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Can an alternative backround-corrected [^{18}F] fluorodeoxyglucose (FDG) standard uptake value (SUV) be used for monitoring tumor local control following lung cancer stereotactic body radiosurgery?

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Original Article

Abstract

Purpose: Although [^{18}F] FDG-positron emission tomography (PET) provides vital information in diagnosing lung malignancies, the inherent uncertainties of standard uptake value (SUV) compromises its confidence. People have attempted to reduce this uncertainty by comparing the normal tissues, such as liver and spleen. However, those common reference structures may be inappropriate in some cases when pathological conditions exist. Hence, using alternative reference structures becomes valuable in such practice. The purpose of this study is to explore an alternative reference-correction method to reduce the inherent variation of SUV in the tumor or irradiated region. **Methods**: 106 analyzable FDG-PET scans from 49 cases who received lung SBRT for non-small cell lung cancer were retrospectively analyzed. The follow-up time ranges from 14.5 weeks to 113.2 weeks. The maximal SUV (SUVmax) was measured within the lung lesion or its corresponding region in post-SBRT. SUVmax was then corrected (or divided) by a reference SUV, or the mean SUV of the adjacent aorta, and results in the new SUVcmax. **Results:** SUVcmax of the positive group are significant higher than that of locally controlled cases (5.82 ± 3.10 vs. 1.45 ± 0.55, p = 0.026), while inconsequential differences were identified between the groups (p = 0.086). Respectively 85.2% and 96.3% of locally controlled cases post SBRT showed decreased values in the latter PET using SUVmax and SUVcmax. PET taken 24 weeks or sooner post-SBRT yielded higher uncertainties. **Conclusion**: Comparing with the conventional SUVmax, the alternative regional background-corrected SUV indicator, SUVcmax of PTV suggests a stronger correlation between low (<2.5 - 3.0) values and the local tumor control post lung SBRT for NSCLC. However, FDG-PET images taken earlier than 24 weeks post-SBRT presents larger variations in SUV of the irradiated region due to underlying radiation induced inflammatory changes, and is not recommended for assessing local tumor control after lung SBRT.

Keywords: Lung SBRT; FDG-PET; Local Control

Introduction

Today, lung cancer is still the leading cause of cancer-related death in men and women in the United States.[1] In addition to surgical resection and radiation therapy, lung stereotactic radiation therapy (SBRT) has become a popular option for early stage non-small cell lung carcinoma (NSCLC).[2] With improved image guidance and respiratory motion control, lung SBRT has shown excellent local control in comparison to surgery.[3, 4, 5] Functional imaging, such as [^{18}F] FDG-positron emission tomography (PET) provides helpful metabolic information in diagnosing, staging, and in predicting the local control of lung malignancies post lung SBRT.[6, 7] However, no standard uptake value (SUV) level has been widely accepted for suggesting a local lung cancer recurrence due to large inherent and post-irradiation added variations. Efforts have been suggested in reducing the inherent variations of SUV with limited success.[8, 9, 10] However, those

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common reference structures may be inappropriate in some cases due to the preexisting pathologies, alternative reference structures shall bring value to such practice. Furthermore, approximately 10% to 20% of all lung cancer patients treated with radiotherapy present evidence of radiation-induced lung changes [11, 12] making the assessment of the tumor local control of post lung SBRT more difficult.

The purpose of this study is to explore an alternative reference-correction method to reduce the inherent variation of SUV in the tumor or irradiated region, and provide a modified SUV indicator for monitoring the tumor local control of NSCLC treated with lung SBRT.

Methods and Materials

A total of 49 qualified or 50% of all lung cancer patients treated with intensity modulated lung SBRT in this institute from May 2009 to August 2010 were analyzed retrospectively. From them, 106 PET image sets were obtained and included in this investigation. The selected case must provide a pathological report NSCLC, and an analyzable pretreatment PET or at least one post-SBRT PET studies. The mean age of the group was 82.3 ± 9.3 years old. The pre-SBRT PET images and four post-SBRT PET from the only two locally relapsed cases comprise the "Positive" group (n = 37). The "Controlled" group consisted of the remaining 69 PET images from the 47 locally controlled cases following lung SBRT.

All the cases had 4D CT simulation and the treatment volume or planning tumor volume (PTV) contains the entire internal tumor volume (ITV) plus a 3-7 mm margins according to the tumor motion. The setup alignment was guided by 3D cone-beam CT and accomplished by joint the 4D patient support system (Varian Medical Systems, Palo Alto, CA) and Protura™ 6D robotic couch system (CVICO Medical Solutions, Coralville, IA). The SBRT was executed by multiple 6 MV photon beams gated for full-range of respirations using a Novalis TX CLINAC (Varian Medical, California) for a dose of 50 Gy in 5 consecutive fractions. In this collection, all FDG-PET studies were conducted with a GE Discovery STE™ or a Philips TF™ scanner, in which those reported in non-SUV format were excluded from database. The sampling of background reference SUV (SUVref) was taken from the adjacent aorta. The SUVmax of the PTV or irradiated volume were measured, as shown in **Figure 1**.

To ensure the consistency of the process, all PET images and pretreatment 4D simulation CT images were first transferred to Brainlab (Feldkirchen, Germany) iPlan™ Image v4.1 and fused to the average intensity projection 4DCT set. SUVref was measured within three or four consecutive slices of the aorta adjacent to the tumor, excluding visible hotter or colder spots. This value can be expressed as:

$$SUV_{ref}(g/ml) = \frac{1}{n}\sum_{i=0}^{n} x_i$$

where,

$$x_i = \frac{Radioactivity\ Concentration\ (kBq/ml)}{Injected\ Activity\ (kg)/Body\ Weight\ (g)}$$

The error associated with SUVref is the product of the standard deviation of SUV within the aorta by square root of number of voxels, n:

$$\delta SUV_{ref} = \frac{\sqrt{1/n\sum_{i=0}^{n}(x_i - \bar{x})}}{\sqrt{n}}$$

The ratio of the SUVmax to the SUVref defines the SUVcmax of the tumor or its corresponding site in post-treatment PET:

$$SUV_{cmx} = \frac{SUV_{\max}}{SUV_{ref}}$$

In this study lung tumor local control was analyzed independently from mediastinal failure, distant metastases, and overall survival.

Results

The mean PET follow-up time post-SBRT is 49.4 weeks (11.5 months), ranging from 14.5 weeks (3.4 months) to 113.2 weeks (26.4 months). The SUVref of the regional aorta over the entire 106 PET images ranges from 1.06 ± 0.14 to 2.40 ± 0.23 with a mean of 1.76 ± 0.32.

The mean SUVmax (6.34 ± 5.20) of the Positive is indistinguishable from the mean SUVmax of the controlled ($p > 0.05$), as tabulated in **Table 1**. However, SUVcmax signified this comparison with a larger difference between the two groups means (5.82 ± 3.10 vs. 1.45 ± 0.55, $p = 0.026$).

TABLE 1: Comparison of PET between the positive and locally controlled groups during 14 to 113 weeks post SBRT

	SUVmax		SUVcmax	
Group	Positives	Controlled	Positives	Controlled
Mean value	6.34	2.55	5.82	1.45
SD	5.20	1.13	3.10	0.55
Minimum	0.58	1.31	0.34	0.75
Maximum	25.14	7.62	13.38	3.90
Observations	37	69	37	69
p-value(2x controlled SD)	0.086		0.026	

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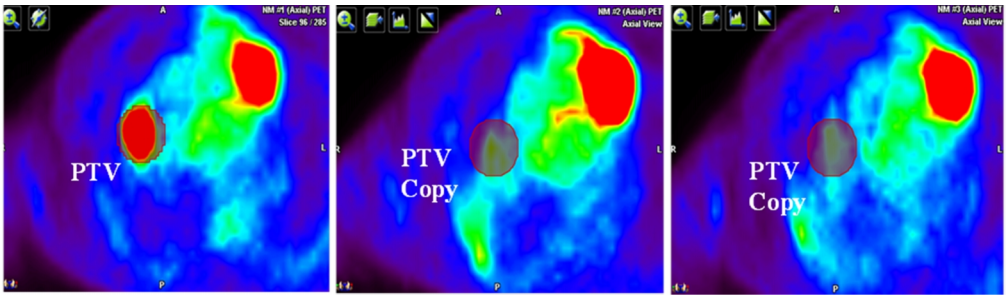

Pre-SBRT PET PET1 Post-SBRT PET2 Post-SBRT

FIG.1: Tumor SUVmax of pre- and post-SBRT PET scans.

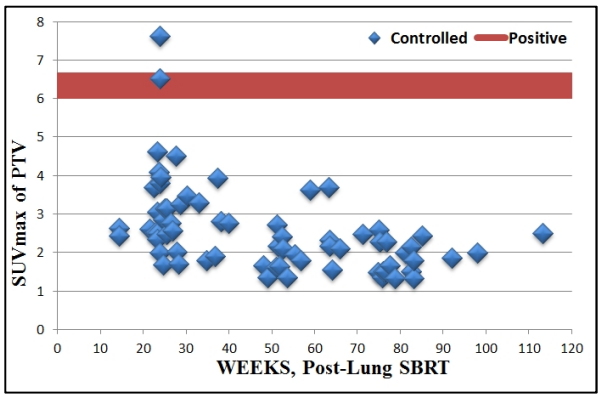

FIG. 2: SUVmax comparison between the locally controlled cases post lung SBRT (shown as blue diamonds) and the mean of positive lung cancer cases (marked as red band), where moderate separation can be seen especially with late PET studies.

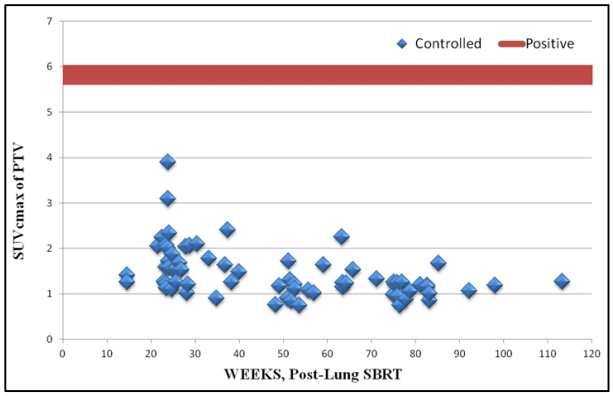

FIG 3: SUVcmax comparison between the locally controlled cases post lung SBRT (shown as blue diamonds) and the mean of positive lung cancer cases (marked as red band), where clear separation can be seen especially with late PET studies.

When comparing post-SBRT PET images up to 65 weeks after irradiation, no significant differences can be concluded between the Positive and Controlled in SUVmax ($p > 0.05$) and SUVcmax ($p > 0.05$). However, when PET images earlier than 24 weeks post-SBRT are excluded from the comparison, the locally controlled group displays noticeably lower SUV with either SUVmax ($p = 0.013$) or SUVcmax ($p = 0.008$). In addition, the false positive rates are also reduced from 34.7% to 26.5% when using cutoff value of 3.0 for SUVmax (as in **Table 2**) and from 26.5% to 17.6% when using cutoff value of 1.8 for SUVcmax (as in **Table 3**).

TABLE 2: Comparison of PET scans of recurrent lung cancer cases and locally controlled cases post SBRT during selected periods presented in SUVmax.

SUVmax	Positives	Locally controlled	PET
Post-SBRT (weeks)	Pre/post	14-65	24-65
Mean value	6.34	2.82	2.47
SD	5.20	1.22	0.81
Minimum	0.58	1.33	1.33
Maximum	25.14	7.62	4.49
Observations	37	49	34
SUVmax > 3.0	70.3%	34.7%	26.5%
p-value(2x controlled SD)	N/A	0.224	0.013

TABLE 3: Comparison of PET scans of positive group and locally controlled cases post SBRT during selected periods presented in SUVcmax.

SUVcmax	Positives	Locally controlled	PET
Post-SBRT (weeks)	Pre/post	14-65	24-65
Mean value	5.82	1.57	1.41
SD	3.10	0.60	0.44
Minimum	0.34	0.75	0.75
Maximum	13.38	3.90	2.41
Observations	37	49	34
SUVcmax > 1.8	70.3%	26.5%	17.6%
p-value (2x controlled SD)	N/A	0.068	0.008

In the locally controlled group, 27 out of 69 cases had more than one post-SBRT PET collected, in which 85.2% or 23 cases with SUVmax and 96.3% or 26 cases with SUVcmax showed progressively lower values.

Discussion

FDG-PET is now a common tool used in lung cancer diagnosis, radiation treatment planning, and post irradiation monitoring. While providing visual differentiation, SUVmax of the volume of interest has been frequently employed as the crucial indicator in the diagnostic or treatment evaluating process for NSCLC. Its thresholds vary around 2.5 [13, 14], often ranging from 2.0 [15] to 5 or higher.[16] One study reported that

the outlined tumor volumes using a threshold of 3.0 ± 1.6 matched closely to the dimension measured pathologically in nine NSCLC cases.[17] Alternatively, the percent constant threshold between 20% and 42% of maximum concurs with results from pathology. An adaptive threshold method suggests an improvement in using SUVmax when the ratio of tumor to background levels is used [18], even though its adaptability varies depending on the background variable defined by the user.[19, 20] At present there is still no clear consensus as to the appropriate threshold for tumor detection.

The inherent variations of SUV have been broadly acknowledged. The common variables include physiological (metabolic activity changes, blood glucose level), pathological (local inflammatory changes), and physical (relative activity per body volume at imaging, acquisition parameters, efficiency of the PET system) changes.[21] In addition, tumor motion reduces SUVmax and SUV-defined volume in conventional PET.[22, 23] Hence, simple quantitative techniques for SUV analyses to separate benign from malignant tissues are still highly debatable. When a threshold of SUVmax for defining malignancy is derived from a retrospective study, it may introduce a risk of misguidance for patient data groups [24] using PET from different facilities. Regardless of such limitations, the impartiality of quantitative classification by the SUV still makes it a valuable and subjective adjunct to visual analyses. To overcome these uncertainties, some investigators have proposed the subtraction of normal tissue uptakes from tumor SUV.[25] However, those studies fail to show reproducibility, mainly due to inconsistent tissue sampling and SUV variations in the reference organs.[26] In our study, the aorta nearby the lesion was chosen as the reference site, which inherently provides more reliable and reproducible reference values as long as hot or cold spots are avoided. In contrast to other organs, the aorta generally shows more constant SUV values with less motion or pathological effect. Such SUVref values can always be measured at the proximity to the tumor in the similar condition of data acquisition. In fact, each scan introduces a group of variables causing uncertainties in SUV values. Therefore, there was a pressing need for a method to allow corrections to be made within each PET study using a reproducible correction factor. With this optimized correction method, a new SUV, represented by the ratio of SUV's between the tumor site and reference, reveals the reality of canceling most potential variables between scans, such as those in dynamic evaluation of lung lesions. During aortic reference sampling, visible hot or cold spots of the aorta due to motion artifact or pathological changes on the arterial wall [27] were carefully avoided. Often the elevated value is associated with atherosclerosis, dissection vasculitis (ie Takayasu's) and thoracic stent graft placement related to the thoracic aortic wall inflammatory changes.[28] Although SUVref is the measurement of the FDG concentration in the blood flow, it is relatively equivalent in principle to the reference using SUV of other FDG accumulated regions, such as liver and spleen if the variation is not of concern. Comparatively, SUVcmax in this study demonstrated a stronger correlation with locally controlled NSCLC cases post lung SBRT than the conventional SUVmax did ($p = 0.026$ vs. 0.086). This correlation between low SUVcmax (< 3.0) value and the prediction of local control post-treatment is further suggested in **Figure 3**, while less separation from the recurrent cases is shown when using SUVmax (**Figure 2**).

Table 1 displays large deviations in SUVmax within the Positive mainly caused by a few extremely low SUVmax cases in the pre-SBRT PET scans. Clinically lung lesions less than 0.6 - 1 cm in diameter often show exceptionally low SUV in PET, and are difficult to quantify with the limited resolution of a PET scanner. Furthermore, lesions in the lower lobes of the lungs exhibit larger motions which lead to a reduction of SUV. Authors include the low SUV images in the Positive to make the statistical results more conservative.

Although IMRT based lung SBRT may show some reduction of normal tissue toxicities [29], in post lung SBRT the acute inflammatory changes at the lung are unavoidable.[30] These acute inflammatory changes are often difficult to distinguish from the uncontrolled local malignancy, and interfere with clinical judgment. Since FDG itself is a nonspecific tracer, it also detects local inflammatory changes such as a region of enhanced FDG uptake. Many cohort studies for lung SBRT follow-ups also address such concerns.[31] Since the irradiation induced inflammation tends to subside within 3-6 months [32], most investigators prefer the initial post-irradiation scan to be no sooner than 6 months after radiation is complete. Contrarily, at least one author believes that a single PET scan at 12 weeks could be used to tailor further follow-up according to the risk of failure.[33] To promote this early prediction, Koike et al reported a dual-time FDG-PET imaging method with potential usefulness for predicting early relapse of malignant tumors as early as 3 months after lung SBRT.[34] Our results however showed that PET scans earlier than 24-weeks post lung SBRT introduced huge uncertainties in predicting local control, as implied in **Table 2 and 3**. Only when the early PET studies were excluded, both SUVmax and SUVcmax of post-treatment fell in false positive rates ($p < 0.015$) and showed less standard deviation. Dunlap *et al* suggested that three consecutive increases in volume of FDG PET and an increase in volume at 12 months after lung SBRT in mass-like consolidation were highly specific for tumor recurrence.[35] In our 27 out of 47 locally controlled cases who had two available post-therapy PET images, 23 (85%) and 26 (96%) showed decrease in SUVmax and SUVcmax with their subsequent PET and provided further support for the tumor control. In comparing figure 2 to 3, post-treatment SUVcmax appeared more convincing in differentiating the controlled group from the Positive by a value of 2.5 - 3.0 than SUVmax did. The author believes that the SUVcmax is promising in predicting local control of post lung SBRT although studies with a larger case number, especially with more recurrent cases may be warranted.

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Conclusion

Comparing with the conventional SUVmax, the alternative regional background-corrected SUV indicator, SUVcmax of PTV suggests a stronger correlation between low (<2.5 - 3.0) values and the local tumor control post lung SBRT for NSCLC. However, FDG-PET images taken earlier than 24 weeks post-SBRT presents larger variations in SUV of the irradiated region due to underlying radiation induced inflammatory changes, and is not recommended for assessing local tumor control after lung SBRT.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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