428 Chinese Journal of Clinical Oncology Dec. 2007, Vol. 4, No. 6 P 428~432 Suyu Zhu et al.
[SpringerLink] DOI 10.1007/s11805-007-0428-6

The Dilemma of Target Delineation with PET/CT in Radiotherapy Planning for Malignant Tumors

Suyu Zhu
Bingqiang Hu

Department of Radiation Oncology, the Hu-Nan Province Cancer Hospital, Changsha 410013, China.

Correspondence to: Suyu Zhu
E-mail: suyuzhu@yahoo.com

Received August 14, 2007; accepted November 7, 2007.

CJCO http://www.cjco.cn E-mail:cocr@eyou.com
Tel(Fax):86-22-2352 2919

ABSTRACT Currently there are many unanswered questions concerning contouring a target with PET/CT in radiotherapy planning. Who should contour the PET volume-the radiation oncologist or the nuclear medicine physician? Which factors will contribute to the dual-observer variability between them? What should be taken as the optimal SUV threshold to demarcate a malignant tumor from the normal tissue? When the PET volume does not coincide with the local area CT findings, which portion should be contoured as the target? If a reginal lymph node draining area or a remote region is shown to be PET positive but CT negative, or PET negative but CT positive, how is the target identified and selected? Further studies concerning the relationship between PET/CT and the cancerous tissue are needed. The long-term clinical results showing an increased therapeutic ratio will finally verify the applicability of guidelines to contour the target with PET/CT in radiotherapy planning.

KEYWORDS: PET/CT, radiotherapy planning, target delineation.

With the widespread clinical implementation of three dimensional conformal radiotherapy (3D CRT) and intensity modulated radiotherapy (IMRT), accurate target delineation is becoming increasingly important. The integration of positron emission tomography (PET) into radiotherapy planning may influence target delineation by providing biological characteristics of the tumors. PET has definitely changed the traditional concept of the tumor volume which is based on the anatomical morphological imaging. Since integrated PET/CT was put into clinical use in 2000, it has spared the inconvenience of multi-scans and reduced the errors of image registration. PET/CT can integrate metabolic information with the anatomical structure and directly produce a fusion image. From a series of studies it was concluded that PET may influence the strategy of management for malignant tumors by changing the intent of 10%~40% of the radiotherapy plans from radical to palliative[1-3]. Furthermore, it may guide more accurate target contouring[4-6], and may permit escalation of the target dose without exceeding normal tissue tolerance[7-9]. However, a consensus as how to delineate the PET/CT volume has not been reached.

Dilemma 1: Who should contour the PET volume-the radiation oncologist or the nuclear medicine physician?

Results of studies on the dual-observer differences in identifying the PET/CT tumor volume were not totally in agreement. Cadwell et al.[10] reported that the dual-observer differences among three radiation oncologists were dramatically decreased when contouring non-small cell lung cancer (NSCLC) tumor volumes with PET/CT compared with CT alone. Similar conclusions were also reported

from the studies of Ciernik et al.[3] and Syed et al.[11] on delineation of the head and neck tumor volume. However, Riegel et al.[12] recently reported that there were marked differences among 4 physicians contouring 16 cases of the head and neck tumor volumes with PET/CT (P=0.0002). Their analyses showed that the preference and tendency of each individual physician in their decision-making process was somewhat a deciding factor when they drew conflicting regions with multi-imaging modalities. Some preferred to contour the overlapping portion between PET and CT, some would place more weight on a single imaging modality, and others would split the difference and contoured a compromise between a drawn CT contour and PET avidity.

Worthy to mention here is that there is no statistically significant difference between contouring by radiation oncologists compared to nuclear physicians. This finding is based on the prerequisite that an institutional consensus guideline was clear and strictly followed, and most importantly, that all the participants had more than 10 years of experience in clinical work, and all were well educated in both fields of diagnostic CT and PET. Therefore, a deep understanding of diagnostic CT and PET was the key factor in narrowing the variance between radiation oncologists and nuclear medical physicians in this study mentioned.

When CT simulation first came into widespread use, a number of radiation oncologists did not feel confident in defining a target and normal structures. Now almost all physicians who participate in conformal treatments feel confident with outlining most normal and target structures. This is true because they have had more exposure to three-dimensional radiotherapy techniques forcing them to become more knowledgeable about diagnostic radiology. However, PET is more difficult to interpret. Increased FDG uptake may be due to a high tumor metabolic rate, but may also be secondary to an artifact or part of normal physiologic processes characteristic of the brain, myocardium, urinary tract, or gastrointestinal system. Increased uptake can also be seen in post-surgical sites and irradiated areas where inflammation is present. Furthermore, standard uptake values (SUV) can vary depending on the patient's lean body weight, body surface area, and activity of the injected isotope. At the present time, normal limits are not well defined according to the tumor type. Therefore currently, it is recommended that a nuclear medicine physician contour the tumor or be available to assist the radiation oncologist to produce the outlines. As experience and confidence with this technique grows, this requirement will become far less frequent.

Dilemma 2: What is the FDG SUV threshold for PET which can optimally demarcate a malignant tumor from normal tissue, i.e. define the real tumor volume?

SUV is a semi-quantitative index of PET to measure the concentration of the glucose analog, FDG (^{18}F-fluorodeoxyglucose), taken up by malignant cells. Its value has been commonly used to differentiate malignant from benign tissues; hence it can serve as a valuable diagnostic tool. When used in target contouring for radiotherapy planning, there are numerous factors that can influence the accuracy of the SUV which should be taken in consideration. These factors mainly consist of the following: ①Blood glucose competitively inhibits the uptake of FDG and can decrease the calculated SUV. Whenever blood glucose is higher than 200 mg/ml, the PET examination should be postponed. Insulin should best not be administered before the injection of FDG as its uptake by muscles will be increased and the target/background ratio will be decreased. ②SUV is time-dependent, and usually reachs a peak level at around 90 min in the malignant tissue after injection of the FDG. Within a definite range of time, the SUV will gradually increase, so the time set should be standardized and normalized for a PET scan after FDG injection. ③Size of the region of interest (ROI). Due to the low spatial resolution of PET images, a partial volume effect will result in underestimating the real SUV of the ROIs. When the size of the ROI is only 1.5 times the PET resolution, the calculated SUV is just equal to 60% of its actual value. Only when the size of the ROI reaches 4 times the PET resolution will the gap of the calculated from the actual SUV be narrowed down to less than 5%[13]. ④Weight or surface area. The injected dose of FDG should be normalized based on the patient's weight or surface area, so that the measured SUV can be compared among patients. ⑤The modality of image reconstruction. The filtered inverse reconstruction will result in an underestimation of 20% of the real radioactive counts, and the extent of its underestimation is far larger than the iterated reconstruction (5% underestimation).

The SUV is also notably influenced by the number of times of iteration of the ordered-subsets expectated maximization (OSEM). From 5 to 40 iterations, the peak SUV will incrementally increase by 28%. Other disturbing factors include residual FDG inside the syringe or leakage out of vessels, incorrect calibration for the collimator of the detectors and dose correction, and the heterogeneity of tumors themselves, all of which will influence the accuracy of the measured SUV[14]. Because the SUV is just a semi-quantitative

index representing the nature of malignancy, and since its accuracy is influenced by many factors, the threshold value demarcating malignant from benign tissue has not been uniformly reported in the literature. At present there is no consensus on its value. Ciernik et al.[3]correlated the size of the vials embedded in a phantom filled with various activity of FDG with the cutoff value of the SUVmax. They found that a cutoff of 50% of the SUVmax. was a best match to the diameter of the cylindrical vials. However, a growing tumor in the human body is unlike a cylinder with an absolute sharp boundary that separates it from normal tissue. The irregular shape and distribution of a density gradient within the tumor makes such a comparison questionable. Even though, an arbitrary cut-off threshold of 40% or 50% of the SUVmax. to define GTV is still widely used in clinical settings[4,15,16].

Another means to delineate the FDG-avid volume is to contour the entire area with a SUV of 2.5. By using a SUV of this value most nuclear medicine physicians are confident in interpreting non-small cell lung cancer as positive. For other tumors, such as lymphomas and head-and-neck carcinomas, the SUV threshold for positive sites of disease needs to be further defined. Visual inspection based on the nuclear medicine physician's experience is another way to delineate the PET volume. This method will cause a larger inter-observer variability[17]. A more complicated means involves using the source-to-background ratio to define PET-avid volume[18,19]. It is evident that the PET volume is heavily influenced by the background FDG activity. For example, the SUV for lungs is less than 1 but more than 3 for the liver. Such background differences will result in various thresholds, which is especially not applicable for cancers of the organs with a low SUV. Therefore these organs should be irradiated with much caution.

It is not clear now as to which method of defining the PET volume will most closely represent the real tumor area in vivo, especially in relation to the subclinical region around the GTV. It is essential that studies be conduct on the relationship between the PET-avid region and the biological characteristics of the tumor. The M.D. Anderson Cancer Center has been studying the co-relationship between anatomical functional imaging and its registered pathological specimen[20]. Such studies will aid in a closer delineation of the PET volume with the in vivo tumor volume.

In conclusion, choosing a different threshold or using different means to delineate the PET volume will heavily influence the biological target volume. Increasing or decreasing the threshold arbitrarily will result in serious under-dosing of the tumor target or over-dosing of the normal tissue. The applicability of an algorithm to define the PET volume will need to be finally verified by the long-term clinical results.

Dilemma 3: How to determine the target volume when the PET findings do not coincide with the CT target?

In most situations, the PET findings do not wholly coincide with those of the CT imaging with respect to the number of tumors, location sites and extending area. Those scenarios include the PET volume crossing over with the CT target, PET findings within the CT target and PET findings outside of the CT target. These situations will be separately discussed in this review.

Most studies in the literature concerned with the impact of PET or PET/CT on radiotherapy treatment planning, have not stated clearly their detailed guidelines for target delineation when faced with the situations mentioned above. In the absence of these guidelines the determination of the clinical target represents a quandary. In cases with atelectasis, pleural effusion and obstructive pneumonitis with NSCL, there is a consensus that the target is difficult to define based on the CT, but easily determined by PET. The PET-based target is usually a much tighter one which will result in a dose reduction to the lungs, esophagus, heart and spinal cord[4,8].

The in vivo pathological target can not be convincingly displayed by current imaging modalities. Therefore, a comprehensive composite target has been in clinical use, which is defined as the composition of the structural target (CT target) with the functional biological target (PET target). Paulino et al.[16] studied IMRT for 40 cases of head and neck cancers scanned with both CT and PET. They found that the CT-GTV was larger than the PET-GTV in 30 cases, and more than 5 times larger in 7 cases. The PET-GTV was larger than the CT-GTV in 7 cases and the maximal ratio was 2.5. If the IMRT plan had been based on the CT-GTV, there would have been 10 cases of PET-GTV receiving less than 95% of the prescribed dose, and the minimal prescribed dose for 95% PET-GTV would be less than 75% for 5 cases, and in around 25% of the cases, the PET-GTV was not covered by 95% of the prescribed dose. Therefore, they suggested that there are good reasons to combine CT-GTV with PET-GTV to make up a comprehensive GTV that can be applied in IMRT. In cases where the PET target is within the CT target, which are very common situations when special radioactive tracer like hypoxic imaging is used in a PET scan, a consensus strategy was to contour the PET target as a boost region and thus

be escalated to a much higher dose or be dealt with by other special tumorcidal treatment[7,21].

As for an examination of local residual tumor tissue and recurrence after treatment, PET is superior to CT as it has a higher sensitivity and specificity for most cancers. Using CT, which is mainly based on the density changes of the anatomic structures, it is sometimes difficult to make a differentiation from the treatment-induced changes[5,22]. Therefore, the biological metabolic information provided by PET is more meaningful for target delineation when a second-time radiotherapy is planned. For this radiotherapy a higher priority is given to sparing the normal tissues requiring a tighter boost region. However, the impact of PET on RT planning as described above has not been thoroughly investigated.

Other factors like image resolution and intermittent physiological movements can make a difference between PET and CT. The axial resolution for CT is usually less than 1 mm, but 5~7 mm for PET. The partial volume penumbra effects are bigger for PET than for CT. This will compound the target delineation with fused PET/CT images. Furthermore, the viewing window set for CT target contouring is also very important. An increase or decrease in a window's level for CT display will manually enlarge or shrink the target volume and make an inaccurate target. At the present time there have been no studies clearly stating which window setting will reflect the real tumor volume. In the usual case, the window settings for diagnosis are accepted as the conditions to delineate the target. If otherwise, the settings should be separately stated.

Because a longer time is required for a PET scan compared to a CT scan (usually 10 s or more for CT and 10~20 min for PET), the effects of breathing, the heart rhythm and difficulty in maintaining the same position may result in errors for the image registration of PET with CT . A maximal deviation was found in the chest region, ranging up to 6.4 mm in the x axis, 8 mm in the y axis and 4 mm in the z axis. This mismatch in the thorax is mainly the result of breathing as its impact on CT is different from that on PET. With a long scanning time, the PET volume is influenced by physiological movements and uncertainties in representing an average volume. However, for tumors of the head and neck and pelvis, a mismatch error of 1~3 mm was smaller[3]. For future development, a 4 dimensional PET/CT simulation scan has been reported to be a more precise means to reduce the fusion error[23].

Dilemma 4: What about tumors that are positive with CT but negative with PET and vice versa?

The accuracy of PET on target delineation has only been studied on a few types of tumors. Up to now, there have not been convincing reports concerning the effect of PET on RT planning for head and neck tumors. There has been more interest in the usefulness of PET on target delineation for NSCLC.

Gould et al.[24] performed a meta-analysis to compare the accuracy of FDG-PET and CT for identifying mediastinal metastasis in patients with NSCLC by using several search engines. They identified 39 relevent articles published in any language before 2003. Their results indicated that the median sensitivity and specificity for CT were respectively 61% and 79%, while for FDG-PET they were 85% and 90%. When CT showed no mediastinal lymph node enlargement, the median sensitivity and specificity for PET were respectively 82% and 93%. They concluded that PET was more accurate than CT for mediastinal staging and that PET was more sensitive but less specific when CT showed enlarged mediastinal lymph nodes. The results from this study suggest that when the PET findings are negative while the CT results are positive, the mediastinal lymph nodes should be considered to be involved with no metastatic disease. Because of the highly negative prognostic value of PET scans, enlarged lymph nodes by CT should not be contoured as the gross target, or be contoured as the clinical target volume and be selectively delivered a reasonably low irradiation dose. At the same time the authors also reported a relatively high false positive PET finding (25%) when the CT showed no enlarged mediastinal lymph nodes. Therefore if all of the mediastinal PET positive nodes were contoured as a target, a fraction of the over-volumed target would be irradiated. However, Bradley et al.[25] reported around 40% of CT negative nodes were PET positive in examination of mediastinal lymph nodes. De Ruysscher et al.[26] prospectively implemented a clinical trial so that only PET positive mediastinal lymph nodes would be delineated and irradiated. Their results showed there were few cases with a recurrence outside the target. Based on those findings, at the present time it is reasonable to delineate the PET positive mediastinal lymph nodes as the irradiation target.

Currently there is no strong evidence to guide target contouring after chemotherapy when CT shows residual disease while PET results are negative. In the treatment of lymphomas, for example, one may still have a small mediastinal mass after chemotherapy with a negative PET. Because there is no increased metabolic activity in the tissue mass, it is likely to appear as fibrosis, or the low metabolic activity may be transient, but not represent killed cancer cells after treatment. That said, the current data are too incom-

plete to correlate negative PET data with long-term outcomes with any degree of confidence.

Discussion

When incorporating PET/CT into radiotherapy planning, the PET-avid volume should be delineated by nuclear medical physicians or they should be available to assist contouring. At the present time the SUV threshold by which to define the target has not been determined. A study correlating PET-avid volume with its registered pathological specimen will be helpful in developing a consensus SUV threshold. For a local disease, when the PET and CT findings do not coincide, it is reasonable to combine the PET and CT volumes to formulate a comprehensive target and to use the PET volume as a boost target.

For contouring mediastinal lymph nodes in cases of NSCLC, when CT shows enlarged nodes while PET is negative, the PET results are more convincing. A cautious method is to deliver a low preventive dose of irradiation to the CT-enlarged nodes. When PET shows positive nodes while the CT results are negative, the PET-avid nodes should be contoured as the target, and undergo a high radiation dose. For other tumors, when the PET and CT findings fail to coincide, the current data are incomplete to recommend a consensus guideline to resolve the target delineation dilemma.

REFERENCES

1 Czernin J, Phelps ME. Positron emission tomography scanning: Current and future applications. Annu Rev Med 2002; 53: 89-112.
2 Dizendorf E, Baumert BG, von Schulthess GK, et al. Impact of whole-body 18F-FDG PET on staging and managing patients for radiation oncology. J Nucl Med 2003; 44: 24-29.
3 Ciernik IF, Dizendorf E, Baumert BG, et al. Radiation treatment planning with an integrated positron emission and computer tomography (PET/CT): A feasibility study. Int J Radiat Oncol Biol Phys 2003; 57: 853-863.
4 Mah K, Caldwell CB, Ung YC, et al. The impact of (18)FDG-PET on target and critical organs in CT-based treatment planning of patients with poorly defined non-small-cell lung carcinoma: A prospective study. Int J Radiat Oncol Biol Phys 2002; 52: 339-350.
5 Schechter NR, Gillenwater AM, Byers RM, et al. Can positron emission tomography improve the quality of care for head-and-neck cancer patients? Int J Radiat Oncol Biol Phys 2001; 51: 4-9.
6 Nishioka T, Shiga T, Shirato H, et al. Image fusion between 18FDG-PET and MRI/CT for radiotherapy planning of oropharyngeal and nasopharyngeal carcinomas. Int J Radiat Oncol Biol Phys 2002; 53: 1051-1057.
7 Solberg TD, Agazaryan N, Goss BW, et al. A feasibility study of 18F-fluorodeoxyglucose positron emission tomography targeting and simultaneous integrated boost for intensity-modulated radiosurgery and radiotherapy. J Neurosurg 2004; 101(suppl3): 381-389.
8 Del Wel AV, Nijsten S, Hochstenbag M, et al. Increased therapeutic ratio by 18FDG-PET CT planning in patients with clinical CT stage N2-N3M0 non-small-cell lung cancer: A modeling study. Int J Radiat Oncol Biol Phys 2005; 61: 649-655.
9 Chapman JD, Bradley JD, Eary JF, et al. Molecular (functional) imaging for radiotherapy applications: An RTOG symposium. Int J Radiat Oncol Biol Phys 2003; 55: 294-301.
10 Caldwell C, Mah K, Ung Y, et al. Observer variation in contouring gross tumor volume in patients with poorly defined non-small-cell lung tumors on CT: The impact of 18FDG-hybrid PET fusion. Int J Radiat Oncol Biol Phys 2001; 51: 923-931.
11 Syed R, Bomanji TB, Nagabhushan N, et al. Impact of combined (18)F-FDG PET/CT in head and neck tumours. Br J Cancer 2005; 92: 1046-1050.
12 Riegel AC, Berson AM, Destian S, et al. Variability of gross tumor volume delineation in head-and-neck cancer using CT and PET/CT fusion. Int J Radiat Oncol Biol Phys 2006; 65: 726-732.
13 Geworski L, Knoop BO, de Cabrejas ML, et al. Recovery correction for quantitation in emission tomography: A feasibility study. Eur J Nucl Med 2000; 27: 161-169.
14 Weber WA. Use of PET for monitoring cancer therapy and for predicting outcome. J Nucl Med 2005; 46: 983-995.
15 Bradley J, Thorstad WL, Mutic S, et al. Impact of FDG-PET on radiation therapy volume delineation in non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2004; 59: 78-86.
16 Paulino AC, Koshy M, Howell R, et al. Comparison of CT- and FDG-PET-defined gross tumor volume in intensity-modulated radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2005; 61: 1385-1392.
17 Paulino AC, Johnstone PAS. FDG-PET in radiotherapy treatment planning: Pandora´s box? Int J Radiat Oncol Biol Phys 2004; 59: 4-5.
18 Daisne JF, Sibomana M, Bol A, et al. Tri-dimensional automatic segmentation of PET volumes based on measured source-to-background ratios: influence of reconstruction algorithms. Radiother Oncol 2003; 69: 247-250.
19 Black QC, Grills IS, Kestin LL, et al. Defining a radiotherapy target with positron emission tomography. Int J Radiat Oncol Biol Phys 2004; 60: 1272-1282.
20 Frank SJ, Chao KS, Schwartz DL, et al. Technology insight: PET and PET/CT in head and neck tumor staging and radiation therapy planning. Nat Clin Pract Oncol 2005; 2: 526-533.
21 Chao KS, Bosch WR, Mutic S, et al. A novel approach to overcome hypoxic tumor resistance: Cu-ATSM-guided intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys 2001; 49: 1171-1182.
22 Yao M, Graham MM, Smith RB, et al. Value of FDG PET in assessment of treatment response and surveillance in head-and-neck cancer patients after intensity modulated radiation treatment: A preliminant report. Int J Radiat Oncol Biol Phys 2004; 60: 1410-1418.
23 Bucci MK, Bevan A, Roach M 3rd. Advances in radiation therapy: Conventional to 3D, to IMRT, to 4D, and beyond. CA Cancer J Clin 2005; 55: 117-134.
24 Gould MK, Kuschner WG, Rydzak CE, et al. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer. Ann Intem Med 2003; 139: 879-892.
25 Bradley JD, Perez CA, Dehdashti F, et al. Implementing biologic target volumes in radiation treatment planning for non-small cell lung cancer. J Nucl Med 2004; 45 (suppl1): 96-101.
26 De Ruysscher D, Wanders S, van Haren E, et al. Selective mediastinal node irradiation on the basis of the FDG-PET scan in patients with NSCLC is safe: results of a prospective clinical study. Radiother Oncol 2004; 73 (suppl1): 135-143.