Original Article

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Comparison of Tumor Target Volume on Four-Dimensional Computed Tomography and ^{18}F-FDG PET/CT in Lung Cancer

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Abstract:

Objective: The correlation between ^{18}F-fluorodexyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) and four-dimensional computed tomography (4DCT) based-tumor volumes is unclear. This prospective study was conducted to determine the optimal threshold of PET/CT for gross tumor volume (GTV) delineation using 4DCT as the standard reference for locally advanced lung cancer patients.

Material and Methods: Ten patients with histologically proven primary lung cancer who underwent radiotherapy from June 2017 to March 2018 in Ramathibodi Hospital were enrolled in the study. The 4DCT simulation and ^{18}F-FDG PET/CT simulation were performed on the same position and same date. Eight standard uptake value (SUV) thresholds of SUV 1.5.0-2.0 and 15.0-35.0% of maximum SUV were selected for contouring in order to be compared with 4DCT based tumor volumes. The comparison methods used were the mean percentage volume change, dice similarity coefficient (DSC), and 3D-centroid shift of the targets between ^{18}F-FDG PET/CT-based gross tumor volume (GTV_{PET}) and internal gross tumor volume (IGTV) from 4DCT.

Results: The largest and smallest volume of primary tumors were 422.6 cm^3 and 5.9 cm^3. GTV_{PET} contoured using SUV 1.5 ($GTV_{PET1.5}$) approximated closely to IGTV in all the parameters, including volume change, DSC, and 3D-centroid shift. The best median percentage volume change, median DSC, and median centroid shift between IGTV and $GTV_{PET1.5}$ were 5.55, 0.745 and 0.37, respectively.

Conclusion: GTV_{PET} contoured by ^{18}F-FDG PET at SUV1.5 corresponded most closely to the IGTV in all parameters. Further study with a larger sample size and clinical outcome analysis is needed.

Keywords: 4DCT, lung cancer, PET/CT, taget volume

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Introduction

One of the most common causes of cancer-related mortality is lung cancer.[1] The high rates of local failure and distant metastases are the major causes of poor prognosis in lung cancer patients,[2,3] with high local recurrence rates of up to 50.0% after definitive radiotherapy.[4] The major consideration related to local failure is geometric target miss induced by tumor motion during radiotherapy.[5]

In order to avoid missing the target from respiratory motion, four-dimensional computed tomography (4DCT) is widely used for radiation planning of lung cancer treatment because of its reliability and effectiveness for assessing the tumor and organ motions in all phases of the respiratory cycle.[6,7] It has been shown that 4DCT imaging can reduce motion artifacts and provides more accurate delineation of the tumor and other critical structures.[8-10] However, 4DCT is not commonly available in cancer centers in Thailand and patients have to be highly cooperative in order to provide regular respiratory cycle.

Positron emission tomography/computed tomography (PET/CT) has been used widely with ^{18}F-fluorodexyglucose (^{18}F-FDG) to differentiate malignant from benign pulmonary lesions. PET/CT sensitivities for the detection of lung cancer have ranged in various reports between 83 and 100.0%, with specificities of 63.0-90.0% using standard uptake values of equal to or greater than 2.5.[11,12] Moreover, when the ^{18}F-FDG PET/CT image is used for tumor volume delineation, the interobserver and intra-observer variabilities are significantly reduced.[13,14]

Many studies have compared 3DCT volumes with ^{18}F-FDG PET/CT volumes of non-small cess lung cancer.[15-17] However, the best method for applying ^{18}F-FDG PET/CT to internal gross tumor volume (IGTV) on 4DCT definition is not currently well established. The scan time for PET/CT is around 20-30 minutes, which could be long enough to detect tumor positions in all respiratory phases. The purpose of this prospective study is to determine the optimal threshold of ^{18}F-FGD PET/CT-based gross tumor volume (GTV_{PET}) delineation using 4DCT as a standard eference for locally advanced lung cancer patients treated with definitive concurrent chemoradiation (CCRT) in Ramathibodi Hospital.

Material and Methods

Patients

We prospectively reviewed patients with histologically proven primary lung cancer, locally advanced stage without lung atelectasis, pneumonia or distant metastasis from June 2017 to March 2018 at the Radiotherapy Division, Ramathibodi Hospital. Ten patienand who had undergone definitive CCRT using ^{18}F-FDG PET/CT and 4DCT simulation for radiation planning were enrolled. Baseline patient characteristics including sex, age, clinical stage, tumor location, and tumor histology were identified. This study was approved by the institutional review board for the protection of human subjects in research (IRB).

4DCT simulation

During the CT simulation, all the patients were immobilized using wing boards and vacuum bags (VAC lok®) in the supine position with both arms over their heads. An axial non-enhanced 3DCT scan of the thoracic region was performed followed by non-enhanced 4DCT scan under training free breathing conditions on a 64-slice CT scanner (GE Optima 580 CT simulator). The CT simulation was performed on a flat table top and slice thickness was 2.5 mm per slice. Respiratory waveform was performed by the varian real-time position management respiratory gating system (Varian Medical Systems). The maximum intensity projection (MIP) images were generated using the GE Advantage system (GE Medical Systems). Eclipse planning software version 13.6 was used for GTV contouring.

PET/CT simulation

On the same day as the 4DCT scan, the ^{18}F-FDG PET/CT scans were performed with an integrated PET/CT scanner (Philips Gemini TF Big Bore) on a flat table top and 2.5 mm of slice thickness. Patient positioning and

immobilization devices were identical to the 4DCT scan. All patients were injected with 0.1 mCi/kg of ^{18}F-FDG; after which, they rested for about 1 hour before PET scanning.

Image registration

4DCT images and PET/CT images were initially registered by automatic rigid registration then manual registration was applied by a radiation oncologist. Bony and tumor matching were used for optimal CT image registration using the Eclipse planning software version 13.6.

Target volume delineation

In order to determine the optimal ^{18}F-FDG PET/CT threshold for GTV contouring, we delineated IGTV on MIP images and checked the tumor coverage on 10-respiratory phases from 4DCT as references images. The lung window of window width (W)=1,000, window center (C)=-600 and the mediastinal window of W=400, C=40 were set for IGTV delineation. All IGTV delineations were performed by radiation oncology residents and verified by radiation oncologists and radiologists. Based on the literature, GTV_{PET} was contoured using eight ^{18}F-FDG PET/CT thresholds in order to be compared with IGTV from 4DCT, which were 15.0%, 20.0%, 25.0%, 30.0%, 35.0% of maximum standardized uptake value (SUVmax), standardized uptake value (SUV) 1.5, 2.0 and 2.5. GTV_{PET} was generated by the auto-contouring function of the Eclipse planning software. Due to the uncertainties of GTV_{PET} auto-contouring in SUV values less than 1, the 15.0% of SUVmax values that were less than 1 were excluded from the analysis.

Volume comparison

The differences in the volume, size, and position between the GTV_{PET} and the IGTV were compared using 3 parameters: the median percentage volume change, the Dice similarity coefficient (DCS) and 3D centroid shifts.

The median percentage volume change is the median value of the volume change between IGTV and GTV_{PET} calculated in percent. The most appropriate GTV_{PET} volume was the one with the smallest value of the volume change. The formula is as follows:

$$\text{The percentage volume change} = \frac{GTV_{PET}\ \text{volume} - \text{IGTV volume}}{\text{IGTV volume}} \times 100$$

The DCS of IGTV and GTV_{PET} was defined as the ratio of overlap between both volumes. The DCS of 1 means both volumes are totally overlapped and the value of 0 means none of the two volumes are overlapped. The DSC can be calculated with the equation below:

$$\text{Dice similarity coefficient} = \frac{2(A \cap B)}{A+B}$$

The three dimensional (3D) centroid shifts were generated from both GTV_{PET} and IGTV positions using target coordination in the left-right, anterior-posterior, and cranial-caudal directions. The less the difference of 3D shift number between GTV_{PET} and IGTV, the more identical both volumes are. The median value of 3D centroid shift was selected to represent each GTV_{PET} threshold compared with IGTV. The centroid shifts in the 3D directions were calculated. According to the following formula:

$$\text{3D centroid shifts} = \sqrt{LR^2 + AP^2 + CC^2}$$

LR=the shift between GTV_{PET} and IGTV in the left-right direction

AP=the shift between GTV_{PET} and IGTV in the anterior-posterior direction

CC=the shift between GTV_{PET} and IGTV in the cranial-caudal direction

Results

Baseline characteristic

All the patients were male with a median age of 62 years (range=45-87 years). Fifty percent of the patients had clinical T2 and N3 diseases. Most (40.0%) patients had

tumors located in the right upper lobe and the median SUVmax of the primary tumor was 10.73 (range=5.9–14.5). The majority (80.0%) of tumor histology was adenocarcinoma (Table 1). The largest and smallest volume of primary tumors were 422.6 cm^3 and 5.9 cm^3 (Table 2).

The median percentage volume changes

The GTV_{PET} contoured using an SUV of 1.5 was the most identical to IGTV with the lowest median percentage volume change of 5.6%. The median percentage volume change between the IGTV and the GTV_{PET} delineated by the SUV values of 2.0, 2.5, 15.0% of SUVmax, 20.0% of SUVmax, 25.0% of SUVmax, 30.0% of SUVmax and 35.0% of SUVmax were –20.5%, –43.3% 15.7%, –9.7%, –26.6%, –42.1%, and –47.9%, respectively (Figure 1).

The Dice similarity coefficient

The median DSC ranged from 0.640 to 0.735. The best fit of GTV_{PET} volume when compared with IGTV was the highest DSC, which was the GTV_{PET} contoured by SUV 1.5; the DSC was 0.735, followed by the 20.0% of SUVmax; DSC was 0.725 (Figure 2).

The 3D centroid shifts

The median of 3D centroid shifts between GTV_{PET} at SUV 1.5, 2.0, 2.5, 15.0% of SUVmax, 20.0% of SUVmax, 25.0% of SUVmax, 30.0% of SUVmax and 35.0% of SUVmax, and IGTV were 0.37, 0.41, 0.41, 0.47, 0.49, 0.42, 0.45 and 0.48. The use of an SUV of 1.5 for GTV_{PET} contouring was the fittest to the IGTV with the lowest median centroid shifts (Figure 3).

Table 1 Baseline patient characteristics

Lesions (N)	Sex	Age (y)	Stage	Tumor location	Histology	SUVmax
1	M	60	T2N3	RML	Adenocarcinoma	6.3
2	M	69	T2N3	RUL	Adenocarcinoma	7.6
3	M	67	T2N3	RUL	Adenocarcinoma	14.5
4	M	52	T4N3	LUL	Adenocarcinoma	11.7
5	M	52	T4N3	LUL	Adenocarcinoma	8.5
6	M	83	T2N2	RUL	Adenocarcinoma	10.5
7	M	63	T2N0	LUL	Small cell carcinoma	11.7
8	M	87	T3N1	LLL	Small cell carcinoma	10.9
9	M	45	T3N2	RLL	Adenocarcinoma	11.8
10	M	60	T1N3	RUL	Adenocarcinoma	5.9

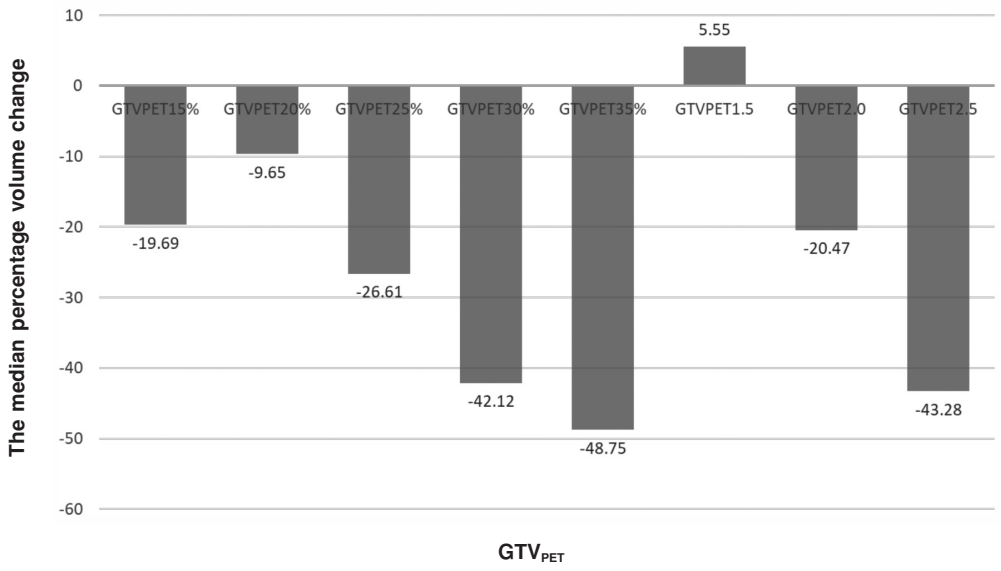
SUV_{max}=maximal standardized uptake value, M=male, RML=right middle lobe, RUL=right upper lobe, LUL=left upper lobe, LLL=left lower lobe, RLL=right lower lobe

Stage is based on the 8th edition Amarican Joint Committee on Cancer (AJCC) tumor/nodal/metastasis (TNM) classification.

Table 2 Volume of primary tumor measured by ^{18}F-FDG PET/CT and 4DCT (cm^3)

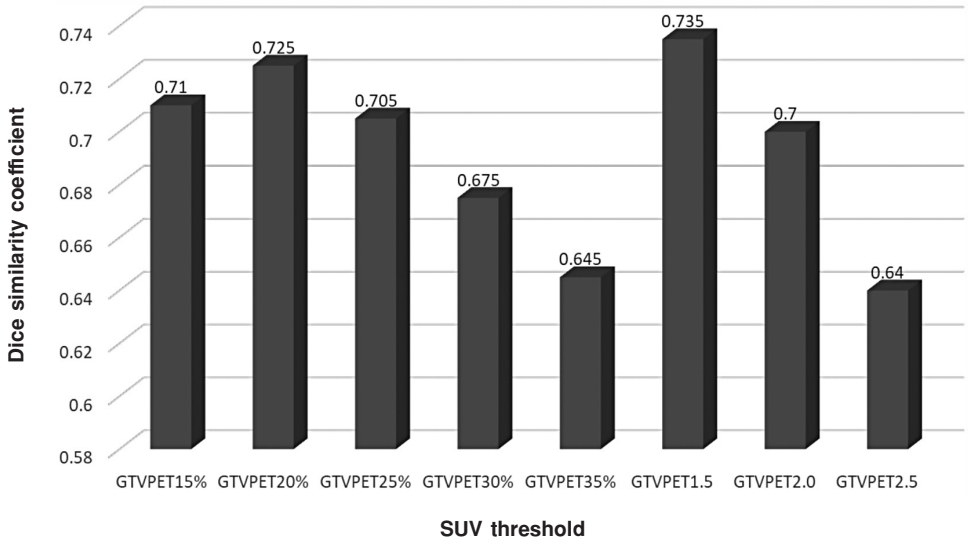
Lesions (N)	$GTV_{PET15\%}$	$GTV_{PET20\%}$	$GTV_{PET25\%}$	$GTV_{PET30\%}$	$GTV_{PET35\%}$	$GTV_{PET1.5}$	$GTV_{PET2.0}$	$GTV_{PET2.5}$	IGTV
1	-	15.2	13.0	11.2	9.3	13.8	10.8	8.5	21.7
2	-	20.6	17.3	13.2	11.6	20.6	14.7	11.2	19.0
3	65.2	55.7	48.1	43.0	37.5	85.9	70.8	61.6	83.7
4	4.5	3.1	2.4	1.7	1.4	5.0	3.7	2.6	5.9
5	64.4	46.2	35.6	26.1	20.8	93.5	64.4	48.4	94.6
6	170.0	104.3	69.8	54.7	44.3	203.3	136.8	97.6	182.2
7	46.9	39.3	35.7	30.7	26.3	53.2	44.5	38.8	33.4
8	227.5	187.2	160.7	140.8	123.5	244.5	195.8	168.3	176.1
9	759.6	573.8	477.6	376.7	353.2	552.9	387.0	370.9	422.6
10	-	20.5	12.0	8.9	6.8	11.4	7.4	5.0	9.0
Range	4.5-759.6	3.1-573.8	2.4-477.6	1.7-376.7	1.4-353.2	5.0-522.9	3.7-387.0	2.6-370.9	5.9-422.6

^{18}F-FDG PET/CT=^{18}F-fluorodexyglucose positron emission tomography/computed tomography, 4DCT=four-dimensional computed tomography, GTV=gross tumor volume, IGTV=internal gross tumor volume



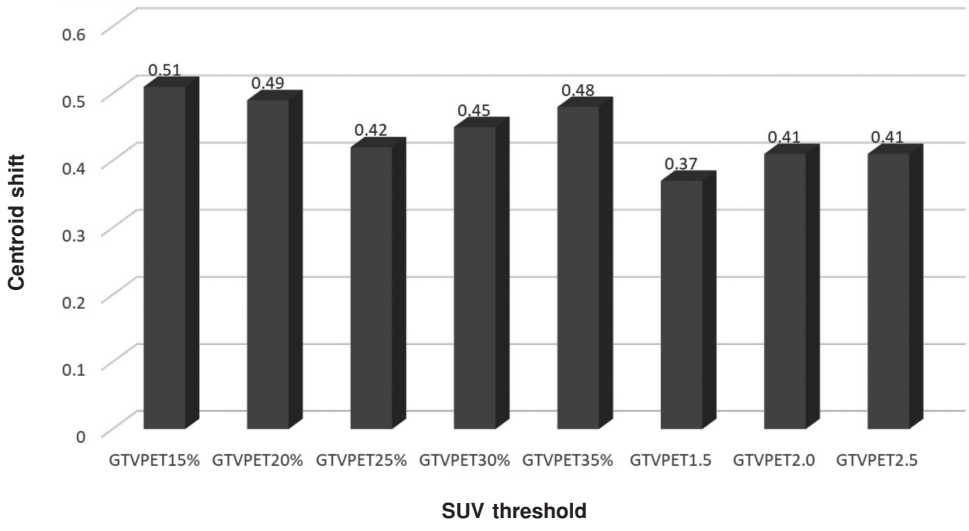
GTV_{PET}=^{18}F-FDG PET/CT-based gross tumor volume, IGTV=internal gross tumor volume, SUV=standard uptake value

Figure 1 The median percentage volume change of the GTV_{PET} and IGTV. GTV_{PET} contoured by SUV 1.5 had the lowest median percentage volume change (5.6%) when compared to IGTV.



GTV_{PET}=^{18}F-fluorodexyglucose positron emission tomography/computed tomography-based gross tumor volume, IGTV=internal gross tumor volume, SUV=standard uptake value

Figure 2 The Dice similarity coefficient (DSC) of GTV_{PET} and IGTV, the DSC of GTV_{PET} contoured by SUV 1.5 overlapped most with IGTV, DSC=0.735.



GTV_{PET}=^{18}F-fluorodexyglucose positron emission tomography/computed tomography-based gross tumor volume, IGTV=internal gross tumor volume, SUV=standard uptake value

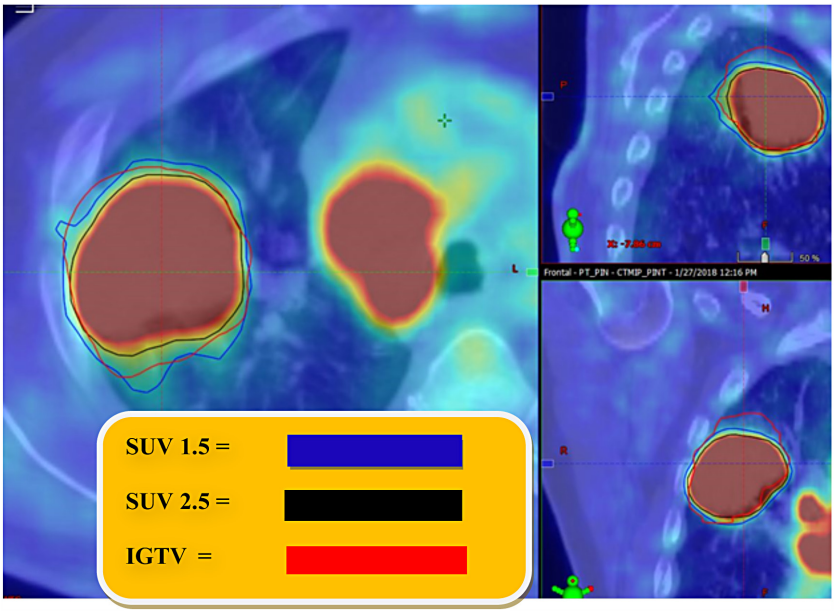
Figure 3 The 3D centroid shifts of the GTV_{PET} and IGTV. The 3D centroid shift calculated using GTV_{PET} at SUV 1.5 and IGTV positons had the lowest shifting value, 3D centroid shift=0.37.

Discussion

Our study demonstrated that GTV_{PET} contoured using SUV at 1.5 was the most identical to IGTV in all parameters, including the median percentage volume change, DCS, and 3D centroid shifts. These reflect the correspondence between GTV_{PET} at SUV1.5 and IGTV volumes in size, shape, and position.

Due to the previous studies,[18,19] ^{18}F-FDG PET contouring at SUV 2.5 is widely used for GTV_{PET} delineation, but those studies compared GTV contouring between PET/CT and conventional CT simulation. Our study presents that the use of ^{18}F-FDG PET for tumor contouring at SUV 2.5 generates smaller GTV volumes than IGTV from 4DCT (Figure 4). There are 2 studies that have investigated the correlation between threshold of tumor uptake volumes and IGTV.

Hanna et al.[20] compared GTV_{PET} volumes at SUV 2.5, 35.0%, and 40.0% of SUVmax to IGTV from 4DCT and found that none of the FGD PET-derived target volumes corresponded well to those derived from the 4DCT target volumes. This study did not include SUV1.5 threshold, and the method to compare volumes was only DSC, unlike in our study which enrolled a greater range of PET thresholds and more methods of comparison. Also, patients in the prior study underwent PET/CT and 4DCT simulation on different dates, but patients in our study did both procedures on the same day. Moreover, the ^{18}F-FDG PET at SUV 2.5 in Hanna's study showed that the closest corresponding value to IGTV and DSC was 0.64. Our results demonstrated that the ^{18}F-FDG PET at SUV 1.5 had the strongest correlation to IGTV, with higher volume overlap represented as DSC of 0.735.



GTV_{PET}=^{18}F-fluorodexyglucose positron emission tomography/computed tomography-based gross tumor volume, IGTV=internal gross tumor volume, SUV=standard uptake value, ^{18}F-FDG PET=^{18}F-fluorodexyglucose positron emission tomography

Figure 4 A 69-year-old male was diagnosed with non-small cell lung cancer stage T2N3M0. The GTV_{PET} contoured using ^{18}F-FDG PET at SUV 2.5 (black line) was much smaller than IGTV (red line) and the GTV_{PET} using SUV 1.5 was more identical to IGTV.

Duan et al.[21] also explored the relationship between GTV_{PET} and IGTV using the mean percentage volume change, the 3D centroid shift, median concordance index, and median degree of inclusion. The SUV 2, 2.5, 15.0-40.0% of SUVmax were included for GTV_{PET}. Again, this paper did not include SUV 1.5 for GTV_{PET} contouring and the results showed that none of the PET/CT-based contours had a close approximation to the IGTV. Since the IGTV has a larger volume than conventional CT simulation based GTV, the low ^{18}F-FDG uptake threshold, such as SUV 1.5, should be enrolled in the study. Although the major limitation of our prospective review is its small sample size, the initial outcome is promising because all comparison parameters are consistent to SUV 1.5.

4DCT simulation is the standard method for radiotherapy planning in lung cancer to overcome missing target problems by respiratory motion because 4DCT images provide tumor position in 10 phases of the respiratory cycle. Nonetheless, the limited number of 4DCT simulation machines in Thailand is problematic. Furthermore, the procedure requires cooperative patients. In these situations, the contouring of GTV using ^{18}F-FDG PET/CT at SUV 1.5 in conjunction with conventional CT simulation might be approximate to cover tumors in all respiratory phases. However, further research with a larger sample size and clinical outcome analysis is needed in order to confirm our results.

Conclusion

GTV_{PET} contoured by ^{18}F-FDG PET at SUV1.5 corresponded most closely to the IGTV in all parameters.

Conflict of interest

None

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