Original Article

Optimal Standardized Uptake Value Threshold for Auto contouring of Gross Tumor Volume using Positron Emission Tomography/Computed Tomography in Patients with Operable Nonsmall-Cell Lung Cancer: Comparison with Pathological Tumor Size

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Abstract

Purpose: Incorporating ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG-PET/CT) for gross tumor volume (GTV) delineation is challenging due to varying tumor edge based on the set threshold of the standardized uptake value (SUV). This study aims to determine an optimal SUV threshold that correlates best with the pathological tumor size. **Materials and Methods:** From January 2013 to July 2014, 25 consecutive patients of operable nonsmall-cell lung cancer (NSCLC) who underwent staging^{18}F-FDG-PET/CT before surgical resection were included in the test cohort and 12 patients in the validation cohort. GTVs were delineated on the staging PET/CT by automatic delineation using various percentage threshold of maximum SUV (SUVmax) and absolute SUV. The maximum pathological tumor diameter was then matched with the maximum auto-delineated tumor diameter with varying SUV thresholds. First-order linear regression and Bland–Altman plots were used to obtain an optimal SUV threshold for each patient. Three radiation oncologists with varying degrees of experiences also delineated GTVs with the visual aid of PET/CT to assess interobserver variation in delineation. **Results:** In the test set, the mean optimal percentage threshold for GTV was SUVmax of 35.6%±18.6% and absolute SUV of 4.35 ± 1.7. In the validation set, the mean optimal percentage threshold SUV and absolute SUV were 36.9 ± 16.9 and 4.1 ± 1.6, respectively. After a combined analysis of all 37 patients, the mean optimal threshold was 36% ± 17.9% and 4.27 ± 1.7, respectively. Using Bland–Altman plots, auto-contouring with 40% SUVmax and SUV 4 was in greater agreement with the pathological tumor diameter. **Conclusion:** Automatic GTV delineation on PETCT in NSCLC with percentage threshold SUV of 40% and absolute SUV of 4 correlated best with pathological tumor size. Auto-contouring using these thresholds will increase the precision of radiotherapy contouring of GTV and will save time.

Keywords: *Auto-contouring, nonsmall-cell lung cancer, positron emission tomography-computed tomography, Radiotherapy, standardized uptake value*

Introduction

^{18}F-Fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) is a widely used staging investigation for nonsmall-cell lung cancer (NSCLC). Lobectomy with mediastinal lymph node dissection is the standard treatment for early-stage (ES) NSCLC.[1] Stereotactic Body Radiotherapy (SBRT) is the standard of care for inoperable ES NSCLC.[2] Target delineation is of crucial importance in SBRT, and inaccurate delineation can lead to poor local control rates owing to geographical miss due to its highly conformal nature and rapid dose fall-off.

Target volume (TV) delineation in radiotherapy (RT) planning is usually done on CT dataset. In NSCLC, manual visual-aided delineation becomes challenging, especially when the tumor is adjacent to or within the portion of the lung that has atelectasis or postobstructive pneumonia, and when located close to the mediastinum or the chest wall.[3,4] This leads to a significant inter and intra-observer variability in target delineation. Preferential accumulation of the ^{18}F-FDG in malignant tissue during the PET scan increases the contrast between tumor and normal tissue, which aids in target delineation after

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fusion with planning CT and improves its accuracy and reproducibility.[5-7]

Accurate identification of tumor edge on PET and whether to segment images manually or automatically are the challenges that need to be addressed while using PET/CT for TV delineation.[8] Accurate delineation of tumor edge depends on the standardized uptake value (SUV) threshold of ^{18}F-FDG used in PET.[9] Commonly used methods to identify the tumor edge on the PET/CT scan are the percentage threshold of maximum SUV (SUV_{max}) (e.g. SUV 42%), or an absolute SUV value (e.g. SUV 4.0).[10] PET/CT-based RT planning has been done using the different thresholds of SUV in various studies;[11,12] however, there is no clear consensus as to which SUV value should be used.

Validation of any manual or automated method of TV delineation is done by its comparison with pathological tumor size, the gold standard in resected NSCLC. In this study, we measured tumor size using various SUV thresholds of PET/CT-based tumor delineation (automatic) and compared it with the pathological tumor size. The rationale was to standardize the PET/CT based tumor delineation process to maximize the delineation accuracy while minimizing the inter-observer variability. In this study, we evaluated the SUV thresholds (percentage and absolute) that correlated best with pathological tumor size by various methods of delineation in ES NSCLC patients.

Materials and Methods

Consecutive patients of ES-NSCLC with staging ^{18}F-FDG-PET/CT acquired within 8 weeks of the surgical resection and that were available in hospital archives were retrospectively selected for this study. Patients who received neoadjuvant therapy and with positive margins on histopathology were excluded. A total of 37 patients from January 2013 to July 2014 were included, the first 25 patients were used as a test cohort and the remaining 12 were used as a validation cohort. This study was approved by the institutional ethics committee (IEC-1373), and a waiver of consent was obtained. All patients were staged according to the 7th edition of AJCC.

^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography technique and acquisition

Imaging was performed on dedicated PET/CT scanners (Philips Astonish TF systems, Cleveland, Ohio, USA) containing LYSO scintillation crystals with the time-of-flight algorithm incorporating 16 and 64 slice CT components. Image acquisition was performed 60–90 min after intravenous administration of 5 MBq/kg of ^{18}F-FDG and included a whole-body CT scan followed by the PET scan from the skull-base to mid-thigh. An intravenous contrast for the CT scan was administered to all patients unless there was a specific request or clinical indication against it. Contrast-enhanced CT scans were obtained during delayed venous phase at 120 kVp/250 mAs, collimation of 16 mm × 1.5 mm and a pitch 0.938 with a slice thickness of 5 mm for whole-body CT. The PET data were acquired in 3D mode with 60 s per bed position. Raw data were reconstructed using iterative reconstruction, including all the corrections such as normalization, scatter, and CT-based attenuation correction. The SUVmax were automatically generated according to the following equation: $SUV_{max\ (bw)} = C_{tis}/D_{inj}/bw$, where SUV_{max} is the SUVmax normalized for the bodyweight, C_{tis} is tissue concentration expressed as MBq/mL, D_{inj} is injected dose expressed as MBq and bw is bodyweight in kilogram.

The cine display of maximum-intensity projections of the PET data, as well as the attenuation-corrected PET images, CT images, and fused PET/CT images, were reviewed on manufacturer's review station (Philips, Extended Brilliance Workspace-NM).

Pathological tumor size estimation

The tumor was located by palpation and was sliced serially in the horizontal plane from one end to the other (preferably craniocaudal). Lung slices were placed serially. The size of the gross tumor was measured by caliper in all X, Y, and Z dimensions, as seen on gross examination. The maximum dimension was used for the analysis and labeled as L-PATH. Shrinkage of tumor during tissue processing was not considered.

Study procedure

The automatic delineation of the primary tumor was done using different percentages, and absolute SUV thresholds on Philips extended brilliance workstation platforms. Manual tumor delineation was also done by three different radiation oncologist (RO) with the visual-aid using the PET/CT.

Automated contouring at different percentage threshold of maximum SUV (20%, 30%, 40%, 50%)

The SUV_{max} of the primary tumor was determined by creating the volume of interest on the attenuation-corrected FDG-PET reconstruction images. The primary tumor gross tumor volume (GTV) was generated using automated software programmed that helps to delineate areas having SUV more than the desired percentage threshold of the SUV_{max}. Different GTVs for different percentage threshold of 20%, 30%, 40%, and 50% of SUV_{max} were labeled as GTV_20, GTV_30, GTV_40, and GTV_50, respectively.

Automated contouring at different Absolute SUV (2, 2.5, 3, 3.5 and 4)

Similar to the procedure of using percentage thresholds, the primary tumor GTV was also generated using automated software programmed to delineate areas with an absolute SUV value more than 2, 2.5, 3, 3.5, and 4 (labeled as GTV_2, GTV_2.5, GTV_3, GTV_3.5, and GTV_4 respectively).

Visual method

Primary tumor GTV was contoured in three dimensions on CT scan images as visualized by RO with simultaneous visual incorporation of information from PET/CT images. This GTV was contoured by 3 RO with different degrees of experience (≤3 years, 4–10 years, and >10 years) in lung cancer contouring independently for each patient (labeled as GTV_A, GTV_ B, and GTV_C).

Nine different GTVs were automatically generated with different SUV thresholds for each patient, as depicted in Figure 1. Measurements were taken for each GTV in all three dimensions by evaluating axial, coronal, and sagittal slices, and maximum diameter was noted in centimeters. For correlation with the pathology specimen, the maximum diameter of the GTV in any of the three orientations on the PET/CT scan was used for analysis. The protocol included a fixed lung window setting (window width, 1500 HU and window center– 500 HU) and mediastinum setting (window 350/40).

Statistical analysis

Continuous data have been reported as mean ± standard deviation (SD) and categorical data as frequency and percentages. Comparison was made between the L_PATH and L_%SUV (maximum diameter of GTV with designated percentage threshold of SUV_{max}) for each case to determine the optimal percentage threshold of SUV_{max} that gives the best agreement between pathologic and PET/CT maximum tumor diameters. Similarly, comparison was made between L_PATH and L_PET absolute SUV (maximum diameter of GTV with designated absolute SUV). First-order linear regression function was used to assess the best agreement of L_PET (%SUV) and L_PET (Abs SUV) with L_PATH. Thus, values of optimal cut off for absolute SUV and the percentage threshold SUV were obtained for each patient. Wilcoxon signed-rank test was used to compare the tumor diameter between PET and pathology. Bland–Altman plots were used to evaluate the agreement between the pathological diameter and auto-delineated tumor diameter. In the Bland–Altman, difference between pathological tumor diameter and auto-delineated tumor diameter was plotted on Y-axis, and an average of two diameter was plotted on X-axis. The limits of agreement were defined as the mean difference ± 1.96 times. SD of the differences is identified. Any value exceeding the limits of agreement was considered an outlier. The GTVs delineated by three different observers were compared by the concordance index (CI), defined as the ratio of the intersection and the union of the two volumes (CI = [A ∩ B]/[AUB]). SPSS for Windows, version 21.0 (SPSS, Chicago, IL, USA) was used to perform statistical analysis.

Results

The patient and tumor characteristics are summarized in Table 1. The median age was 61 years (range, 45–74 years). The median duration between PET/CT and surgery was 32 days (range 6–56). The mean pathological tumor size was 5.66 cm ± 1.96 cm and mean SUV_{max} was 16.31 ± 11.4 for the test cohort. The mean of the maximum tumor diameter by various methods is given in Table 2.

The pathological tumor diameter for a single patient measured on the basis of each SUV percentage threshold value (viz. 20%, 30%, 40%, 50%) is shown in Figure 2. The optimal threshold value was determined by the linear approximation with the best agreement between the L_%SUV and L_PATH. In this patient, 29.4% threshold SUV was in the best agreement with 7 cm histopathological diameter. Thus, 29.4% threshold SUV was determined as optimal cutoff % threshold SUV for this patient. Similarly, an absolute SUV of 4.76 was in the best agreement with 7 cm diameter for the same patient [Figure 3].

In the test cohort of 25 patients, the mean (±SD) optimal threshold values for tumor delineation were 35.6% (±18.6%) for percentage threshold SUV and a 4.35 (±1.7) for absolute SUV. In the validation set, the mean optimal cutoff values were 36.9% (±16.9%) for percentage threshold SUV and a 4.1 (±1.6) for absolute SUV. After the combined analysis of all 37 patients, the mean optimal percentage threshold

Table 1: Patient and tumor characteristics

Characteristics	*n* (mean±SD)
Age (range)	62 (45-76)
Gender	
Male	31
Female	6
Histology	
Adenocarcinoma	21
Squamous	16
Tumor stage	
pT1	5
pT2	22
pT3	10
Interval between PET CT and surgery (days), median (range)	32 (6-56)
SUVmax	16.3±11.4
Pathological tumor size (cm)	5.65±1.96

SD: Standard deviation, PET CT: Positron emission tomography computed tomography, SUVmax: Maximum of standardized uptake value

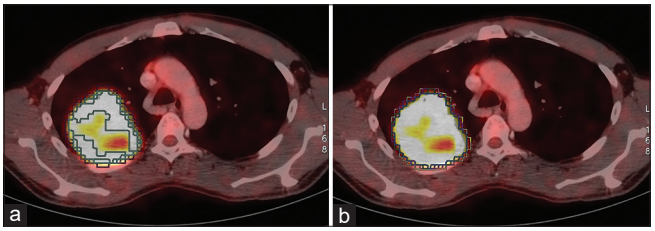

Figure 1: Auto contour delineated using different percentage threshold (a) and absolute SUVs (b). Note in (a), central area of necrosis is left out in 50% threshold auto contour

Table 2: Mean diameter of tumor in centimeter by each contouring method

Method	L_Path	L_A	L_B	L_C	L_20	L_30	L_40	L_50	L_2	L_2.5	L_3	L_3.5	L_4
Mean diameter in cm	5.66	6.81	6.81	6.73	6.78	6.10	5.48	4.83	7.47	7.02	6.61	6.24	6.03

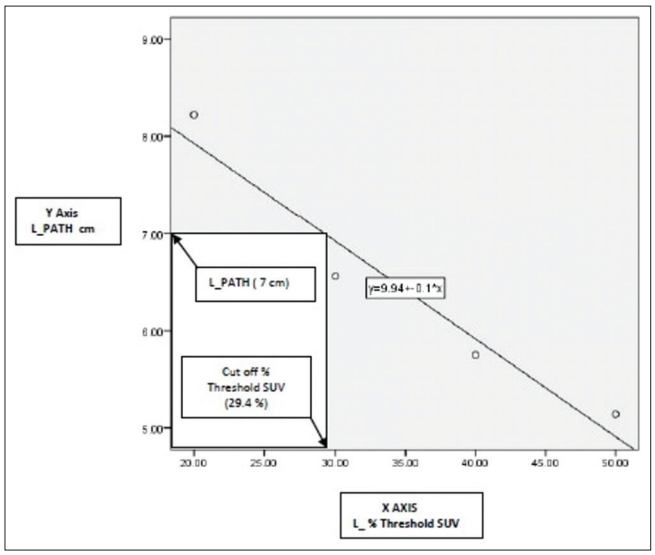

Figure 2: Optimal percentage threshold of SUVmax for one patient by linear regression. Y-axis denotes pathological tumor diameter and X-axis denotes various percentage threshold of SUV max. Hollow circle indicates largest tumor dimension auto-delineated with SUV_20%, SUV_30%, SUV_40% and SUV_50%. SUV: Standardized uptake value, L_PATH: Maximum pathological tumor diameter, L_% threshold SUV: Maximum diameters of auto-delineated tumor using percentage threshold SUV

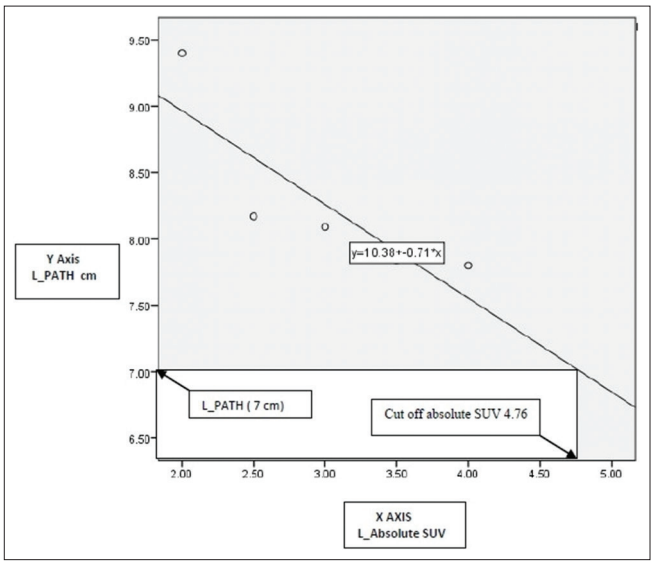

Figure 3: Optimal threshold of absolute SUV for one patient by linear regression. Y-axis denotes pathological tumor diameter and X-axis denotes various absolute SUV. Hollow circle indicates largest tumor dimension auto-delineated with SUV_2, SUV_2.5, SUV_3, SUV_3.5 and SUV_4. SUV: Standardized uptake value, L_PATH: Maximum pathological tumor diameter, L_Absolute SUV: Maximum diameters of auto-delineated tumor using absolute SUV

value for GTV delineation on FDG-PET/CT images were 36% (±17.9) and mean absolute SUV of 4.27 (±1.7).

All the methods of TV delineation were also evaluated using Bland-Altmanplots to determine agreement with pathological tumor diameter [Figure 4]. The mean difference represents the estimated bias. Lesser the value of the mean bias, more the agreement between the test method and the gold standard method. The mean difference for 40% and 30% threshold was 0.17 and −0.43, respectively. The mean difference values for various methods analyzed in Bland–Altman plots are shown in Table 3. Similarly, for the absolute value SUV 4 and SUV 3.5, the mean difference value was −0.34 and −0.55, respectively. This supports the initial results of analysis by linear regression.

Mean CI for observer A versus B, A versus C and B versus C were 0.819, 0.802 and 0.801, respectively. On comparison using Wilcoxon-signed rank test, mean CIs between three pairs were not significantly different statistically (*P* value for A vs. B and A vs. C is 0.548, *P* value for A vs. B and B vs. C is 0.666, *P* value for A vs. C and B vs. C is 0.638). This showed that there exists a good agreement in the delineation of GTV using integrated PET/CT information for operable NSCLC between three RO despite the difference in the degree of experience. Also, there was no statistically significant difference between the tumor sizes contoured by the three RO (using PET/CT as a visual aid) and the pathological tumor size.

Discussion

Accurate delineation of primary tumor volume on a RT planning CT scan is the most critical step, especially in the era of high precision techniques such as intensity-modulated radiation therapy and stereotactic body radiation therapy (SBRT). These techniques are highly conformal, and any geographical miss due to inaccurate tumor delineation can lead to local recurrence. Studies correlating pathological tumor size with the delineated target on the preoperative imaging have shown that this CT-based volume is larger than the actual tumor size. Over-contouring can lead to a higher volume of normal lung irradiation, which can lead to an increased probability of radiation pneumonitis. Integrated^{18}F-FDG PET/CT is commonly used as a staging investigation for NSCLC and can be used for RT planning. PET/CT-based tumor delineation can be done with various methods like absolute SUV, source to background ratio (SBR), fixed SUV threshold, and gradient-based methods.[4,13,14]

The aim of this study was to find the optimal SUV threshold with both the percentage and the absolute SUV

Table 3: Mean difference in Bland-Altman plots for all methods of delineation comparing maximum diameter of tumor on pathology and positron emission tomography computed tomography

Method	L_20	L_30	L_40	L_50	L_2	L_2.5	L_3	L_3.5	L_4
Mean difference	−0.78	−0.43	0.17	0.82	−1.81	−1.34	−0.92	−0.55	−0.34

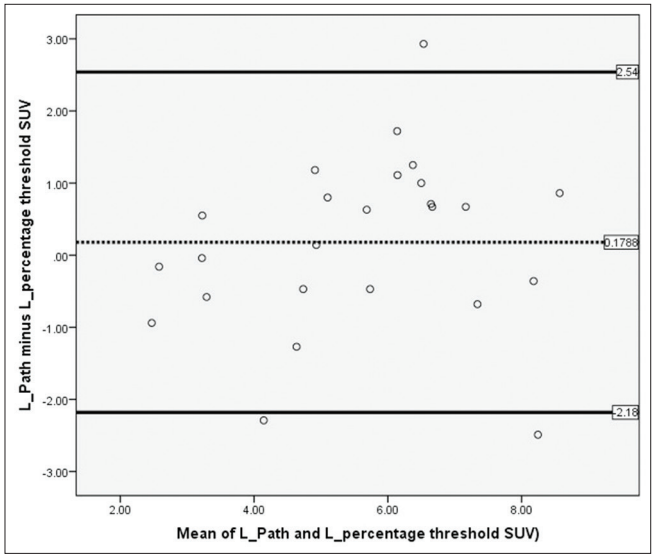

Figure 4: Bland-Altman plot of auto-delineated tumor diameter using various percentage threshold of SUVmax versus pathological tumor diameter. Middle dotted line represents mean difference. Upper and lower continuous line represents 95% limits of agreement (mean difference ± 1.96 standard deviation of the difference). SUV: Standardized uptake value, L_Path: Maximum pathological tumor diameter, L_ percentage threshold SUV: Maximum diameters of auto-delineated tumor using percentage threshold SUV

values for auto delineation of gross tumor volume (GTV), which matches most accurately and consistently with the pathological tumor size of the lung primary. In this study, we calculated tumor size in three dimensions and have taken the largest dimension for analysis. We used different percentage thresholds and different absolute SUV values to determine which auto-delineated maximum tumor diameter best correlated with the largest dimension of the pathological tumor size. Our results demonstrated that the tumor size delineated with mean percentage threshold SUV of 36% and mean absolute SUV of 4.27 was in best agreement with pathological tumor size.

Various studies have compared PET or PET/CT based auto delineated tumor volumes using various methods and PET thresholds with CT tumor volumes.[4,15,16] PET/CT based tumor delineation has shown to be identical with CT tumor volumes, especially in well-defined tumors but more accurate than CT in cases of tumors adjacent to or within atelectasis.[4,15] However, very few published studies compared auto delineated maximum tumor dimension with the pathological tumor size of surgical specimens, which is considered to be the gold standard.[4,14,17] PET/CT based tumor volume corresponds more accurately to the pathological tumor volume as compared to the CT based tumor.[4] Furthermore, tumor delineation using PET/CT improves precision, especially in poorly defined tumors and reduces interobserver variation.[18,19] However, the optimal method and threshold to be used for accurate tumor delineation are largely unclear.[16,20,21]

Yu *et al*. used a single absolute SUV of 2.5 for PET and PET/CT-based tumor size correlation with pathological tumor size and demonstrated no significant differences between them. However, combined PET/CT-based tumor size was more similar to pathological tumor size. Contrary to Yu *et al*., our study with an SUV of 2.5 overestimated the pathological tumor size. van Baardwijk *et al*.[13] compared SBR-based auto delineation in 23 tumors with macroscopic pathological tumor diameter and showed a strong correlation with correlation coefficient of 0.90.

Wanet *et al*. compared GTV delineated with gradient-based method, SBR method, and 40% and 50% threshold of SUV_{max} in 10 stage I-II NSCLC patients and showed no significant difference between these methods when compared to pathological GTV. Gradient-based method best estimated the pathological tumor volume and threshold-based approach, especially 50% underestimated the volume. Mercieca *et al*., in a study of 30 patients, demonstrated that the mean optimal percentage threshold of 47% ± 10% of SUV_{max} based tumor volume correlated best with the pathological tumor volume.[17] The optimal threshold of the above two studies closely matches our optimal threshold of 36%, and the difference could possibly be because we used the largest tumor dimension rather than tumor volume. van Loon *et al*. also showed 42% threshold of SUV_{max} correlated best with pathological GTV.[10]

The optimal percentage threshold values of SUV_{max} obtained in these studies can be used for precise target delineation in small-sized tumor just as in SBRT. Their use in larger tumors of locally advanced NSCLC needs caution as microscopic disease extension is poorly picked by CT and PET-based delineation.[10] van Loon *et al*.[10] in a study of 34 patients, demonstrated that GTV delineated on CT and PET under-estimated microscopic disease extensions on pathology by 19.2 and 26.7 mm in high-risk group.

There are limitations of using single PET threshold for auto delineation of tumor as reported by some studies.[16,17,22,23] The optimal percentage threshold for SUV_{max} ranged from 15% to 60% in some studies, with 42% SUV_{max} being commonly used.[4,11,12,17] Uniformity of SUV within the tumor is crucial for deciding single threshold. Because of factors such as tumor size, hypoxia, and necrosis, which are more likely to occur in larger tumors there appears to be a lack of uniformity of ^{18}F-FDG concentration within

the tumor. Stroom *et al*., in their study on 5 patients auto delineated GTV at 42% SUV level and suggested that one single PET threshold is not sufficient for all patients.[23] Biehl *et al*. compared PET-based GTV to CT-based GTV in 20 patients with peripheral well-defined tumors and showed a mean optimal percentage thresholds varies with tumor size.[16] In our study, optimal SUV threshold values varied among patients, ranging from 6% to 69% for percentage threshold and 1.97–8.29 for absolute SUV. This can be possibly explained by the fact that there is an inverse correlation between the largest pathological diameter and SUV.[16]

Various studies have shown integrated PET/CT based delineation is more accurate than using CT or PET alone, and hence in this study, we auto delineated tumors on integrated PET/CT. CT-based tumor delineation overestimates pathological tumor volumes, especially in atelectatic tumors, and has large interobserver variability. Steenbakkers *et al*.[18] evaluated the significance of PET/CT-based delineation compared to CT among 11 RO. All RO in 22 lung cancer patients delineated tumor plus nodal volume on CT and then on matched PET-CT images. Interobserver variation reduced from 1.0 cm on CT to 0.4 cm on PET/CT, the amount of disagreement also reduced from 45% to 18%, respectively, and delineation time from 16 min to 12 min ($P < 0.001$). Our results also confirmed that even with different levels of experience in lung contouring, interobserver variation in PET/CT based delineation between ROs was low. This could be reduced further if there is a single optimal threshold-based auto delineation of the target where the RO needs to just edit the contours manually for any mismatch.

Our study though simple has some limitations. First, the average time interval between PET/CT and surgery was 32 days, where the tumor size could have increased, leading to errors in the SUV value selection. In the study of Mercieca *et al*. study, this interval was 20 days. Second, the effect of tumor shrinkage during the processing of specimens on pathological diameter was not taken into consideration during the analysis. In the study by Hsu *et al*.[24] comparison of tumor samples before and after fixation with formalin indicated a reduction to 82% ±10% of the original tumor volumes (range, 62%–100%). Third, we did not delineate the nodal volumes along with the primary tumor in PET node-positive patients. Our study is also limited by small patient numbers.

The auto delineation of tumor using any method of PET is fraught with challenges. Inter-and intra-institutional differences in the reconstruction of images and reconstruction filters may alter the SUV values. Patient factors such as the dose of ^{18}F-FDG administered, lean body mass, blood glucose levels, blood perfusion of tissue of interest, and time from the injection of 18F-FDG until the patient is scanned may have their effect by changing percentage threshold SUV. SUV max to SUV mean ratio is affected by the method of the reconstruction as well as by the choice of reconstruction filters, which may ultimately change percentage threshold contours. These criteria have the potential to bring about inter-institutional changes unless uniform protocols are designed and followed. Although the percentage threshold method is designed to standardize against these differences, problems association with institutional variations cannot be ignored and may impact the generalizability of our findings.

There are inherent limitations to create a 1:1 volumetric match between PET and CT delineated tumors. Tumor respiratory motion is known to cause blurring of FDG signal as PET/CT is acquired over a longer duration than planning or diagnostic CT. As the FDG signal is expected to average out tumor motion, PET tumor volume should be larger than the CT tumor volume. On the contrary, studies have shown PET tumor volume using single SUV threshold underestimates CT tumor volumes.[15,21] Fernando *et al*. demonstrated that the SUV threshold of 40% significantly underestimated the composite GTV volumes contoured on inhale and exhale scans and rather showed 20% threshold best estimated the composite CT volume. The use of PET as a surrogate for tumor motion has not been validated, and the extent of tumor motion may be better quantified using four-dimensional (4D) PET by comparing with RT planning 4DCT. Future studies with 4D multi-slice PET/CT may help to individualize the appropriate threshold setting for each patient. Alternatively, methods like the SUV peak, which is not affected by background noise like the SUV_{max} can also be studied in future for auto delineation of TVs.[17]

Conclusion

The optimal percentage threshold value of 36 ± 17.9 and an absolute SUV value of 4.27 ± 1.7 for TV delineation correlated best with maximum pathological tumor diameter in our study. Auto-contouring of GTV with these optimal SUV thresholds in FDG-PET/CT can be used to improve accuracy, especially in high precision treatments of SBRT.

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Conflicts of interest

There are no conflicts of interest.

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