INTRODUCTION

In recent years, 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has emerged as an essential tool in the staging of non-small cell lung cancer (NSCLC) (1). Tumor imaging through FDG-PET is achieved based on the difference in glucose metabolism between malignant and normal tissue, which leads to relatively increased FDG accumulation in tumor cells. FDG undergoes positron emission decay, which ultimately leads to the production of a pair of positron annihilation gamma (γ) rays (511 keV each) traveling in opposite directions (2). These two gamma rays are then detected by two opposing coincidence detectors in a PET scanner for imaging (2). Because of the ability of FDG-PET to detect malignancy prior to the development of any noticeable anatomical changes, it was consistently found to have superior sensitivity and specificity in the staging of lung cancer (3, 4). This is especially true for mediastinal staging. As shown in a meta-analysis by Gould et al., FDG-PET has superior median sensitivity and specificity over CT (85 vs. 61%, 90 vs. 79%, p < 0.001) in the identification of lymph node involvement by NSCLC (5). CT’s median specificity improves to be superior to FDG-PET in the evaluation of enlarged lymph nodes in the same study (93 vs. 78%, p = 0.002). However, FDG-PET may provide additional information on the extent of tumor involvement at the primary site and in the regional lymph nodes during target volume delineation for radiotherapy planning in the treatment of NSCLC to avoid geometric tumor miss, and unnecessary inclusion of normal tissue. In the following sections, the impact of FDG-PET on radiotherapy target volume delineation for NSCLC, which may increase the likelihood of dose escalation with IGRT, the commonly used methods of defining gross tumor on FDG-PET, 4D-PET/CT imaging, and FDG-PET’s impact on treatment outcome will be discussed.

IMPACT OF FDG-PET ON TARGET VOLUME DELINEATION

The incorporation of FDG-PET during target volume delineation has frequently led to changes in the shape and size of the target volumes; as well as the tumor stage when FDG-PET was not done as a part of the initially staging evaluation in patients with NSCLC. This fact has been well illustrated in multiple studies (6–14). As shown in Table 1, changes in the target volumes of over 20% and stage alteration of 20–50% have been consistently observed when FDG-PET was incorporated in target volume delineation and when FDG-PET was not a part of the initial staging studies. Most prominent changes are often associated with the presence of atelectasis in the treated areas (Figure 1), or the identification of additional nodal disease, which is difficult to visualize on CT (6–9, 11, 14) (Figure 2). This is well illustrated by Bradley et al., who demonstrated PTV and stage alteration of 58 and 31% in patients with stage I-II NSCLC when FDG-PET was incorporated in target volume delineation (9). Among 24 patients planned for definitive three-dimensional conformal radiotherapy (3D-CRT), PET led to a GTV reduction in 3 patients with atelectasis, and an increase in GTV due to the identification of additional regional nodal disease in 10 patients, and the identification of an additional parenchymal disease in 1 patient. GTV-reduction due to the utilization of PET resulted in dose reduction to the normal lungs and esophagus in patients with tumor-related atelectasis in this study, which suggests a potential advantage in the sparing of thoracic organs at risk (OAR) with the incorporation of FDG-PET in target volume delineation. This is corroborated in similar studies, which demonstrated similar PET-related target volume alterations, and the resulting decrease in the dose to the heart, esophagus, spinal cord, and the normal lungs (7, 8, 11, 12, 14). In one study, PET-related exclusion of metabolically inactive lymph
PET-related increase in the GTV has been mainly due to the identification of additional regional nodal disease (Table 1). This has been shown to result in an increase in the dose to the surrounding normal tissue (9, 11). However, this increase may not be clinically significant in all patients. As shown by Ceresoli et al., PET-related increase in GTV only resulted in an increase of the MLD by 1.08 Gy, and the V20 by 2.4% on average (11). In addition, incorporation of FDG-PET in the delineation of regional nodal disease may lead to a decrease in the nodal GTV. This has been demonstrated in patients with N2-N3 disease by van Der Wel et al., who showed a PET-related decrease of the nodal GTV from 13.7 ± 3.8 to 9.9 ± 4.0 cm³ (p = 0.011) (10). It led to significant decrease in radiation dose to the esophagus (V55 decreased from 30.6 ± 3.2 to 21.9 ± 3.8%, p = 0.004); and the normal lungs (V20 decreased from 24.9 ± 2.3 to 22.3 ± 2.2%, p = 0.012). As a result, dose escalation from 56.0 ± 5.4 to 71.0 ± 13.7 Gy (p = 0.038) became feasible, which led to improved TCP from 14.2 ± 5.6 to 22.8 ± 7.1% (p = 0.026) without accounting for geometric misses, and improved TCP from 12.5 to 18.3% when that is accounted for (p = 0.009). These findings further demonstrate the advantage of incorporating FDG-PET information in target volume delineation especially for stage III NSCLC, which makes dose escalation possible.

### Table 1 | FDG-PET-related alteration of target volumes in NSCLC

| Reference | Stage | Volume changes due to FDG-PET | Dosimetric impact |
|-----------|-------|-------------------------------|------------------|
| Nestle et al. (6) | IIIB-IV | Change in size and shape of radiation fields: 35% | PET-related increase in GTV only resulted in an increase of the mean lung dose (MLD) and volume of the normal lungs receiving 20 Gy (V20) by 6.1 Gy and 12% on average (11). In the same study, the median dose to the spinal cord was reduced from 45.7 to 41.7 Gy with the incorporation of FDG-PET in target volume delineation (p < 0.05). In another study, GTV reduction was observed in 73.3% of patients with stage III NSCLC in the presence of atelectasis, which possibly led to statistically significant decrease in commonly used dosimetric parameters, such as V20 for the normal lungs, and V55 for the esophagus. PET-related increase in the GTV has been mainly due to the identification of additional regional nodal disease (Table 1). This has been shown to result in an increase in the dose to the surrounding normal tissue (9, 11). However, this increase may not be clinically significant in all patients. As shown by Ceresoli et al., PET-related increase in GTV only resulted in an increase of the MLD by 1.08 Gy, and the V20 by 2.4% on average (11). In addition, incorporation of FDG-PET in the delineation of regional nodal disease may lead to a decrease in the nodal GTV. This has been demonstrated in patients with N2-N3 disease by van Der Wel et al., who showed a PET-related decrease of the nodal GTV from 13.7 ± 3.8 to 9.9 ± 4.0 cm³ (p = 0.011) (10). It led to significant decrease in radiation dose to the esophagus (V55 decreased from 30.6 ± 3.2 to 21.9 ± 3.8%, p = 0.004); and the normal lungs (V20 decreased from 24.9 ± 2.3 to 22.3 ± 2.2%, p = 0.012). As a result, dose escalation from 56.0 ± 5.4 to 71.0 ± 13.7 Gy (p = 0.038) became feasible, which led to improved TCP from 14.2 ± 5.6 to 22.8 ± 7.1% (p = 0.026) without accounting for geometric misses, and improved TCP from 12.5 to 18.3% when that is accounted for (p = 0.009). These findings further demonstrate the advantage of incorporating FDG-PET information in target volume delineation especially for stage III NSCLC, which makes dose escalation possible. |

- Average; TCP, tumor control probability.
- Atelectasis present in all patients.
- Median.
To further investigate the accuracy of FDG-PET in identifying nodal disease, 73 NSCLC patients with known positive lymph nodes by CT, or PET and pathology data for all suspected lymph nodes were further assessed by Vanuytsel et al. (12). Using PET-CT data, inclusion of pathological nodes in the nodal GTV was found to increase from 75% with CT alone to 89% ($p = 0.005$). In their study, PET-related GTV alteration was observed in 62% of the patients. Among them, PET-related GTV increase was observed in 16/45 patients. While 11 of these 16 patients’ GTV increase was supported by pathologic findings, it was unnecessary in five patients. PET incorporation resulted in GTV reduction in 29/45 patients. Twenty-five of them were correlated with pathological findings. Overall, 80% of all the PET-related GTV alterations were correct and inappropriate changes often were due to low tumor burden that is beyond the resolution of FDG-PET, or misinterpretation of the location of nodal disease. Pathology correlation in this study supports the utilization of FDG-PET in the delineation of nodal disease for NSCLC, which is shown to be more accurate than CT alone. The improved accuracy in identifying nodal disease with FDG-PET was shown by Faria et al. as well (13). However, how to improve the accuracy of PET-based identification of nodal disease from NSCLC remains to be investigated in the future. PTV reduction due to PET-related GTV reduction was again demonstrated in the study by Vanuytsel et al. in 10 selected stage III NSCLC patients, which led to a decrease of $V_{20}$ of the normal lungs by $27 \pm 18\%$ ($p = 0.001$) (12). Thus, further demonstrates an advantage in OAR sparing with incorporation of PET information in target volume delineation for NSCLC, which may increase the likelihood of dose escalation in the treatment of loco-regionally confined NSCLC with definitive radiotherapy.

METHODS OF TARGET VOLUME DELINEATION ON FDG-PET

Given the multiple variables that exist in PET imaging for NSCLC (2, 3), there is no consensus on how to best delineate gross tumor on FDG-PET at the current time. Visual interpretation of the PET or PET/CT images with an expert nuclear medicine physician remains to be a frequently used approach when delineating the GTV. The maximum standardized uptake value (SUV$_{\text{max}}$) was quantitatively used to determine FDG-PET activity because it is the most consistent and reliable parameter used to assess tumor activity in clinical practice. It is defined as the maximum tumor concentration of FDG divided by the injected dose of FDG, corrected for the body weight of the patient [$\text{SUV}_{\text{max}} = \text{maximum activity concentration}/(\text{injected dose}/\text{body weight})$]. In 87 patients with malignant and benign focal pulmonary lesions who had a
firm pathological diagnosis and at least 2 years of follow up, the sensitivity, specificity, and accuracy of 97, 82, and 92% were found when a SUV threshold of 2.5 was used for the diagnosis of lung cancer (15). This SUV threshold of 2.5 was proposed to be used as a cut-off for GTV delineation in radiotherapy planning (16). Slightly lower SUV threshold of 2 ± 0.4 has been proposed based on the PET/CT of 19 patients with stage II-III NSCLC, which could be distinctively visualized (17). Alternatively, fixed threshold from 36 to 44% of the SUV<sub>max</sub> based on the source-to-background ratio for volumes larger than 4 mL has been shown to accurately identify the tumor volume in phantoms (18).

Various approaches of PET-GTV delineation of the primary tumor were compared in a study by Nestle et al. (19). The fixed 40% thresholding method was found to be inadequate especially in the setting of inhomogeneous FDG-uptake within the tumor. However, PET-GTV contoured based on direct visualization, the SUV ≥2.5, and an algorithm accounting for the source-to-background FDG-uptake ratio all correlated well with GTV of the primary tumor contoured on CT. The poor correlation between CT-based GTV and PET-GTV generated with percent thresholding was also demonstrated in a study by Devic et al. (20). Upon further analysis of 20 peripheral NSCLC, the optimal threshold was found to be dependent on tumor size: 15 ± 6% for tumors >5 cm, 24 ± 9% for tumors 3–5 cm, 42 ± 2% for tumors <3 cm (21). Larger SUV<sub>max</sub> was found in larger tumors in this study. Thus, a single fixed percent-threshold method of GTV delineation appears to be inadequate and this may be due to multiple factors, such as the background FDG-uptake, heterogeneous FDG-uptake in the tumor, as well as respiratory motion and tumor size.

Multiple studies have attempted to investigate how well different GTV delineation strategies correlate with the true tumor volume in surgical specimens for NSCLC (Table 2). In correlation with surgical pathology findings, PET/CT has been shown to be more accurate than CT or FDG-PET alone in the estimation of

### Table 2 | Methods of GTV delineation on PET in correlation with surgical specimens.

| Patient no. | Method of GTV delineation on PET | Correlation between CT, PET, PET/CT, and pathological tumor size |
|-------------|---------------------------------|---------------------------------------------------------------|
| Lin et al. (22) | 37 Halo for tumor observed in fused PET-CT images | Stronger correlation between GTV and pathological tumor dimensions were observed with PET/ICT |
| Yu et al. (23) | 52 SUV of 2.5 | FDG-PET/CT has significantly better correlation with surgical specimens than CT or PET alone, especially in the presence of atelectasis |
| Yu et al. (24) | 15 Thresholding with 20–55% of SUV<sub>max</sub> | Best correlation between PET GTV and the actual tumor was found at the SUV threshold of 31 ± 11%, and absolute SUV cut-off of 3.0 ± 1.8 |
| Wu et al. (25) | 31 Tumor threshold = A*mean SUV<sub>70%</sub> + B*background | Maximal primary tumor dimension was more accurately predicted by CT at the window-level of 1,600 and ~300 HU than PET GTVs (best correlation with pathological tumor volume at 50% SUV<sub>max</sub>) |
| Schaefer et al. (27) | 15 | Pathological tumor volume: 39 ± 51 mL |
| van Baardwijk et al. (28) | 33 Source-to-background ratio auto-segmentation | PET tumor volume: 48 ± 62 mL |
| Wanet et al. (31) | 10 Gradient-based method | CT tumor volume: 60.6 ± 86.3 mL |
| Cheebsumon et al. (32) | 19 Absolute SUV cut-off (2.5) | Both CT and PET volumes are highly correlated with pathological volumes (p < 0.001). Increased variation between PET and pathological tumor volumes were observed in lower lobes |
| | Fixed threshold at 40 and 50% of the SUV<sub>max</sub> Adaptive thresholding based on the source-to-background ratio | Comparison of both CT and PET GTV |
| | Adaptive thresholding 41–70% SUV<sub>max</sub> Contrast-oriented algorithm | Gradient-based method led to the best estimation of the GTV PET GTVs were smaller than CT GTVs in general |
| | Gradient-based method | Adaptive 50% and gradient-based methods generated the most consistent maximal tumor dimension, which had a fair correlation with the pathological tumor size |
tumor size for NSCLC (22, 23). In a study of 37 patients, the mean SUV at the edge of the PET tumor halo which corresponded to the edge of the tumor on pathology was $2.41 \pm 0.73$ (22). In a different study, GTV delineated on PET/CT using a SUV cut-off value of 2.5 resulted in the best correlation with the pathological tumor volume (23). In an analysis of 15 lobectomy specimens after PET/CT imaging, the most optimal percent threshold, and absolute SUV cut-off that correlated with the pathologic tumor volume (GTV$_{\text{path}}$) were found to be $31 \pm 11\%$, and $3.0 \pm 1.6$, respectively (24). Only the SUV percent threshold was correlated with the GTV$_{\text{path}}$ and the tumor diameter in this study ($p < 0.05$). However, limitations have been observed with both approaches of GTV delineation based on pathological correlation. The SUV cut-off at the edge of the tumor on PET has been shown to be dependent on tumor size and histology by Lin et al. (22). In their study, higher mean SUV is observed with tumors over 3 cm and of squamous histology. In contrary to the studies described above, thresholding has been shown to be less accurate than CT in predicting the maximal tumor dimension in pathological tumor specimens in 31 patients who underwent lobectomy shortly after PET/CT (25). The uncertainties associated with percent thresholding or the use of an absolute SUV cut-off for GTV delineation appear to be influenced by the background FDG concentration and the tumor size, which are reflected by the mean SUV. To minimize the impact of these factors, it was proposed to adjust percent thresholding based on the mean target SUV in order to accurately define the gross tumor (26).

To account for the effects of tumor volume and background FDG concentration, a contrast-oriented thresholding algorithm (COA) was proposed for the delineation of PET GTV for NSCLC (27). This approach was shown to reduce the GTV volume when compared to CT alone. Also, it was shown to be highly correlated to the pathological tumor volume. Similar findings were obtained in a study of 33 patients with NSCLC when a source-to-background ratio based auto-segmentation approach was used (28). These studies demonstrate the feasibility of an adaptive thresholding approach for GTV delineation on PET. However, higher variation between pathological and PET tumor volumes were observed in the lower lobes with the COA, suggesting respiratory motion to be a source of inaccuracy in GTV delineation on PET (27).

A gradient-based approach for PET-GTV delineation has been proposed to minimize the statistical noise, and resolution blur (more pronounced in the setting of large respiration induced tumor motion) (29). When compared to other methods of GTV delineation on PET, this method was found to be the most accurate in a phantom study by Werner-Wasik et al. (30). This approach was also compared with other methods of GTV delineation in surgical specimen correlations studies (31, 32). It was found to be superior to manual, fixed thresholding at 40 and 50%, and the source-to-background ratio methods of PET-GTV delineation, and manual CT GTV delineation on 4D-PET/CT in 10 patients with stage I-II NSCLC who underwent lobectomy (31). In another study of 19 patients who underwent free-breathing PET/CT prior to surgery, the gradient method was found to be highly correlated with the maximal tumor size in surgical specimens as well (32). Thus, the gradient-based method is highly promising, which warrants further investigation in future trials. While the various methods discussed are shown to be feasible, they are often confounded by factors, such as statistical noise, blurring effect due to respiratory motion, and uncertainties in the estimation of pathological tumor size in surgical correlative studies. Thus, further studies need to be conducted to explore what would be the best method for the most accurate GTV delineation on PET.

**IMPROVING PET-GTV DELINEATION WITH 4D-PET/CT**

Respiratory motion often causes blurring and alteration of the FDG-uptake within the tumor, which lead to uncertainties in the delineation of the gross tumor volume on PET (33). These uncertainties may potentially be minimized with 4D-PET/CT imaging for more accurate identification of the true extent of the tumor in various portions of the respiratory cycle, and low volume disease, which may be missed on free-breathing PET/CT (34, 35). As shown by Lamb et al., tumor volumes delineated on PET not only correlates better with that delineated on 4D CT, but also enhances the estimation of the true extent of tumor in the vicinity of similar density soft tissues, such as the diaphragm, chest wall, and the heart (36). Thus, the GTV delineation on PET can be improved with 4D-PET/CT imaging. This is, especially, helpful in image-guided radiotherapy (IGRT) due to the very small PTV margins used, which allows for dose escalation to the gross disease without significantly increase the risk of severe toxicities to normal thoracic structures. Therefore, 4D-PET-based tumor target delineation should be used as often as possible when a high dose of radiation is delivered in the thorax.

**DELINERATION OF NODAL DISEASE ON PET**

The delineation of regional nodal disease on PET has been conducted in similar ways as that for the primary tumor. Various methods were compared by Nestle et al., who again demonstrated that an algorithm accounting for the source-to-background FDG-uptake ratio was superior to direct visualization, 40% thresholding, or the SUV $\geq 2.5$ cut-off methods (37). Furthermore, the nodal volume delineated on PET tends to be larger than that delineated on CT, which was felt to be possibly caused by respiratory motion. This was corroborated in a study on 4D-PET-based nodal disease delineation (38). As shown in this study, a 3D nodal internal target volume (ITV) expansion of over 1 cm is required to cover 91% of the lymph nodes while accounting for respiratory motion. While it is still inadequate in situations of highly mobile lymph nodes. On the contrary, 4D-PET-based ITV was able to not only adequately encompass nodal disease in the setting of respiratory motion, but also sparing additional normal tissue ($45 \pm 34$ cm$^3$) when compared with 3D nodal ITV generated with large margins that would be required to account for respiratory motion in the majority of the cases. Thus, 4D-PET imaging may improve precise and accurate localization of mediastinal disease over CT, which can potentially improve targeting in the mediastinum for the delivery of IGRT in the treatment of lung cancer.

**CLINICAL OUTCOME FOLLOWING PET-BASED PLANNING**

In recent years, two studies have reported the clinical outcome following concurrent chemo-radiation for stage II-III NSCLC when the target volumes were delineated based on FDG-PET findings (39, 40). In a pilot study of 32 patients, only one regional failure and one local progression were observed shortly after concurrent chemo-radiation when only PET-avid disease was included.
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Conflict of Interest Statement: The Guest Associate Editor UL Lennart Karlsson declares that, despite having collaborated with Nam P. Nguyen, the review process was handled objectively and no conflict of interest exists. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 31 March 2014; accepted: 20 September 2014; published online: 07 October 2014.

Citation: Chi A and Nguyen NP (2014) The utility of positron emission tomography in the treatment planning of image-guided radiotherapy for non-small cell lung cancer. *Front. Oncol.* 4:273. doi:10.3389/fonc.2014.00273

This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology.

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