Assessment of tumor response after chemotherapy using 18F-FDG PET metrics is gaining acceptance. Several studies have suggested that the parameters metabolically active tumor volume (MTV) and total lesion glycolysis (TLG) are superior to SUV_max for measuring tumor burden. However, the measurement of MTV and TLG is still controversial; the most common method uses an absolute threshold of 42% of SUV_max. Currently, we implemented a background-adaptive method to determine the background-subtracted lesion activity (BSL) and the background-subtracted volume (BSV). In this study, we investigated the correlation between such PET metrics and histopathologic response in non–small cell lung carcinoma (NSCLC). Methods: Forty-four NSCLC patients were retrospectively identified. Their PET/CT data on both types of scan before and after neoadjuvant chemotherapy were analyzed regarding SUV_max, MTV, TLG, BSL, and BSV, as well as the relative changes in these parameters. The tumor regression score as an indicator of histopathologic response was scored on hematoxylin- and eosin-stained sections of the surgical specimens using a 4-tiered scale (scores 1–4). The correlation between score and the absolute and relative PET metrics after chemotherapy was analyzed using Spearman rank correlation tests. Results: Tumors that demonstrated a good response after neoadjuvant chemotherapy had significantly lower 18F-FDG activity than non–responding tumors (scores 3 and 4: SUV_max, 4.2 [range, 1.8–7.9] vs. scores 1 and 2: SUV_max, 8.1 [range, 1.4–40.4]; P = 0.001). The same was found for change in SUV_max and score (P = 0.001). PET volume metrics based on a 42% fixed threshold for SUV_max did not correlate with score (TLG, P = 0.505; MTV, P = 0.386). However, both of the background activity–based PET volume metrics—BSL and BSV—significantly correlated with score (P < 0.001 each). Conclusion: PET volume metrics based on background-adaptive methods correlate better with histopathologic tumor regression score in NSCLC patients under neoadjuvant chemotherapy than algorithms and methods using a fixed threshold (42% SUV_max).

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measurement of lesion activity and volume: MTV and TLG based on a relative threshold using SUV$_{\text{max}}$ (e.g., 42%) will underestimate lesional uptake with a high activity and overestimate lesions with an SUV$_{\text{max}}$ close to the background level (19). Other authors have used a fixed SUV threshold, most commonly 2.5 (20–22), with the obvious limitations of an arbitrary cutoff. Lesions with low activity are thereby underestimated or not even measurable. We have therefore developed a background-based estimation including background-subtracted lesion activity (BSL) and background-subtracted volume (BSV) (Fig. 1). Our method uses a single volume of interest (VOI) that surrounds the tumor and reads its histogram to measure the total activity within the lesion (19). It is based on our previously published study showing that background activity can be assessed automatically within the tumor VOI using histogram analysis (23). Because background voxels have more homogeneous values, they will always represent the mode in a selected VOI with a normal gaussian distribution. Therefore, background voxels can be removed from the VOI by subtraction of a normal distribution fitted to the first peak in the histogram (19).

In this study, we used $^{18}$F-FDG PET to test the performance of the relative change in several tumor volume metrics—MTV, TLG, BSV, and BSL—for NSCLC after treatment with neoadjuvant chemotherapy. As an independent reference for tumor response, we chose the histopathologic tumor regression score of the corresponding formalin-fixed and paraffin-embedded surgical specimens, as described by Junker et al. (24,25).

MATERIALS AND METHODS

Patient Selection

Patients with locally advanced stage II, stage III, or oligometastatic stage IV disease underwent neoadjuvant chemotherapy according to international guidelines following the decision of our local tumor board (20). To be selected for our study, between January 2002 and December 2012 the patient must have undergone $^{18}$F-FDG PET/CT before receiving neoadjuvant treatment and before undergoing surgery. This retrospective study was approved by the Ethical Commission of the Canton of Zurich, and the requirement to obtain informed consent was waived.

From a total of 92 NSCLC patients undergoing surgery after neoadjuvant chemotherapy, 44 met all inclusion criteria. Most patients were stage III at diagnosis. After neoadjuvant treatment, only 3 patients showed tumors with ypT0, whereas ypT3 predominated. Demographic details are given in Table 1.

PET/CT Acquisition and Analysis

The inclusion criteria for $^{18}$F-FDG PET/CT were as follows: scans of adequate quality, a fasting period of at least 4 h, no elevation in blood glucose, an $^{18}$F-FDG uptake time of 45–60 min, and an adequate $^{18}$F-FDG injection (<100-MBq difference between the two $^{18}$F-FDG injections).

All patients were examined using a routine clinical protocol in the Institute of Nuclear Medicine on dedicated PET/CT scanners (DSTE, [GE Healthcare], 16- or 64-slice CT, 7–8 frames, frame time of 1.5 or 2 min) with injection of 350 MBq of $^{18}$F-FDG 45–60 min before examination. A low-dose unenhanced CT scan was performed for attenuation correction and used for anatomic localization (80 mA, 120 kV). The imaging findings were analyzed by a physician dually board-certified in nuclear medicine and radiology, who was masked to the histopathology results.

A VOI was placed around the primary tumor in such a way that the entire tumor activity was enclosed and regions of physiologically increased activity were avoided (e.g., cardiac $^{18}$F-FDG uptake). If high-activity structures could not be avoided, they were cut out before the analysis. Instructions on VOI placement were previously published (23). In brief, the VOI had to be slightly larger than the tumor. For lesions with a heterogeneous background (e.g., tumors abutting lung and mediastinal tissue or hilar vessels), the VOIs were adjusted to include more of the background tissue with higher $^{18}$F-FDG activity (e.g., mediastinum). Within the selected VOI, SUV$_{\text{max}}$, MTV, TLG, BSL, and BSV were measured. The change in these 5 PET metrics before and after neoadjuvant chemotherapy was also calculated. On CT, the maximal tumor diameter was measured in 3 dimensions (a, b, and c) and tumor volume, $\text{CT}_{\text{vol}}$, was estimated as an ellipsoid using the formula $4/3\pi(\text{a}/2 \times \text{b}/2 \times \text{c}/2)$, along with the corresponding change in $\text{CT}_{\text{vol}}$ (27).

Histopathologic Assessment of Tumor Regression

For histopathologic assessment, the inclusion criteria were the availability of at least 2 representative original whole-tumor hematoxylin- and eosin-stained slides for regression scoring, no secondary simultaneous tumor, and a histologic subtype of either adenocarcinoma or squamous cell carcinoma. Only the primary tumors were analyzed. All hematoxylin- and eosin-stained resection specimens processed for the original sign-out were reviewed by two of the authors to determine the score, which was based on a 4-tiered scale as described by Junker et al. (24,25). This system evaluates the proportion of viable tumor cells in relation to the degree of tumor necrosis and fibrosis. In brief, score 1 is defined as no tumor regression or only minor, mostly spontaneous, regression; score 2 is defined as the presence of more than 10% vital tumor tissue; score 3 is defined as less than 10% vital tumor epithelia in all tumors; and score 4 is defined as the presence of complete tumor regression whereby only fibrotic and necrotic areas with macrophage-rich xanthomatous inflammation remain in the original tumor volume.

For dichotomized data analysis, scores of 1 and 2 were regarded as indicating low regression and therefore the tumors nonresponding, whereas tumors with scores 3 or 4 were considered responders.

Statistical Analysis

The distribution of changes in PET metrics for the various regression scores was analyzed using box plots. Correlations between scores and the absolute and relative PET metrics, as well as $\text{CT}_{\text{vol}}$ were calculated.
TABLE 1
Characteristics of the 44 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age at surgery (y)</td>
<td>62 (range, 38–75)</td>
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</tr>
<tr>
<td>Median body weight (kg)</td>
<td>70 (range, 43–123)</td>
<td></td>
</tr>
<tr>
<td>Median 18F-FDG dose (MBq)</td>
<td>352 (range, 274–430)</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>25/19</td>
<td>56.8/43.2</td>
</tr>
<tr>
<td>Histology</td>
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<td></td>
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<tr>
<td>Squamous cell carcinoma</td>
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<tr>
<td>Adenocarcinoma</td>
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<tr>
<td>Clinical stage at diagnosis</td>
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<td></td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>13.6</td>
</tr>
<tr>
<td>III</td>
<td>35</td>
<td>79.5</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>6.8</td>
</tr>
<tr>
<td>Tumor location</td>
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<tr>
<td>Left lower lobe</td>
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<td>13.6</td>
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<tr>
<td>Left upper lobe</td>
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<td>Right lower lobe</td>
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<td>13.6</td>
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<td>Right middle lobe</td>
<td>3</td>
<td>6.8</td>
</tr>
<tr>
<td>Right upper lobe</td>
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<td>31.8</td>
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<tr>
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<td>0</td>
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<td>6.8</td>
</tr>
<tr>
<td>I</td>
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<td>11.4</td>
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<tr>
<td>II</td>
<td>10</td>
<td>22.7</td>
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<tr>
<td>III</td>
<td>25</td>
<td>56.8</td>
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<td>IV</td>
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<td>2.3</td>
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<tr>
<td>CT-based clinical</td>
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<td>T-stage at diagnosis</td>
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<tr>
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</tr>
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<td>Median cycles</td>
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</tr>
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<td>51.6</td>
</tr>
<tr>
<td>Platinum/taxane</td>
<td>25</td>
<td>56.8</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>6.8</td>
</tr>
</tbody>
</table>

*Data are n, except where otherwise indicated.

RESULTS

Thirteen patients had a tumor regression score of 3 or 4 and thus were considered responders. Only 1 patient did not show any histologic regression (score 1), whereas 30 patients had a score of 2 on histopathology. Lesions with a good response to neoadjuvant chemotherapy (score 3 or 4) had a mean SUVmax of 4.2 (range, 1.8–7.9), whereas lesions regarded as nonresponders (score 1 or 2) had a mean SUVmax of 8.1 (range, 1.4–40.4). An SUVmax cutoff of less than 6.4 after neoadjuvant chemotherapy yielded a sensitivity and specificity of 85% and 58%, respectively, for predicting a good pathologic response.

Differences between responders and nonresponders were significant for change in SUVmax (P = 0.001), BSL, and BSV (P < 0.001, respectively), whereas change in TLG and MTV was not significantly different between responders and nonresponders (Table 2).

Using the Spearman rank test, the correlation between change in SUVmax and score had a P value of 0.001. PET volume metrics based on a fixed SUVmax threshold did not correlate with score (P = 0.505 for change in TLG and 0.386 for change in MTV). However, both of the background activity–based PET volume metrics correlated significantly with score (P < 0.001 for both BSL and BSV) (Fig. 2).

Receiver-operator-characteristic analysis showed the largest AUC to be for BSV (0.799), followed by BSL (0.777) and SUVmax (0.767), whereas TLG and MTV had AUCs of 0.529 and 0.387, respectively (Fig. 3). A –68% cutoff for change in SUVmax showed a sensitivity and specificity of 69% and 84%, respectively. For change in BSV, a –88% cutoff gave a sensitivity and specificity of 69% and 81%, respectively, and for change in BSL, a –90% cutoff gave a sensitivity and specificity of 77% and 74%, respectively (Table 3).

DISCUSSION

Our results showed that SUVmax after neoadjuvant chemotherapy could distinguish responders from nonresponders with a high sensitivity of 85%, although the specificity, at 58%, was rather low. Change in SUVmax was associated with tumor regression, and a –68% cutoff predicted good to complete tumor regression with a specificity of 81% (scores 3 and 4). This finding is in line with previous studies that suggested a decrease in SUVmax to be associated with good tumor response (29–31). One study investigated the relation between quantitative 18F-FDG metrics and pathologic tumor response and showed a linear relation between change in SUVmax and percentage of nonviable tumor (32). Those investigators also came to the conclusion that metabolic parameters were superior to CT.
morphology for response assessment. This conclusion agrees with our results showing that a decrease in change in CT yield led to an AUC of 0.677, compared with 0.767 for \( \text{SUV}_{\text{max}} \) and 0.799 for BSL.

An increasing number of studies are using an SUV of 2.5 as an absolute threshold, especially for segmentation of lung tumors (20–22). In our cohort, one adenocarcinoma had an \( \text{SUV}_{\text{max}} \) of 2.4 before chemotherapy, which, for a threshold of 2.5, would not have been measurable with TLG or MTV. Moreover, this adenocarcinoma showed a decrease of only 50% and 60% in BSL and BSV, respectively, suggesting only a partial metabolic response, which was confirmed by histopathology (score 2). Furthermore, 8 lesions had an \( \text{SUV}_{\text{max}} \) of less than 2.5 after chemotherapy but only 4 were complete responders; of the 4 nonresponding lesions, BSL and BSV suggested complete response for only one.

Previously published papers suggest that PET volume metrics such as MTV and TLG are superior to SUV max for predicting overall and progression-free survival. However, MTV and TLG based on a fixed threshold (SUV max, 42%) failed to predict histopathologic response in the current study, whereas the background-adapted segmentation methods correlated with the tumor regression score. This might be explained by phantom results showing that a fixed threshold can substantially underestimate TLG and MTV for lesions with high \(^{18}\text{F}-\text{FDG} \) uptake (19). A decrease in \( \text{SUV}_{\text{max}} \) during therapy therefore may falsely increase MTV because a larger volume of less active tumor will be included in the MTV. This possibility can be illustrated by \(^{18}\text{F}-\text{FDG} \) PET/CT examinations before and after neoadjuvant chemotherapy as shown in Figure 4, in which MTV overestimated the volume after therapy whereas BSV showed a good response. Histopathologic examination confirmed tumor regression with a score of 3 (Fig. 5).

The original paper that established the 42% threshold by Erdi et al. also suggested that PET tumor segmentation requires an adapted threshold based on the tumor-to-background ratio (33). Drawing a separate VOI over the background for every lesion is time-consuming, especially in patients with multiple metastases. Therefore, we suggest our histogram-based 1-step method of measuring tumor activity and estimating volume. For tumor volume definition before radiotherapy planning, however, Nestle et al. (34) have already suggested

<table>
<thead>
<tr>
<th>PET metric after chemotherapy</th>
<th>Nonresponder (score 1 or 2, ( n = 31 ))</th>
<th>Responder (score 3 or 4, ( n = 13 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{SUV}_{\text{max}} )</td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>TLG</td>
<td>59.3</td>
<td>38.7</td>
</tr>
<tr>
<td>MTV</td>
<td>13.9</td>
<td>9.1</td>
</tr>
<tr>
<td>BSL</td>
<td>82.2</td>
<td>32.3</td>
</tr>
<tr>
<td>BSV</td>
<td>19.5</td>
<td>9.6</td>
</tr>
</tbody>
</table>

Min = minimum; max = maximum.
background-based tumor segmentation with a separate VOI drawn over the background area. Other investigators have looked at histogram indices such as SD, skewness, kurtosis, entropy, and energy, but the results are controversial and those metrics were not part of the current study (35).

In the present study, change in SUV\textsubscript{max} was not significantly inferior to change in BSL or BSV for predicting tumor regression. This result may reflect the importance of finding the most aggressive part within a tumor as reflected by the highest SUV, compared with MTV, and needs to be investigated in larger cohorts.

The study had several limitations. The retrospective nature of the analysis led to some inconsistencies in uptake time, and the injected \(^{18}\)F-FDG dose varied over time. Care was taken to exclude patients with high blood sugar, paravenous injection, or scan artifacts (motion, metal implants). In addition, the cohort represented a real patient population within the selected clinical setting, and quantification measures should be reliable in such a setting, too. Also we did not perform outcome analysis; we investigated the direct correlation between PET quantification and histopathology and believe that this patient population is too small and heterogeneous (stage, therapy, histology) to allow a meaningful assessment of correlation with progression-free and overall survival. Therefore, follow-up projects on larger homogeneous patient cohorts that underwent primary surgery without neoadjuvant chemotherapy are planned.

BSL and BSV are not intended to serve as a PET segmentation tool, since spatial information is lost in the histogram and therefore selected voxels do not necessarily correspond one-to-one to the voxels in the images. BSV therefore may not provide the accurate segmentation of the tumor boundary that is necessary for radiation therapy planning. Subtraction of background activity from the tumor VOI will show the BSL to be the entire amount of activity coming from the tumor regardless of its location; that is, spill-out and

<table>
<thead>
<tr>
<th>PET metric</th>
<th>Area</th>
<th>SE</th>
<th>Asymptotic significance</th>
<th>Asymptotic 95% CI</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{SUV}_{\text{max} \ II})</td>
<td>0.759</td>
<td>0.073</td>
<td>0.007</td>
<td>0.615–0.903</td>
<td>6.4</td>
<td>85%</td>
<td>58%</td>
</tr>
<tr>
<td>Change in...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT volume</td>
<td>0.677</td>
<td>0.097</td>
<td>0.066</td>
<td>0.488–0.867</td>
<td>−92%</td>
<td>54%</td>
<td>90%</td>
</tr>
<tr>
<td>(\text{SUV}_{\text{max}})</td>
<td>0.767</td>
<td>0.086</td>
<td>0.006</td>
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<td>69%</td>
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<tr>
<td>TLG</td>
<td>0.529</td>
<td>0.087</td>
<td>0.767</td>
<td>0.357–0.700</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MTV</td>
<td>0.387</td>
<td>0.092</td>
<td>0.242</td>
<td>0.206–0.568</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>BSL</td>
<td>0.777</td>
<td>0.080</td>
<td>0.004</td>
<td>0.620–0.934</td>
<td>−90%</td>
<td>74%</td>
<td>77%</td>
</tr>
<tr>
<td>BSV</td>
<td>0.799</td>
<td>0.069</td>
<td>0.002</td>
<td>0.663–0.935</td>
<td>−88%</td>
<td>69%</td>
<td>84%</td>
</tr>
</tbody>
</table>

CI = confidence interval; \(\text{SUV}_{\text{max} \ II}\) = \(\text{SUV}_{\text{max}}\) in the second scan; NA = not applicable.

**FIGURE 4.** 52-y-old woman treated with cisplatin/pemetrexed-based neoadjuvant chemotherapy for stage IIIA central adenocarcinoma of right hilum (\(\text{SUV}_{\text{max}}\), 16.1). (A–C) Staging \(^{18}\)F-FDG PET/CT image with coronal maximum-intensity-projection overview (A) and axial fused PET/CT images with tumor VOI around lesion (B and C), illustrating that MTV gives significantly lower volume than BSV in lesion with high activity. (D–F) Restaging \(^{18}\)F-FDG PET/CT study after 3 cycles of chemotherapy, showing significant decrease in \(\text{SUV}_{\text{max}}\) to 4.9, correlating with score of 3. Although BSV decreased by 96%, MTV decreased by only 17%, not entirely reflecting a good tumor response.

**FIGURE 5.** Corresponding histologic whole section for patient in Figure 4, with score of 3. (1) Extensive fibroelastotic scar tissue after neoadjuvant chemotherapy (partial response), with normal, partially emphysematic lung seen at bottom left. (2) Central portion of tumor, consisting of large calcifications, heavy elastosis, complete vessel remodeling, and enclosed anthracotic pigment. (3) Small residual focus of vital adenocarcinoma growing in lepidic fashion along alveolar walls. (Hematoxylin and eosin, \(\times10\)).

**TABLE 3**

<table>
<thead>
<tr>
<th>PET metric</th>
<th>Area</th>
<th>SE</th>
<th>Asymptotic significance</th>
<th>Asymptotic 95% CI</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
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<td>0.073</td>
<td>0.007</td>
<td>0.615–0.903</td>
<td>6.4</td>
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<td>58%</td>
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<tr>
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<tr>
<td>MTV</td>
<td>0.387</td>
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<td>BSL</td>
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</tr>
</tbody>
</table>

CI = confidence interval; \(\text{SUV}_{\text{max} \ II}\) = \(\text{SUV}_{\text{max}}\) in the second scan; NA = not applicable.
spillover will be included. As a result, for delineation of tumor volume, a spillover correction is necessary but was not performed in this study because we were interested in the change in total activity/volume and not the boundary. The 42% SUV\textsubscript{max} threshold suggested by Erdi can be applied only for homogeneous spheres with high lesion-to-background ratios (33). The heterogeneous nature of real tumors might be better reflected by Nestle’s suggestion of taking 15% of the average activity plus background to delineate the tumor area for radiotherapy (34). In assessing tumor burden through imaging, the fact that spillover is regarded as a part of tumor volume might only weakly affect overall accuracy, as suggested by the fact that the correlation between the tumor regression score and BSV and BSL was stronger compared with MTV and TLG.

**CONCLUSION**

The current data confirm that PET volume metrics based on a fixed SUV\textsubscript{max} threshold (42%) lead to a significant bias and do not correlate with response to chemotheraphy as assessed by histopathological examination. PET volume metrics based on background-adapted measurements, however, correlate with tumor regression.

**DISCUSSION**

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**REFERENCES**

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