Comparison of PET/CT and CT-based tumor delineation and its effects on the radiation treatment planning for non-small cell lung cancer

Original Article

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ABSTRACT

Introduction: Tumor volume delineation is the most important step in the radiation treatment planning. In this study the impact of PET/CT data on the tumor delineation precision of non-small cell lung cancer (NSCLC) was investigated.

Methods: PET/CT images of 20 patients with primary NSCLC were obtained and imported to the treatment planning system for image fusion, contouring and radiation treatment planning. For each patient two separate gross tumor volumes were delineated based on CT and PET/CT images as GTV_{CT} and $GTV_{PET/CT}$, respectively. In addition, three different indices including conformity index (CI), geographic miss index (GMI) and geographic include index (GII) were calculated to quantify the match and mismatches degree between derived volumes. Then, for each patient an appropriate 3D conformal treatment plan was made based on the PTV_{CT} and then these plans were applied on the $PTV_{PET/CT}$. Afterwards, the dose coverage of $PTV_{PET/CT}$ was estimated through several dosimetric parameters.

Results: The $GTV_{PET/CT}$ was larger than GTV_{CT} for majority of cases. The 25% exceeded volumetric alterations were observed in 8 of all cases (40%). Mean values of CI, GMI and GII were 0.43, 0.42 and 0.34, respectively. Also, dosimetric parameters indicated inadequate dose coverage of $PTV_{PET/CT}$ in CT-based RT plans for most of the patients.

Conclusion: Incorporating PET data into tumor delineation process had a great potential to improve the quality of radiation treatment planning for NSCLC.

Key words: PET/CT; Lung Cancer; Tumor volume delineation; Radiation treatment planning

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INTRODUCTION

Lung cancer is one of the most common forms of cancers. Recent investigations have revealed the advantages of PET/CT in different clinical situations such as staging and treatment response assessment [1, 2]. Recently, PET/CT images are used for definition of tumor volume in the radiation treatment planning process [3, 4]. Identifying the location and extent of the tumor volume is one of the most important steps in the treatment planning process that requires utilization of the precise diagnostic imaging modalities [5, 6].

CT imaging is now the only imaging method accepted for radiation treatment planning because attenuation characteristics of tissue for high-energy photons needed for precise dose calculation, could be only identified using CT data [7, 8]. However, in some situations such as atelectasis and cases in which tumor is close to hilar region, distinguishing of tumor borders from adjacent normal tissue is not easy and thus, leading to inaccurate tumor volume definition [9-11]. This is of great importance especially for 3D conformal and intensity modulation radiation therapy (IMRT) methods in which treatment fields are created exactly according to the tumor shape [12].

A number of studies have been performed to determine the effect of combined PET/CT imaging on the precision of tumor volume delineation [13, 14]. The results have shown that the amount of variation between volumes delineated based on CT and PET/CT images is dependent on the several factors such as tumor locations and the methods used for PET/CT based volume definition [15]. Also, there were a significant differences between CT and PET/CT-based tumor volumes [1, 16, 17]. In this study, tumor volumes delineated by CT and PET/CT images for radiotherapy of the non-small cell lung cancer were compared via three volume indices. In addition, induced dosimetric errors caused by CT-based contouring on the radiation treatment planning have been investigated.

METHODS

Study population

20 patients with lung cancer including 14 male and 6 female with mean age of 61 years in the range of 29-81 years were selected. All enrolled cases were cancer patients who had undergone whole body hybrid PET/CT imaging in nuclear medical center between February 2014 and September 2015. Some specifications were considered for selecting patients including: (1) all patients had primary non-small cell lung cancer (NSCLC) with documented pathology; (2) patients who were suspicious to distant metastasis were omitted from the study; (3) tumor volumes were visible in both CT and PET/CT images.

PET-CT imaging techniques

All combined ^{18}F-FDG-PET/CT procedures were performed on the GE Discovery 690 scanner. This integrated system is equipped with a 64 slice CT-scanner, 24 detector ring PET scanner and a common flat table. All images were acquired through the standard Nuclear Medicine protocols as following: the patients were asked to fast 4-6 hours prior to PET/CT examination; a check of blood glucose was done before injection to ensure blood level to be in normal range; after intravenous injection of about 4.6MBq/kg ^{18}F-FDG, patients were instructed to rest for 90 minutes for optimal distribution and uptake of ^{18}F-FDG, positioning set up was done by using immobilization instruments and laser systems.

Diagnostic CT scans were gained with the use of only oral contrast before starting imaging procedure. Reconstruction of axial images was carried out using filter back projection reconstruction algorithm into a matrix size of 512×512 and 3.75 mm slice thickness. All whole body ^{18}FDG-PET scans were performed in average of 7-8 table positions. PET data were acquired in 3D mode and reconstructed by an iterative algorithm. Slice thickness was 3.75 mm in the matrix size of 256×256, and attenuation correction of PET data was performed using CT information.

Tumor volume definition

All images in DICOM format were imported into TiGRT treatment planning system (TiGRT, LinaTech LLC, USA) for fusing images, contouring and treatment planning. The co-registration procedure was accomplished automatically based on the planar method. At the end of process, all integrated images were visually reviewed for controlling their accuracy.

Two different gross tumor volumes were delineated for each patient: GTV_{CT} and $GTV_{PET/CT}$ based on the CT and PET/CT images, respectively. These two were done by the same experienced radiation oncologist with an interval of three weeks. Outlining the GTVs was done manually via contouring tools in all the slices in which the tumor was visible. At first, the GTV_{CT} was contoured by visual assessment and without considering PET/CT information. $GTV_{PET/CT}$ was defined based on the patient's integrated PET/CT dataset. Similarly, this process was entirely based on visual interpretation and no automated algorithm was used. $GTV_{PET/CT}$ definition included areas of increased FDG that could not be attributed to the normal physiological activity of the structures. Subsequently, PTV_{CT} and $PTV_{PET/CT}$ were created by adding 15 mm margin around the GTV_{CT} and $GTV_{PET/CT}$ to take into account all possible invisible pathological expansion, position set up errors and tumor motions. In addition, some organs at risk were contoured manually or automatically including heart, trachea, liver, healthy lungs, breasts, spinal cord and skin.

Treatment planning

After contouring, 3D conformal treatment plans were performed for all cases based on the PTV_{CT}. The isocenter point was placed at the geometric center of PTV_{CT} for all irradiation beams. In general, parameters such as the number of beams, field sizes, angle and weight of beams were such defined to reach sufficient dose coverage in PTV_{CT}. Also the criteria of at least 95% coverage of PTV_{CT} with the 95% of prescribed dose ($V_{95\%}$> 95%) and receiving at least 95% of prescribed dose by 95% of PTV_{CT} were considered as well as respecting critical organs constraints. Multi leaf-collimators (51 pairs) were applied in all plans with a 5 mm margin around the border of PTV_{CT}. A total dose of 6000 cGy was prescribed by 200 cGy per daily fraction 5 days in a week. All plans were designed by using 6 and 15 MV photon energy which were executable by the PRIMUS accelerator. The dose calculations were performed based on the 3D photon beam convolution algorithm by TPS. Eventually, overall plans were reviewed by the oncologist and physicist. Efficiency evaluation of the plans was done via all available tools in software including the isodose distribution, dose volume histogram (DVH) and statistics dose.

Statistical analysis

The following parameters were assessed for statistical analysis:

Volumetric comparison: GTV_{CT} and $GTV_{PET/CT}$ were calculated in cubic centimeter (cc) scale by the treatment planning software. The comparison between two volumes was done by relative and absolute methods. These assessments were also performed for PTV_{CT} and $PTV_{PET/CT}$.

Conformity and mismatches degree: The conformity and mismatch indices were used for assessing the CT-based contouring error for both GTVs and PTVs. The conformity index (CI) was used to estimate the adaption between volumes. The CI defined by Gondi et al [11], represents the ratio of the overlap between two volumes to the overall volumes, quantitatively in the range of 0 to 1. Full conformity of volumes is shown with the CI equal to 1 and complete segregation is expressed by the value of 0. Geographic miss index (GMI) was second index used to assess the contouring mistakes. In this study for the first time, another index was defined as geographic include index (GII) to compare the volumes. CI, GMI and GII formulas are given in Equations 1 through 3.

$$CI = \frac{C}{(GTV_{CT} + GTV_{PET/CT}) - C} \quad (1)$$

$$GMI = \frac{GTV_{PET/CT} - C}{GTV_{PET/CT}} \quad (2)$$

$$GII = \frac{GTV_{CT} - C}{GTV_{CT}} \quad (3)$$

Where C is the overlapping area of the GTV_{CT} and $GTV_{PET/CT}$.

In Figure 1 the relation between volumes is shown. The GMI analyzed the percentage of $GTV_{PET/CT}$ which was cancerous but has missed in the CT-based contours. In contrast, the GII estimated the proportion of GTV_{CT} which was not tumoral but wrongly included as the abnormal area. Although the GMI is related to the tumor recurrence, GII is also associated with radiation side effects. A GMI value of 1 implies that $GTV_{PET/CT}$ to be completely located out of GTV_{CT}, whereas the value of 0 indicates a total envelopment of GTV_{CT} by $GTV_{PET/CT}$. Similar to GMI, the GII value of 1 implies that GTV_{CT} to be completely located out of $GTV_{PET/CT}$, while the value of 0 indicates a total envelopment of $GTV_{PET/CT}$ by GTV_{CT}.

Dose statistic: Assessing the dose coverage of $PTV_{PET/CT}$ by CT-based plan created previously, was performed through the use of DVH, including $V_{90\%}$, $V_{95\%}$, $V_{100\%}$, $D_{90\%}$, $D_{95\%}$ and $D_{100\%}$.

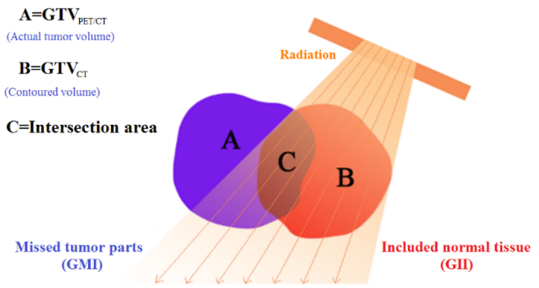

Fig 1. Demonstration of GTV_{CT} and $GTV_{PET/CT}$.

RESULTS

Volume analysis

The results of volumetric analysis are shown in Figure 2. The mean values of the GTVs and PTVs are given in Table 1. The results showed that the mean values of $GTV_{PET/CT}$ and $PTV_{PET/CT}$ are larger than GTV_{CT} and $GTV_{PET/CT}$ by 23.18% and 21.45%, respectively. In addition, in 40% of cases (8 patients), the volumetric differences were more than 25%.

Conformity and mismatches

The mean values of the conformities and mismatches are given in Table 2. The results showed an average CI of 0.43 (ranging from 0.09 to 0.67) and 0.52 (ranging from 0.52 to 0.71) were obtained for GTVs and PTVs, respectively. It means that only about 43% of CT-based tumor volumes are correctly delineated.

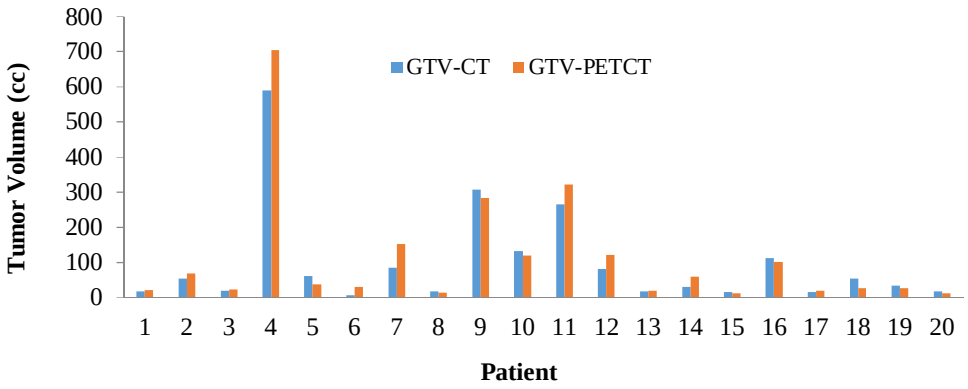

Fig 2. Comparison between GTV_{CT} and $GTV_{PET/CT}$ for all patients with non-small cell lung cancer.

Table 1: The mean value of GTV and PTV derived by CT and PET/CT images.

Target Volume (cc)	GTV	PTV
CT	96.37 ± 141.90 (range: 7.72 - 588.63)	212.37 ± 220.38 (range: 40.73 - 921.79)
PET/CT	108.77 ± 161.19 (range: 12.6 - 703.57)	229.94 ± 250.82 (range: 55.38 - 1066.35)

Table 2: The mean values of conformity and mismatches.

Target volume	CI	GII	GMI
GTV	0.43 ± 0.16 (range: 0.09 – 0.67)	0.34 ± 0.22 (range: 0.03 – 0.85)	0.42 ± 0.18 (range: 0.18 – 0.77)
PTV	0.52 ± 0.12 (range: 0.52 – 0.71)	0.28 ± 0.19 (range: 0.07 – 0.67)	0.32 ± 0.13 (range: 0.09 – 0.60)

The mean value of GII and GMI for GTV were about 0.34 and 0.42, respectively. In the other words, 34% of CT-based tumor volumes were related to the adjacent normal tissues mistakenly recognized as the cancerous cells. In contrast, 42% of cancerous cells were missed through CT-based delineation.

Dose evaluation

In Figure 3 and Figure 4 the values of $V_{95\%}$ and $D_{95\%}$ for $PTV_{PET/CT}$ of all patients are shown. Figure 5 shows tumor volume defined by only CT as well as PET/CT images. Also, the comparison between dose coverage of PTV_{CT} and $PTV_{PET/CT}$ are given in Table 3 and Table 4. These results showed that for most cases, the CT-based plans have not provided adequate tumor dose coverage.

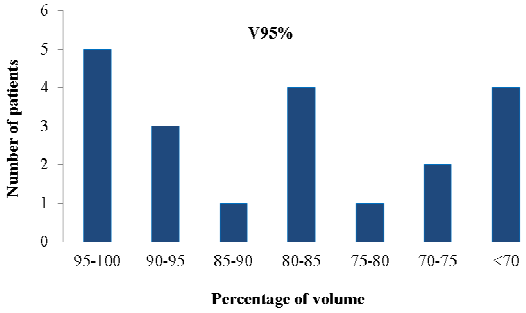

Fig 3. The percentage of $PTV_{PET/CT}$ receiving at least 95% of prescribed dose ($V_{95\%}$).

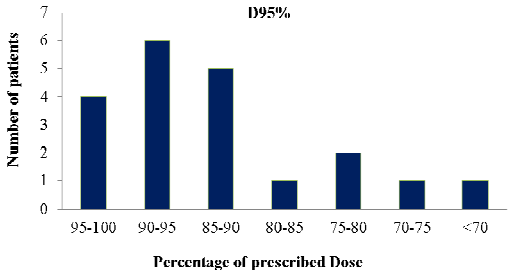

Fig 4. The percentage of prescribed dose absorbed by 95% of $PTV_{PET/CT}$ ($D_{95\%}$).

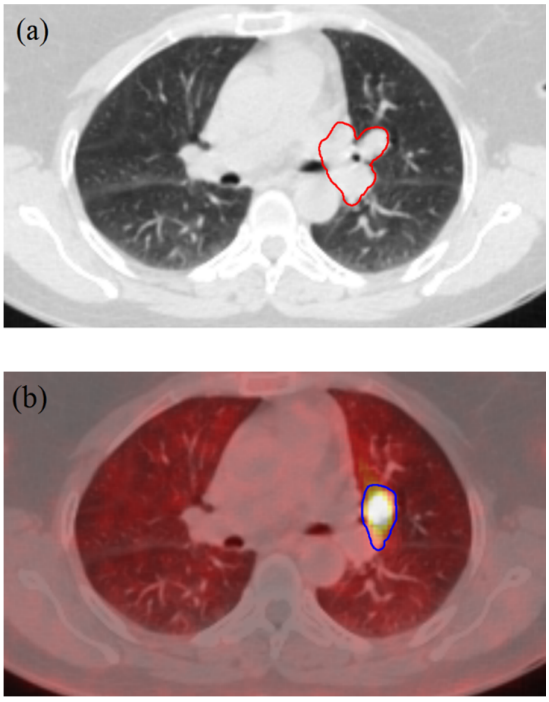

Fig 5. Tumor volume defined by: a) only CT image, b) PET/CT image.

Table 3: The average of $PTV_{PET/CT}$ receiving at least 90%, 95% and 100% of prescribed dose.

Parameter	PTV_{CT}	$PTV_{PET/CT}$
$V_{90\%}$	97.8%	84.2%
$V_{95\%}$	96.8%	80.5%
$V_{100\%}$	88.6%	32%

Table 4: The percentage of prescribed dose which was absorbed by 90%, 95% and 100% of average of $PTV_{PET/CT}$.

Parameter	PTV_{CT}	$PTV_{PET/CT}$
$D_{90\%}$	99.8%	90.7%
$D_{95\%}$	98%	88.5%
$D_{100\%}$	62.6%	52.1%

DISCUSSION

Treatment planning is the key component of radiation therapy. To benefit from modern radiotherapy, it is essential to delineate tumor volume accurately and then create an optimal RT plan. Currently, CT imaging is the base of RT planning process for lung cancer. However, the existence of atelectasis in the lung as well as low accuracy of CT images in diagnosis of involved lymph nodes makes precise tumor volume identification challenging. Previous studies have shown that fused CT and PET images lead to better tumor volume delineation results [18]. Therefore, PET/CT has the potential to improve RT plans and therapy outcomes. Whole contouring process was based on the available pathological information of patients and on the visual interpretation. No automatic algorithms or Standardized Uptake Value (SUV) assessment were used in this procedure. There are a number of studies related to this issue, in which tumor volume delineation has been performed based on SUV methods [19-21]. However, there are some aspects which make the application of SUV dubious. Some believe that SUV is not a reliable parameter since it is associated to several variable factors that may not be related to the lesions activity. Moreover, there is not yet a definite SUV threshold to confidently separate tissue. This is challenging, especially when the tumor is close to structures with high physiologic uptake [3].

Our findings showed that usage of PET/CT data could both increases and decreases in GTV for lung lesions. One of the reasons of volumetric changes in GTV was attributed to the ability of PET/CT in better detection of primary tumor volume from collapsed lung, by comparing their activity level. This condition was observed through 8 of all patients. In addition, among 12 of total patients, PET/CT detected either pathological lymph nodes which were hidden in CT images or uninvolved lymph nodes mistakenly included by CT data. The low resolution of PET images is a factor which causes blurring in tumor borders and often it is not easy to distinguish the boundaries clearly. This drawback of PET images probably leads to increase in tumor volume delineation. The blurring effect may also be caused by the physiologic movements. Since the PET data acquisition takes time, respiratory motions lead to lesion displacement during the PET scan. This may

cause blurring as well as the miss registration effects which makes a challenge to distinguish tumor borders from the adjacent normal tissues. In order to reduce respiratory motion, it is necessary to use the 4D PET/CT imaging [22-23]. However, in this study, imaging process was performed through 3D PET/CT, and the internal motions caused by breathing were ignored.

Our results showed that there is an average of 43% overlapping between GTV_{CT} and $GTV_{PET/CT}$, which was similar to the findings in the similar study by Gondi et al [11]. Although the utilization of PET/CT caused delineation of smaller GTV for 86% of total 14 patients, the CI was 44%, in accordance with our data.

The GMI of 0.42 and the GII of 0.34 are other evidences of CT-based contouring mistakes.

Based on the criteria defined in our research to adopt the treatment plans ($V_{95\%} > 95\%$ and $D_{95\%} > 95\%$), only in 5 patients (25%), CT-based RT plans were adequately covered the $PTV_{PET/CT}$. It means that for most of patients (more than 75%), the PET/CT data had a significant impact on the RT planning. Our findings showed that PET/CT improves the accuracy of tumor volume delineation of NSCLC patients.

CONCLUSION

In this study, comparisons of tumor volumes from CT and PET/CT images for 20 patients with non-small cell lung cancer were carried out. In addition, the effects of CT-based contouring on the dosimeteric results of treatment plans were investigated. Although the oncologist experience is a very important factor, in practice, tumor delineation in the radiotherapy centers is performed by an oncologist. To evaluate the differences between volumes, three different indices were used which indicated the proportion of overlap and mismatches between them, one of them (GII) is introduced and used for the first time in this study that is related to radiation therapy side effects. On the other hand, the movement of the tumor caused by respiration simply increases the size of the tumor in PET images rather than changing its position. Therefore, $GTV_{PET/CT}$ volumes were only expected to be larger than GTV_{CT}. But the results showed that in many cases, the location of the GTVCT is far from the $GTV_{PET/CT}$ location, which is due to misinterpretation of oncologist in the determination of GTV_{CT}. Our findings showed that for 20 NSCLC patients with criteria of V95%>95% and D95%> 95%, CT-based plan of about 80% of them, did not cover the treatment volume defined by PET/CT.

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