-PET/CT data sets were analyzed semiquantitatively with Syngo Multimodality Workplace software (Siemens AG, Erlangen, Germany) by two nuclear physicians who were blinded to all imaging studies and clinical and pathological results. For each lung lesion, the irregular isocontour ROI was determined on the basis of a fixed threshold for the $^{18}$FDG SUV (e.g., SUV $\geq$ 2.5).[21] PET-CT SUV values were standardized according to the European Association for Nuclear Medicine procedure guidelines for tumor imaging, version 2.0.[22]

### Statistical Analysis

To summarize the most relevant features of the clinical variables, descriptive statistics were performed. All the categorical variables were analyzed with contingency tables with Fisher's exact test or Pearson's chi-square test, whereas the continuous variables were analyzed by one-way analysis of variance, *t* tests (with equal or unequal variance), or nonparametric Wilcoxon (Mann-Whitney) and Kruskal-Wallis tests.

Three clinical outcomes were defined: (1) LC as the absence of local recurrence in field (in the prior radiation field), (2) distant metastases–free survival, and (3) overall survival from the end of SABR. These parameters were assessed by using Kaplan-Meier curves.

Logistic regression models were used to assess the relationship between the pre-SABR metabolic parameters ($SUV_{max}$, $SUV_{mean}$, MTV, TLG, $\Delta SUV_{max}$, and $\Delta SUV_{mean}$ considering pre-SABR and post-SABR values) with local failure, distant metastatic progression, and complete response of lung metastasis during follow up. The following dependent variables were taken into account with the metabolic parameters to estimate the possible correlation with local failure and distant metastases: patient's age, number of fractions, BED, type of primary tumor, tumor volume, and number of metastatic lesions. These variables were dichotomized at the median value for the analysis.

The receiver operating characteristic curves were used to assess the sensitivity and specificity of the cutoff of the pre-SABR metabolic parameters in correlation with the probability of complete response of the lung lesion during follow-up after SABR. The area under the curve (AUC) was used to verify the accuracy; in the case

of a moderately accurate test (AUC> 0.7), the product of maximum sensitivity and specificity was chosen as the cutoff value.

A $p$ value of 0.05 or less was considered statistically significant. Statistical analysis was performed with R software, version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Patients

From January 2012 to November 2015, 50 patients met the inclusion criteria of the present analysis, for a total of 70 lung metastatic lesions. Table 1 shows patient and lung metastases characteristics. All patients analyzed in the current study had only lung oligometastases with absence of disease outside the lung. The lesions were metachronous and classified as oligopersistent and/or oligorecurrent[23] in a scenario of metastatic disease after one or two schedules of systemic antiblastic therapies administered according to international guidelines,[24] taking into account the specific primary tumor.

All patients reached a follow-up after SABR of at least 6 months. The median follow-up was 18 months (range 6–53 months). The 1-year overall survival and LC (lack of any recurrence in field) rates were 86% and 78%, respectively. The median distant metastases–free survival was 6 months (range 3–15 months). During the follow-up, the distant metastases sites were the brain (two), liver (four), lymph nodes (two), bone (one), and lung out of field (two). There was an in-field disease progression in seven lesions.

**Table 1.** Characteristics of Patients (n = 50) and Lung Metastases (n = 70)

| Parameter | n | % |
|---|---|---|
| Sex | | |
| Male | 34 | 68 |
| Female | 16 | 32 |
| Median age | 70 y (range 48-85) | |
| Primary lesion site | | |
| Lung | 34 | 49 |
| Colon | 28 | 41.5 |
| Corpus uteri | 6 | 8.7 |
| Larynx | 1 | 1.5 |
| Lesion histologic subtype | | |
| Adenocarcinoma | 50 | 71 |
| Squamous | 20 | 29 |
| Lung lesion side | | |
| Right | 44 | 63 |
| Left | 26 | 37 |
| SABR, no. fractions | | |
| 3 | 7 | 10 |
| 4 | 11 | 16 |
| 5 | 28 | 40 |
| 8 | 10 | 14 |
| 10 | 14 | 20 |
| Lesion diameter, maximum | | |
| Median 2.3 cm (range 1-5) | | |
| Biologically equivalent dose | | |
| Median 110 Gy (range 100-164) | | |
| Gross tumor volume | | |
| Median 3.8 $cm^3$ (range 0.3-33) | | |
| Internal target volume | | |
| Median 7.5 $cm^3$ (range 0.6-35.5) | | |
| Planning target volume | | |
| Median 26 $cm^3$ (range 5.5-78.5) | | |

SABR, stereotactic ablative radiotherapy.

### Pre-SABR Metabolic Findings

The median interval between pre-SABR $^{18}$FDG-PET/CT and the first fraction of SABR was 5 days (range 3–7 days). Before treatment, the median $SUV_{max}$ was 6.5 (range 4–17), the median $SUV_{mean}$ was 3.7 (range, 2.5–6.5), and the median MTV was 2.3 $cm^3$ (range 0.2–31 $cm^3$). For lesions with in-field disease progression, the median TLG was 17.4 (range 2–52.8); for the remaining lesions, the median value was 170.6 (0.5–171).

### Post-SABR Metabolic Findings

Table 2 details the post-SABR median metabolic findings within 3 months after treatment and at 6, 9, 12 and 18 months of follow-up for all the lesions analyzed. Figure 1 shows the $SUV_{max}$ and $SUV_{mean}$ behavior curves during follow-up for lesions with in-field and distant failures.

For lesions without in-field failure (n = 63), an increase in $SUV_{max}$ and $SUV_{mean}$ values was registered at 9 to 12 months after SABR in comparison with the control at 6 months of follow-up after SABR. In particular, $SUV_{max}$ has been estimated at +5.4%, whereas $SUV_{mean}$ has been estimated at +1.6%. This phenomenon was no longer evident in the subsequent metabolic imaging.

**Table 2.** Post-SBRT Metabolic Findings at 3, 6, 9, 12, and 18 Months of Follow-up

| Follow-up | No. Lesions Analyzed | Median Value of $SUV_{max}$ (Range) | Median Value of $SUV_{mean}$ (Range) | Median Value of MTV (Range) |
|---|---|---|---|---|
| 3 mo | 70 | 3.8 (1.9-14) | 3 (1.9-6.5) | 3.9 (0.25-50) |
| 6 mo | 51 | 2.8 (2-20) | 2.7 (1-5) | 5 (1-18) |
| 9 mo | 24 | 2.5 (2-11) | 2.5 (2-4) | 7 (0.05-10) |
| 12 mo | 18 | 2.6 (1.7-11.5) | 2.5 (2-4) | 7.8 (0.05-10) |
| 18 mo | 6 | 2.4 (2-3.7) | 2.4 (2-2.7) | Not evaluable |

SBRT, stereotactic ablative radiotherapy; $SUV_{max}$, maximum standardized fludeoxyglucose F 18 uptake value; $SUV_{mean}$, mean standardized fludeoxyglucose F 18 uptake value; MTV, metabolic tumor volume, defined as total volume with a standardized uptake value of 2.5 or greater.

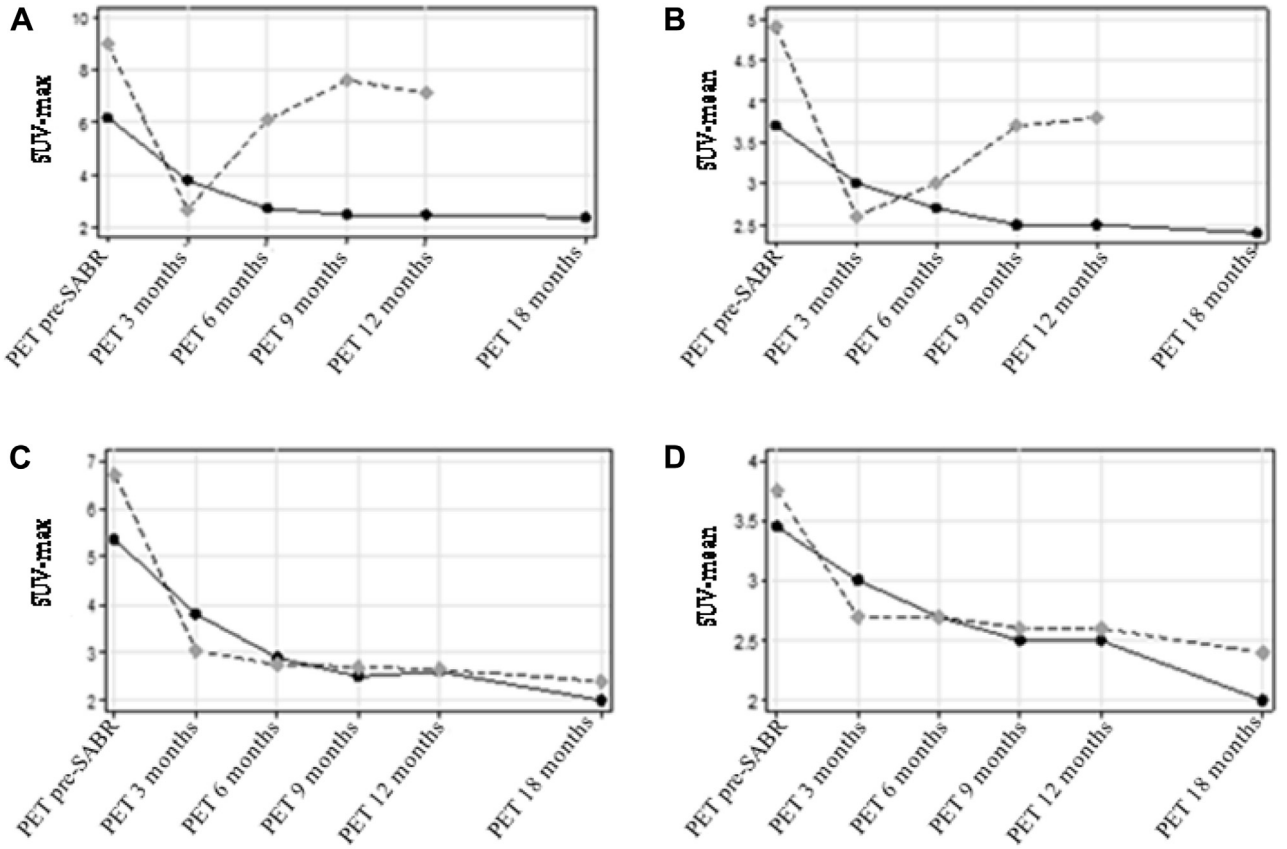


**Figure 1.** Maximum standardized uptake value ($SUV_{max}$) (*A*) and mean standardized uptake value ($SUV_{mean}$) (*B*) curves for patients with local failure (*dashed line*), with solid line representative of patients without local failure after stereotactic ablative radiotherapy (SABR). $SUV_{max}$ (*C*) and $SUV_{mean}$ (*D*) curves for patients with distant metastases after SABR (*dashed line*), with the solid line representative of patients without distant metastases after SABR. PET, positron emission tomography.

### *Metabolic Parameters Predictive of SABR Outcomes*

No statistical correlation was observed between the pre-SABR metabolic variables ($SUV_{max}$ and $SUV_{mean}$, MTV and TLG, and $\Delta SUV_{max}$ and $\Delta SUV_{mean}$) and clinical parameters (patient's age, number of fractions, BED, type of primary tumor, tumor volume, and number of metastatic lesions) with local failure or distant progression. Conversely, a complete lung lesion response at 6 months after SABR was related to the pre-SABR $SUV_{max}$ and $SUV_{mean}$ values.

In fact, at this time point a complete response was observed in 94% of lesions if a pre-SABR $SUV_{max}$ value less than 5 was registered ($p = 0.001$, AUC = 0.90, sensitivity = 88%, and specificity = 94%).

Table 3 showed statistical correlations between pre-SABR metabolic parameters ($SUV_{max}$, $SUV_{mean}$, MTV, and TLG) with in-field failure, distant metastatic progression and response of the lung metastasis 6 months after SABR. Figure 2 shows the receiver operating characteristic curve for a pre-SABR $SUV_{max}$ value less than 5 in correlation with complete lung lesion response at 6 months after SABR. Similarly, a pre-SABR $SUV_{mean}$ value less than 3.5 was related to complete response at 6 months after SABR ($p = 0.03$, sensitivity = 31%, specificity = 34%, and AUC = 0.32).

### *Findings of the Analysis of In-Field Recurrences*

Considering the seven lung metastases with in-field failure, a pre-SABR $SUV_{max}$ value greater than 8 was related to a higher increase in $SUV_{max}$ at 6 months of follow-up (in terms of absolute value) compared with a pre-SABR $SUV_{max}$ value less than 8 ($p = 0.005$). Although there is no statistically significant relation (because of the sample size), an OR of 1.89 for in-field recurrence was found in the case of a pre-SABR $SUV_{mean}$ value of at least 4. Only two of seven lesions with in-field relapse were centrally located. The dichotomization of the sample in terms of tumor location did not give statistically significant results. The 86% of patients with local failure had distant progression versus a rate of only 19% in cases without local failure ($p = 0.004$, OR = 25).

**Table 3.** Correlations between Pre-SABR Metabolic Parameters with Local Failure, Distant Metastatic Progression, and Lung Metastasis Response

| | Local Failure (In-Field) | | | Distant Metastatic Progression | | | Lung Metastasis Complete Response (6 mo after SABR) | | |
|---|---|---|---|---|---|---|---|---|---|
| Parameter | OR | 95% CI | *p* Value | OR | 95% CI | *p* Value | OR | 95% CI | *p* Value |
| $SUV_{max}$ (for values ≥5) | 2.93 | 0.52-5.11 | 0.219 | 1.98 | 0.66-5.91 | 0.221 | 0.313 | 0.09-0.99 | **0.05** |
| $SUV_{mean}$ (for values ≥ 5) | 1.06 | 0.22-5.16 | 0.936 | 1.85 | 0.61-5.68 | 0.281 | 0.237 | 0.06-0.84 | **0.026** |
| MTV | 1.01 | 0.89-1.14 | 0.855 | 1.04 | 0.96-1.14 | 0.281 | 1.01 | 0.91-1.11 | 0.946 |
| TLG | 1.01 | 0.97-1.02 | 0.897 | 1.01 | 0.99-1.02 | 0.294 | 0.99 | 0.97-1.02 | 0.791 |

*Note:* Boldface indicates statistically significant *p* values.
SABR, stereotactice ablative radiotherapy; CI, confidence interval; $SUV_{max}$, maximum standardized fludeoxyglucose F 18 uptake value; $SUV_{mean}$, mean standardized fludeoxyglucose F 18 uptake value; MTV, metabolic tumor volume, defined as total volume with a standardized uptake value of 2.5 or greater; TLG, total lesion glycolysis.

### *Findings on the Δ Values between PET Scans*

A $\Delta SUV_{max}$ between the pre-SABR and first control values (here defined as $\Delta SUV_{max}$ at 0–3 months) was −65% for lesions with in-field progression versus −22.5% for the remaining metastases. Conversely, the $\Delta SUV_{max}$ at 3 to 6 months was +126% for lesions with in-field progression versus −26% for the remaining metastases ($p = 0.002$, two-sample Wilcoxon rank sum test). The $\Delta$ $SUV_{mean}$ at 0 to 3 months was −39% for lesions with in-field progression versus −17% for the remaining metastases. $\Delta$ $SUV_{mean}$ at 3 to 6 months was +15% for lesions with in-field progression versus −26% for the remaining metastases ($p = 0.008$, two-sample Wilcoxon rank sum test).

## Discussion

In the past few years, a growing interest in the use of SABR as a therapeutic option for lung oligometastases has arisen. Post-SABR radiological changes are frequently detected on diagnostic CT scan imaging.[25,26]

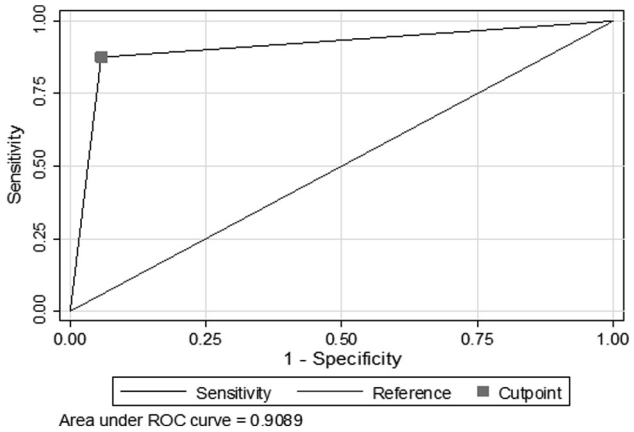


**Figure 2.** Receiver operating characteristic (ROC) curve for pre-stereotactic ablative radiotherapy maximum standardized uptake value less than 5 as a factor predictive of complete lung lesion response 6 months after stereotactic ablative radiotherapy.

In case of mass-like patterns on CT scans after SABR, it is difficult to differentiate between radiation fibrosis or tumor recurrence. Thus, $^{18}$FDG-PET/CT may be utilized as an important tool to monitor tumor response by means of semiquantitative metabolic parameters.[21,27] Furthermore, the role of $^{18}$FDG-PET/CT as a predictor of outcome in patients with primary lung malignancies treated with SABR has been investigated.[28,29]

In a retrospective study, lung lesion volume variations were analyzed by contouring on cone beam CT images to evaluate early predictive parameters of response to SABR. At the last session of SABR, a lung lesion shrinkage of at least 20% was revealed to be predictable of complete response 6 months thereafter.[30] Several metabolic predictive factors for recurrence and survival after SABR for primary lung cancer have already been investigated by several studies.[31–33] Similarly, the present study was designed to investigate the role of $^{18}$FDG-PET/CT parameters as predictive of early response after SABR in the setting of lung oligometastases. In the current analysis, a complete lung lesion response at 6 months after SABR was related to pre-SABR $SUV_{max}$ and $SUV_{mean}$ values. Lung oligometastases with a pre-SABR $SUV_{max}$ value less than 5 as well as a $SUV_{mean}$ value less than 3.5 was revealed to be related to complete response at 6 months.

The issue of pre-SABR FDG uptake as a predictive factor is not new, especially in the setting of primary lung cancer. In a large patient population affected by primary lung cancer, a pre-treatment $SUV_{max}$ value greater than 3 was associated with worse survival and a greater propensity for local recurrence and distant metastasis after SABR.[31] These findings may mean that a low metabolic activity in lung malignancies could identify patients who would benefit from an SABR-approach alone. On the other hand, the present findings could assume more relevance in the scenario of a multidisciplinary approach in lung oligometastases: in the case of pre-SABR high metabolic uptake, a sequential approach with systemic therapies could be

evaluated early. Although these hypotheses need future evaluations, these arguments could appear intriguing in terms of (1) customizing therapeutic management after SABR (adding cytotoxic drugs), (2) monitoring patients with oligometastases according to the probability of tumor response, and (3) adapting the SABR dose prescription according to SUV stratification. PET-SUV thresholds, if standardized, might be helpful for decision making regarding stratification of patients with oligometastases into slowly progressing patients and rapidly progressing patients. The exact therapeutic implication for intervention remains to be determined, and the primary use of systemic therapy in patients with high PET SUV could be an option. Clinical trials with stratification based on SUV PET are needed to justify the different treatment strategies. On the other hand, in this setting of disease, PET could influence the frequency or imaging strategies during follow-up to create a sort of personalization of follow-up allowing for possible health care cost benefits.

Besides the well-recognized and common measurement parameters such as $SUV_{max}$, $SUV_{mean}$, MTV, and TLG derived from $^{18}$FDG-PET/CT scans, more advanced image analysis methods such as radiomics are currently under investigation for evaluation of treatment and prediction of response or as potential biomarkers to adopt in clinical interpretation of molecular images. These radiomics applications could provide promising findings to integrate with the conventional parameters for imaging measurements. Nevertheless, no robust and reliable models seem to be available as yet and no large consensus has been achieved by nuclear medicine physicians, especially in this context.[34] Thus, radiomics features were not used in this study.

The role of $^{18}$FDG-PET/CT in the detection of lung tumor response after conventional RT is well recognized. In this setting, 18-FDG-PET/CT showed high rates of sensitivity and specificity, estimated at 100% and 92%, respectively.[35] In the scenario of patients with lung oligometastases who underwent SABR, it was shown that $^{18}$FDG-PET/CT is effective in detecting responses.[36] However, some concerns remain about the role of $^{18}$FDG-PET/CT versus CT scan alone after lung SABR. First of all, differentiating tumor recurrence from radiation fibrosis remains challenging in lung SABR scenario. Moreover, in the absence of morphological change on a CT scan, $^{18}$FDG-PET/CT allows for a better understanding of tumor response. A decrease in metabolic uptake would indicate a decreased tumor activity and possible response to treatment. Compared with CT scan alone, fused $^{18}$FDG-PET/CT images may allow differentiation of metabolically active recurrent tumor from metabolically inactive radiation-induced fibrosis. $^{18}$FDG uptake after SABR for lung malignancies could be moderate early after treatment. A pathological confirmation of malignancy is generally preferred before the initiation of any curative-intent therapy. Many candidates for SABR have comorbidities, including compromised pulmonary and cardiac function, that could increase the risks associated with transthoracic biopsy or repeated biopsy if the initial attempt is not conclusive.[37] In lung malignancies, a study[38] found that a PET-directed SABR strategy (without prior biopsy) could be warranted thanks to a point estimate of malignancy of 85%. Again, in a Dutch study[39] the use of PET scans has made it possible to obtain a probability of malignancies of 92%. Thus, in the current study $^{18}$FDG-PET/CT parameters were used to evaluate the response rates. Additionally, in the case of metastatic disease, we are reluctant to promote an invasive procedure except in those cases that are really difficult to evaluate and in which histological subtype is easy to obtain (no contraindications to surgery). In a systematic review, an $SUV_{max}$ value of 5 or greater was identified as highly suggestive of recurrence.[40] However, the metabolic uptake usually decreases at 12 months and longer without clear images of mass-like shape uptake.[41] Strangely, in our experience, MTV, which is a metabolic biomarker defined as total volume with an SUV of at least 2.5, increased over the follow-up without statistically significant correlations with local failure or distant progression, as well as with the other pre-SABR metabolic variables here analyzed. From our point of view, the increase in MTV could be related to the enlargement of the phlogistic area in the lung parenchyma after SABR with an SUV of at least 2.5. However, this last aspect needs specific further investigation.

In the case of centrally located lesions that overlap with crucial OAR, the reduced target dose coverage might determine an increased risk of local failure for such centrally located lesions. In the present study population, only two of seven lesions with in-field relapse were centrally located. The dichotomization of the sample in terms of tumor location did not give statistically significant results. A $\Delta$ $SUV_{max/mean}$ value for 0 to 3 months was revealed to be more marked in terms of SUV reduction for patients in which *in-field* progression during follow-up was registered. Conversely, the $\Delta SUV_{max/mean}$ value in the interval from 3 to 6 months was increased for the same patients. These findings could attest that an early $^{18}$FDG-PET/CT evaluation after SABR may be not as necessary for all the patients. Although the identification of the subgroup of patients in whom $^{18}$FDG-PET/CT could be delayed after SABR remains not investigated in the present study, longer-term trials are strongly advocated to improve the personalization of tumor response monitoring in patients with oligometastases and, subsequently, the cost-effectiveness of health care.

Finally, our findings confirm the role of lung SABR in the metastatic setting. In fact, 86% of patients with local failure had distant progression versus only 19% of those without local failure. These results could reflect the postulate by Hellman and Weichselbaum according to which a state of tumor dormancy with reduced ability to metastasize could exist in patients with oligometastases.[42] Thus, ablation of macroscopic *foci* of disease could favorably modify the natural history and management of the oligometastatic phase.

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