Towards Biological Target Volumes Definition for Radiotherapy Treatment Planning: Quo Vadis PET/CT?

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Abstract

This paper reviews efforts of incorporating FDG based PET/CT data into target volume delineation for radiotherapy treatment planning. Relationship between PET-based and CT-based volumes generally suffer from poor correlation between the two image data sets, expressed in terms of large statistical variation in gross tumor volume ratios irrespective of the thresholding method used. Future of biologically tailored target volumes for radiotherapy treatment planning might not be the replacement of CT or MRI based anatomical gross tumor volumes by PET based volumes. Instead, the two target volumes should complement each other into a complex mosaic of biological target volumes.

Keywords: Quantitative PET; Thresholding; Target delineation; Glycolysis

Introduction

Radiotherapy treatment planning (RTP) over the last few decades has been based on anatomical targets, namely gross tumor volume (GTV) and from it derived clinical target volume (CTV) as well as the planning target volume (PTV). Owing to its superb spatial reproducibility and the ability to provide the information on electron density (useful for heterogeneity corrections), computed tomography (CT) was, and it still represents, the backbone of modern/high technology radiotherapy treatment planning. The lack of sufficient soft tissue contrast in CT resulted in the incorporation of other imaging methods, such as the magnetic resonance imaging (MRI), into the target definition through the process of image co-registration (sometimes incorrectly termed as image fusion). Whereas the MRI has widely contributed to a better definition of the GTV, [1] which represents an anatomical volume, functional information has not been readily available in the framework of conformal 3D treatment planning and delivery in radiotherapy until recently. In addition, it has been widely accepted that a homogeneous dose delivery to the PTV is the standard of care one should pursue to achieve the best local tumor control.

Integration of positron emission tomography (PET) and computed tomography (CT) scanners [2-5] introduced a new dimension in nuclear medicine by combining functional and anatomical imaging in one machine: the PET/CT scanner. Main advantages of PET/CT scanners are:

- ✓ Improved quality of reconstructed PET images with the use of a CT map for attenuation correction of emission PET scans

- ✓ Decrease of about half of the PET acquisition time compared to the previous generation of PET scanners, which used an external radioactive source to acquire transmission scan for attenuation correction. In addition, new faster scintillation materials have also contributed to the shortening of the scanning time

- ✓ The combined medical imaging modality is likely helping management of radiotherapy patients

- ✓ Better understanding of tumor metabolic activity spatial localization by the ability to map the distribution of a specific radiopharmaceutical in co-registered PET/CT images, despite the relatively poor spatial resolution of PET image [6,7].

With an increased access to PET/CT information and an apparent appreciation that different sections of the tumor functionally do not behave uniformly, radiation oncologists started to contemplate a change in the traditional concept of uniform dose to the PTV delivery. Instead, a notion of biological targeting and dose painting has come into the play. The first question that comes to our attention is how to define the biological target volumes (BTV) and what do they represent? Ten years after the introduction of the PET/CT scanners into the radiation oncology community, target delineation in radiotherapy treatment planning using FDG-PET/CT scans still has a lot of controversy. The aim of this article is to review the limitations of the current methods for the incorporation of FDG based PET/CT data in the radiotherapy treatment planning, and discuss possible avenues to be explored in order to complement, instead of substituting, the anatomical information (CT, MRI) with the functional information (PET) into biological planning target volume (BPTV).

Thresholding Methods for Target Outlining

Incorporation of functional imaging information into the planning process, both at the level of target definition[1] as well as choice of treatment strategy, [8] is believed to open a door into molecular imaging based radiation treatment delivery [9,10]. Unlike anatomical imaging modalities (CT, MRI) that provide the anatomical extent of morphological changes within the patient body, functional imaging not only carries the spatial information of a particular functional behavior, but it can also provide a certain level of functional expression bringing the possibility for quantitative functional imaging analysis.

Available thresholding methods

While having a convincingly distinct role in the staging process, PET/CT imaging is a relatively new modality for radiotherapy target

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delineation and various guidelines have been proposed. The initial commonly used methods for tumor outlining employing PET were:

- ✓ Qualitative Visual Method (QVM); [11]

- ✓ Gross Tumor Volume (GTV)=2.5 standardized uptake value (SUV) units; [12]

- ✓ Linear adaptive SUV threshold function method; [13]

GTV=40% of local maximum uptake value (GTV_PET_40) [14].

The Qualitative Visual Method was used extensively in early attempts to incorporate PET information into the radiation treatment planning process [15-21] QVM carries personal bias and depends on the window and level set on the PET image by the person performing the target outlining.

The SUV is a useful quantity for diagnostic radiology, where the nuclear medicine specialist has to make a binary decision whether or not the subject has an abnormal uptake in a certain region of the body. However, the SUV as a quantitative expression of the functional activity was argued to be inadequate for radiation treatment planning [14]. Alternatively, for the purpose of target delineation Erdi et al. [14] recommended the use of the "signal to background (S/B) ratio" and argued that the difference between the S/B ratio and the SUV is that the S/B ratio reflects the background activity specific for each local normal tissue, rather than making an assumption that the activity is uniformly distributed over the whole body. Thus, in contrast to the SUV definition, calculation of the S/B ratio accounts for physiological differences in local normal tissue or organ density and metabolism amongst patients.

Following these attempts for target thresholding, numerous variations of the four approaches outlined above have been developed over the years.

Percentage of maximum uptake threshold methods: Based on phantom measurement data, Erdi et al. [14] proposed the use of a fixed percentage (40%) of the maximum uptake S/B value as the threshold value for the GTV definition. Despite the fact that in the same paper it was pointed out that the threshold value should not be fixed because it also depends on target size, the fixed threshold approach was adopted in many clinical studies [22-26]. This target size dependence effect has been subsequently investigated by many researchers and found to be real [27-30].

Brambilla et al. [30] reported on the role of target-to-background ratio and target size for threshold segmentation for PET target volume delineation in radiation treatment planning. They adopted a multivariable approach to study dependence of the percentage threshold used to define the boundaries of ^{18}F-FDG positive tissue on the emission scan duration, on the activity at the start of acquisition for different target sizes, and on the target-to-background (T/B) ratios. An anthropomorphic model was used to study this dependence in conditions resembling the ones that can be encountered in clinical studies. An annular ring of water bags of 3 cm thickness was fitted over an International Electro-technical Commission (IEC) phantom in order to obtain counting rates similar to those found in average patients. They found that both the target size and the T/B ratio play a major role in explaining the variance of the percentage threshold throughout the whole range of target sizes and T/B ratios examined.

Okubo et al. [31] constructed an elliptic phantom and found that when a threshold value of 35% of the measured maximum [18]FDG

activity was adopted, the sizes of PET delineation were almost the same for static and moving phantom spheres of 22 mm or more in the axial plane.

Adaptive thresholding methods: Black et al. [13] proposed an advanced adaptive threshold method for target delineation using PET images in which threshold value varies with the size of the target. However, they employed SUV, which does not represent the quantity of choice for the radiation treatment planning segmentation as mentioned previously [14]. Furthermore, Nestle et al. [32] pointed out that during DICOM transfer PET images arrive to the radiotherapy treatment planning system with uptake values (in Bq/ml) rather than SUV.

El-Bassiouni et al. [33] suggested that for head and neck cancer patients different threshold values of tumor maximum uptake ratios (THR), depending on the actual maximum uptake magnitude (S), should be used to outline PET based GTV that mimics the CT based GTV. They suggest using 20% of THR for S>30 kBq/ml, and 40% of the THR for S ≤ 30 kBq/ml.

Schaefer et al. [34] reported on the feasibility of the contrast-oriented algorithm for PET-based delineation of the GTV in primary lung cancer patients. The authors defined the image contrast as: $C=(mSUV_{70} - BG)/BG$ where BG is the mean background SUV, and $mSUV_{70}$ represents the mean SUV of the region-of-interest (ROI) surrounded by a 70% isocontour that was used to represent the FDG accumulation of each sphere within the phantom specifically designed for that study. Sizes of the spheres were chosen in such a way to cover the range of volumes commonly observed in non-small cell lung cancer (NSCLC) patients. The authors concluded that the threshold SUV value (TS) can be approximated by a linear relationship $TS=a \cdot mSUV70 + b \cdot BG,$ and then used for the delineation of PET-based GTV in lung cancer patients.

Aristophanous et al. [35] reported on the Gaussian mixture model (GMM) based segmentation technique on selected PET tumor regions for NSCLC patients. A GMM relies on the idea that any distribution, in this case a distribution of image intensities, can be expressed as a mixture of Gaussian densities representing different classes. According to their implementation, each class belongs to one of three regions in the image where they attempted to obtain the tumor volume: the background, the uncertain, and the target. The authors demonstrated that GMM gives a better congruence between PET-based and CT-based GTVs when compared to the fixed 40% maximum uptake threshold method.

Li et al. [36] reported on a PET tumor delineation method based on adaptive region-growing and dual-front active contours. First, a region of interest is manually drawn by a radiation oncologist that encloses a tumor. The voxel having the highest intensity in the ROI is chosen as a seed point and an adaptive region growing algorithm successively appends to the seed point all neighboring voxels whose intensities (T) are larger or equal to the mean of the current region. Change in T from 100% to 0% signifies a sharp volume increase, indicating the transition from the tumor to the background. A preliminary tumor boundary is determined just before the sharp volume increase, which was found to be slightly outside of the known tumor in all tested phantoms. A novel dual-front active contour model utilizing region-based information is then applied to refine the preliminary boundary automatically. The authors tested the applicability of the method by comparing the PET based volumes to the known phantom volumes, or the CT based GTV on patient data.

Iterative thresholding methods: Van Dalen et al. [37] proposed a novel iterative method for tumor delineation and volumetric quantification with FDG-PET using background-subtracted relative-threshold level (RTL). The method is based on a convolution of the point-spread function and a sphere with a certain diameter. Phantom data validated that the theoretically optimal RTL depends on the sphere size: RTL=40% (D=15−60 mm), and RTL>50% for small spheres (D<12 mm).

Drever et al. [38] proposed another iterative threshold segmentation method for PET target volume delineation. A phantom study employing spherical targets was used to determine local (slice specific) threshold levels which produce correct cross-sections based on the contrast between target and background. Functions were fit to this data and used to construct an iterative threshold segmentation algorithm. Iterative threshold segmentation was applied using both an axial and tri-axial approach to the spherical targets and also to two irregularly shaped volumes. Of these two approaches, the tri-axial method proved less susceptible to image noise and better at dealing with partial volume effects at the interface between target and background. For comparative purposes, single thresholds of 28% and 40% were also applied to the spherical data sets. The tri-axial iterative method was found capable of delineating cross sections with areas greater than 250 mm^2 to within the maximum resolution possible (1 pixel width). Cross sections of less than 250 mm^2 in area were resolved by the tri-axial method to within 2 pixel widths of their true physical extent.

The above list of thresholding methods is only a brief overview of far much extensive number of various methods tested over the years with the intend to incorporate PET data in target definition for radiotherapy treatment planning [39] A more comprehensive review on this topic was recently presented by Zaidi and El Naqa [40].

PET should not be used for GTV definition

A drawback of the approaches on the use of PET data to define gross target volume is that they create a single PET-based target volume that replaces the traditional CT-based GTV. Ignoring the underlying tumor physiology in the course of radiotherapy treatment planning in the past has mainly been due to the lack of wide-spread functional imaging resources. In the very same way, current efforts to replace the anatomical information with the functional image data has had the same deficiency in excluding the two complementary sources of information on tumor anatomy and physiology. All current quantitative thresholding methods rely on phantom measurements that sample a spatial distribution of a uniformly distributed FDG within a closed and rigid volume. Such an approach resembles more the known anatomical CT-based method based on geometry rather than the real patient-specific physiological activity.

Nestle et al. [32] have shown on a group of 25 NSCLC patients that when actual patient data is used there is no correlation between any of the thresholding methods and the CT-based target volumes (which is still assumed to be the "gold" standard for radiotherapy treatment planning). Similar studies comparing different thresholding methods on NSCLC patients [41] and head and neck cancer patients [42-44] [111213] have reached the same conclusion. To illustrate the magnitude of differences in outlined PET based GTV contours using some of the methods listed above in section II A, Figure 1 shows an example of various contours on a very same PET image. While the thresholding methods illustrated in Figure 1 are based on certain theoretical and/or experimental considerations, the question that emerges from Figure 1 is: which method gives a good surrogate for CT based GTV?
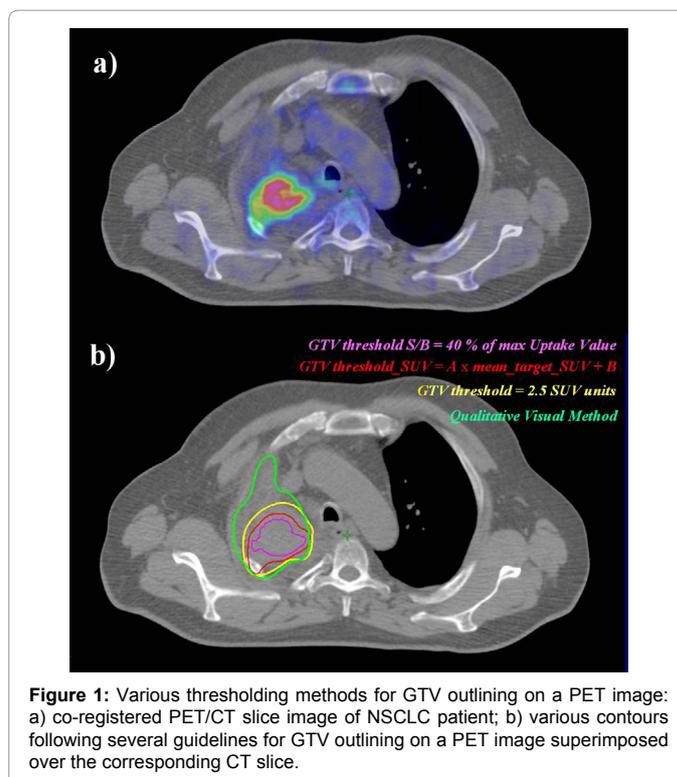

Figure 1: Various thresholding methods for GTV outlining on a PET image: a) co-registered PET/CT slice image of NSCLC patient; b) various contours following several guidelines for GTV outlining on a PET image superimposed over the corresponding CT slice.

Functional Information in Radiotherapy Treatment Planning

Since PET/CT data became readily available to the radiation oncology community, a number of papers have been reporting on the possible changes in CT-based GTV definition. Majority of publications that deal with the incorporation of PET data into radiotherapy treatment planning give an *ad hock* impression that GTV_PET leads to a better tumor definition and consequently the treatment outcome [45]. We do understand that there may be changes in the GTVs, but we still do not know the clinical implications of those changes.

PET/CT scanning protocols for radiotherapy treatment planning

Patient positioning: If a PET/CT scanner is intended to acquire images that will be subsequently used for RTP process, the minimum such a scanner must have is a flat couch table top, and external wall lasers. It is also assumed that patients would be positioned and scanned in the treatment position. Consequently, patient positioning on the flat table top should be performed with the help of radiotherapy technologist in charge of CT-simulations within radiotherapy departments. In daily practice, CT-scan from the PET/CT scanner is not usually used for RTP and the process of radiotherapy CT-simulation is accompanied by the creation of various immobilization accessories. Since additional CT-simulation is commonly performed in addition to the PET/CT scan, it is preferable to perform the CT-simulation within radiotherapy department first and then the PET/CT scan, usually within the Nuclear Medicine department. It is also recommended to have the two scans performed on the same day. Following such a workflow, patient that had a CT-simulation first, would move with immobilizing device to the Nuclear Medicine department, together with the radiotherapy technologist, who would then position the patient in the same way as

during the CT-simulation. Later on, two CT scans would be used for cross-correlation between PET images and the planning CT images obtained from the CT-simulator. While the flat couch on a PET/CT scanner would provide the same geometry of the patient's position as in the case of CT –simulation, and later on treatment, the wall lasers will further help in patient positioning and consequently cross-correlation between two CT image data sets.

Scanning protocols: The primary goal of the PET/CT combination is the accurate anatomical localization of the functional imaging information, represented in the form of the co-registered PET/CT image. Being reconstructed within the almost identical spatial volume, it is usually referred that PET and CT images share the same DICOM coordinates and the image co-registration becomes fairly straightforward process. However, PET/CT scanner is primarily a Nuclear Medicine diagnostic tool, and in most PET/CT scanners the scanning protocols have flexibility towards the PET scans, while the CT scans are commonly performed following one protocol (full body protocol) without flexibility in changing the scanning parameters. The technique of the CT scan on the PET/CT scanner is usually fixed to one kVp value (usually 120 kVp or 130 kVp), even one mAs setting (irrespectively of the patient size), one scanning resolution and fixed slice thickness (values depend on manufacturer), one reconstruction filter, etc.

On the other hand, various CT protocols have been developed for radiotherapy CT simulators over the years to accommodate various needs for different treatment sites and treatment techniques. These protocols are made based on optimal image quality for a given anatomical site as well as the CT image spatial resolution (slice thickness and axial pixel size) governed by the type of the radiotherapy treatment (e.g., conformal, brachytherapy, radio-surgery, etc.). Since the use of PET/CT scanners is primarily dedicated for the diagnostic purposes (predominantly governed by PET scan protocols) the need for undertaking both PET/CT and a CT-simulation scans for treatment planning purposes is justified.

Clinical implementations

Lung carcinoma patients: Giraud et al. [46] reported on the impact of FDG-PET based coincidence mode dual-head gamma camera images co-registered with the planning CT images for 12 NSCLC patients. The radiation oncologist outlined the target volume on the CT images first and then altered (if necessary) these volumes based on the PET/CT co-registration. If one believes that the PET is always right, image co-registration of the anatomic and the metabolic data changed the lymph nodal staging of 4 patients and the distant metastases staging for 1 patient. In these 5 patients, the DVH revealed that the lung volume irradiated at 20 Gy (V20) was decreased by an average of 22.8%, and tumor volume irradiated at the 95% isodose (V95) was increased for two patients (by 22% and 8%), and was decreased for 3 patients (by an average of 59%) after image co-registration. No difference in terms of V20 and V95 was observed for the other 7 patients. No attempt to modify primary GTV using any of the thresholding methods was exercised.

Bradley et al. [47] reported on the RTOG 0515 trial and also found no significant difference in the number of involved nodes (2.1 vs. 2.4), the V20 (32% vs. 30.8%), and the mean esophageal dose (28.7 vs. 27.1 Gy), however the nodal contours were altered by PET/CT for 51% of patients.

Van Loon et al. [48] reported on the impact of [18]FDG-PET based

radiation planning of mediastinal lymph nodes in limited disease small cell lung cancer. They concluded that FDG-PET information changed the treatment field in 5 patients (24%). In 3 patients, this was due to a decrease and in 2 patients to an increase in the number of involved nodal areas. They have also reported that there were no significant differences in gross tumor volume (GTV), lung, and esophageal parameters between CT- and PET-based plans.

Saura et al. [49] studied the pattern of local failure by using FDG-PET scans after radiotherapy in NSCLC patients treated with definitive RT whose GTVs were defined with the aid of pre-RT PET data. At lower doses, the pattern of recurrences was mostly within the GTV, suggesting that the dose might have been a factor for tumor control. At greater doses, the treatment failures were mostly at the margin of the GTV. This suggests that visual incorporation of PET data for GTV delineation might be inadequate, and more sophisticated approaches of PET registration should be evaluated.

Head and neck patients: Ciernik et al. [18] were first to report on the possible change in the GTV when FDG-PET information is used for the treatment planning process. Thirty-nine patients presenting with various solid tumors were investigated. CT and a FDG-PET were obtained in treatment position in an integrated PET/CT scanner, and co-registered images were used for treatment planning. First, volume delineation was performed on the CT data. In a second step, the corresponding PET data were used as an overlay to the CT data to define the target volume. Delineation was done independently by two investigators, employing the Qualitative Visual Method. The GTV increased (by 25% or more) because of PET in 17% of head-and-neck cancer cases (2/12). The GTV was reduced by more than 25% in 33% of patients with head-and-neck cancer (4/12. Overall, in 56% (22/39) of cases, GTV delineation was changed significantly if information from metabolic imaging was used in the planning process. PET may be useful to select patients with true localized disease. In 16% of cases, PET/CT revealed distant metastases, changing the treatment strategy from curative to palliative.

Nishioka et al. [50] reported the benefits of incorporating the FDG-PET information into treatment planning of 21 head-and-neck carcinoma patients. The GTV volumes for primary tumors were not changed by image co-registration in 19 cases (89%), increased by 49% in one, and decreased by 45% in another patient. Normal tissue sparing was more easily performed based on clearer GTV and CTV determination on the co-registered images. In particular, parotid sparing became possible in 15 patients (71%) whose upper neck areas near the parotid glands were tumor-free by [18]FDG-PET. These authors did not attempt to change the primary tumor size by thresholding methods.

Paulino et al. [51] reported on a cohort of 40 head-and-neck patients that PET-based GTV was smaller, the same size, or larger than the CT-based GTV in 30 (75%), 3 (8%), and 7 (18%) cases respectively. Patients were treated with Intensity Modulated Radiation Therapy (IMRT) and plans were obtained using the CT-based GTV. For contours involving the FDG-PET data, the 50% intensity level relative to the tumor maximum was used to delineate the borders of the PET-based GTV. The authors have also performed a retrospective dose calculation study over the same patient cohort using PET-based GTV concluding that in approximately 25% of the patients, the PET-based GTV received less than optimal prescribed dose.

While lung and H&N cancer patients are dominating PET/CT studies for the incorporation of the functional data into RTP process,

today there is virtually no anatomical site where an attempt to use PET data for target definition has been tried for the radiation planning. The common point in all these retrospective studies comparing PET based versus CT based GTVs is that it is not known if those changes in the target volumes would also reflect changes in the outcome. On the other hand the number of reported prospective studies is limited. Wanet et al. [52] reported on the study carried on to validate a gradient-based segmentation method for GTV delineation on FDG-PET in NSCLC through surgical specimen, and to compare the results to other PET threshold-based approaches and CT. They concluded that FDG-PET improved the GTV definition in NSCLC when the primary tumor was surrounded by modifications of the lung parenchyma. However in other cases the conventional mediastinal windowed CT image remained appropriate for the GTV definition.

Current status

Thus far, we believe that the common practice of comparing the GTV_CT to the GTV_PET [32,43,44] is not straightforward and one should be careful with the usually only hypothetical representations of the results commonly obtained in retrospective studies. Reasons for this difficulty are: different nature of the two imaging modalities, poor correlation between the two image data sets expressed in terms of a large statistical variation in the GTV ratios irrespectively on the thresholding method used [32,41]. However, there are two major clinical aspects of the FDG-based PET data incorporation into radiotherapy treatment planning process. The first, is at the level of the inclusion and/or exclusion of the proximal nodes into CTV for both NSCLC and head-and-neck cancer patients. Although the PET provides localized and valuable information, detected nodes (by PET) are still being outlined on the CT data set. The second important aspect of the PET data impact on radiotherapy treatment planning is a change in the treatment strategy from curative to palliative if the functional modality reveals distant metastasis [9]. There is an additional aspect of the PET information on the radiation therapy target definition in the case of NSCLC patients indicated by the presence of atelactasis. However, in so far we were not able to find in the available literature any report on clinical use of the modified GTV by any PET thresholding method. At this time, there are only retrospective dosimetric studies that compare dose volume histograms of actually delivered radiotherapy treatment plans using CT-based GTV and hypothetical treatment plans based on modified PET-based GTV.

Thus far, clinical and phantom studies did not result in clear guidelines on how to incorporate PET data into RTP process. MacManus [53] suggests that the "best judgment" of the radiation oncologist is the guideline to be followed for the GTV definition using PET in patients with lung cancer. In a subsequent review, Nestle et al. [54] stated that "... at this time we can only rely on the qualitative visual approach interpreted by a well-trained nuclear medicine specialist." These recommendations, however, deny the specific role of the quantitative physiological information contained in functional images such as FGD-PET that could have a role in the radiotherapy treatment planning.

Future of Incorporating Biological Information into Radio Therapy Treatment Planning

Anatomy vs. physiology

Figure 2 illustrates a PET/CT slice at the same thoracic location for one NSCLC patient. Figure 2a shows the profile of a line taken through the tumor volume on the CT image, while Figure 2b shows the FDG uptake profile taken through the very same line on the PET image. The FDG-PET data, showing a gradual increase while moving from healthy tissue into the tumor, cannot achieve clear tissue contrast between tumor and healthy lung. In addition, the zigzag type of the FDG uptake profile illustrates the physical realm of the relatively poor PET image spatial resolution in conjunction with the partial volume effect (PVE), and the difference in the spatial accuracy between the two imaging modalities (Figure 2b).
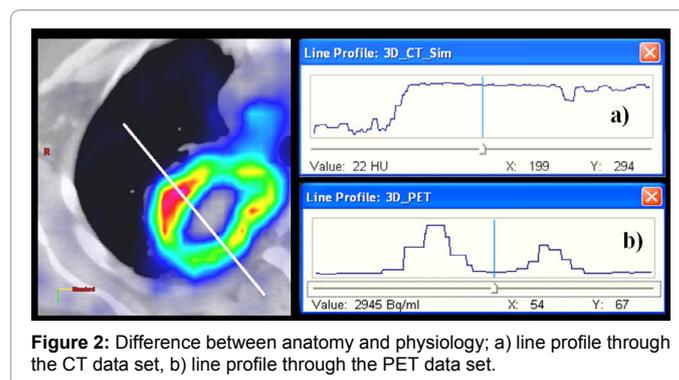
The CT image is recorded in a fraction of a second (especially on a multi-slice CT scanner) and the PET image is acquired with a 3-5 minute acquisition time per bed position. This means that in the case of lung tumors, the CT image is giving us a more of an extent of the actual tumor volume, while the PET image resembles more a clinical target volume that incorporates the tumor motion into its extent. However, this characteristic of time integrated PET image acquisition would not be beneficial for radiotherapy treatment planning purpose once gated or 4D PET acquisitions [55-57] become part of nuclear medicine protocols to obtain PET data for functional target definition in NSCLC patients, followed by gated treatment beam delivery.

Figure 2b also illustrates highly heterogeneous distribution of the FDG uptake throughout the gross primary tumor volume. Based on NSCLC tumor models, [58] it is reasonable to speculate that these variations in the PET line profile could represent indicators of proliferating, [59] glycolytic, [60] hypoxic, [61-63] and necrotic regions within the whole tumor volume. If that is the case, the information seen in Figure 2b should not be used just to replace the information provided in the Figure 2a. The two imaging modalities (anatomical and functional) should complement rather than exclude one another.

While the complementation of the PET and CT data into radiotherapy treatment planning is becoming evident and accepted, [64] methods to actually put this amalgamation in place are not apparent yet. One of the possible scenarios, elaborated by Ling et al. [65] would be creation of biological sub-volumes embedded within previously defined gross-tumor volume. However, such an approach would require deeper understanding of the signals created by various radiopharmaceuticals and metabolic activities of its tracer component on both cellular and tissue level.

Potentials of FDG as a radiopharmaceutical for radiotherapy treatment planning

Various radiopharmaceuticals have been proposed to map different stages of metabolic activities within a cancer volume. The important ones include hypoxia markers (FMISO, FAZA, Cu-ATSM, and others), [66] proliferation markers (C-11-L-methionine, 2-[C-11]-thymidine, F-18-FDOPA), [67,68] necrosis marker (F-18-labeled

Figure 2: Difference between anatomy and physiology; a) line profile through the CT data set, b) line profile through the PET data set.

5-fluoropentyl-2-methyl-malonic acid), [69] apoptosis markers (4-[18F]fluorobenzoylannexin V, Cu-DOTA-Annexin V), [70] and angiogenesis markers (RGD-peptides, 15O-H2O) [71,72]. However, the use of these uncommon radiopharmaceuticals has been limited to a small number of academic centers, and it will take time until one of them becomes a PET marker that maps one physiological process important for the definition of a biological sub-volume.

Recently, interest in tumor metabolism has been revived partly as a result of the widespread clinical application of PET using FDG. In a report by IAEA, [73] it was concluded that the glucose analog tracer [18F]-2-fluoro-deoxy-D-glucose (FDG) is still the most valuable pharmaceutical for radiation oncology and also the most widely available for radiation oncology patients. Thus, it is reasonable for now to concentrate the eventual future potentials of PET with this particular radiopharmaceutical, which should extend far beyond the definition of only the tumor boundaries.

FDG-based PET imaging has confirmed that most primary and metastatic cancers show a significantly increase in the glucose uptake when compared to normal tissues. A common property of cancer cells is up-regulation of glycolysis resulting in an increased glucose uptake, which can be observed by clinical tumor imaging. Glycolysis involves the conversion of glucose to pyruvate and then to lactic acid, the waste product. In non-cancerous cells, mitochondrias oxidize pyruvate to carbon dioxide and water in the presence of oxygen and the glycolytic reaction is inhibited (Pasteur Effect) [74] Conversion of glucose to lactic acid, even in the presence of oxygen is known as aerobic glycolysis or the Warburg effect [75] and represents a hallmark of invasive cancers. Warburg's hypothesis that cancer results from impaired mitochondrial metabolism has been shown to be incorrect, but the observation of increased glycolysis in tumors, even in the presence of oxygen, has been repeatedly verified [76].

Glycolysis (either anaerobic or aerobic) is a highly inefficient process producing only two adenosine-three-phosphate (ATP, representing basic cellular fuel) molecules, whereas complete oxidation produces 38 ATP molecules per glucose molecule. In addition, metabolic products of glycolysis, such as hydrogen ions, cause consistent acidification of the extra cellular space, which might result in increased local toxicity. Nevertheless, even in the face of these drawbacks, cancer cell populations consistently evolve to the inefficient and potentially toxic glycolytic phenotype. Gatenby and Gillies [60] proposed that the consistent expression of up-regulated glycolysis is not accidental, but represents a solution to the environmental growth constraints during tumor development. Transport enzymes of the Glut and hexokinase families are up-regulated in tumor cells expressing the glycolytic phenotype, and the level of Glut-1 glucose transporter expression has been shown to correlate with [18F] FDG uptake in non-small cell lung cancer [77].

Different poor prognostic signs of hypoxic cells including radio-resistance, metastatic phenotype, detriment to the overall patient's survival have been well documented [78-80][171819] making tumor hypoxia one of the most investigated areas for biologically targeted treatment planning [81-83].[202122] Several studies have reported that tumor cells respond to reduction in oxygen tension by an increased level of glucose uptake [78-82]. Given the radio-resistance of the hypoxic cells, identification of this sub-population, located within the larger glycolytic phenotype volume, [84] could be of value in terms of dose painting treatment delivery.

Future aspects and potentials

According to recommendations suggested by Ling et al. [65], and later adopted by others, [85-87] a GTV defined by inherently low spatial resolution functional imaging such as PET should not be a surrogate for a GTV_CT, which has a superior spatial resolution necessary for dose pin-pointing in the future biologically-based dose painting radiotherapy treatment. The incorporation of regions with increased FDG uptake (indicative of the glycolytic phenotype) as the glycolytic BTV within the GTV_CT may allow escalated radiotherapy doses to part of the tumor and lead to a better outcome for NSCLC patients referred for curative radiotherapy [19,88,89]. The use of BTV in dose painting treatment delivery is attractive because it increases the dose to targets considered to require higher doses. At the same time, dose painting could reduce the dose to critical organs that limit the dose escalation approaches in NSCLC treatment. However, the dose painting approach implies deviation from the traditional uniform dose target coverage approach, with the intention of achieving better surrounding tissue sparing and ultimately allowing for dose escalation protocols relying on biologically-based treatment planning.

One possible scenario for BTV definition using FDG as a radiopharmaceutical is depicted in Fig. 3, which represents an example of the PET axial slice containing tumor with various threshold values used to segment related contours (top-left) as well as the corresponding sub-volumes (top-right). In this particular example, the choice of the threshold values is rather arbitrary and is used for demonstrative purposes only. In line with Magritte's expression ("This picture is not an apple"), the future radiotherapy treatment planning volumes may resemble the picture given at the bottom of Fig. 3, which represents a combination of Magritte's famous painting and BTV definition elaborated by Ling et al. in their seminal paper from the beginning of this millennium [65].

Unfortunately, at this moment, the biological PTV (BPTV) is still a futuristic dream for at least three reasons. The first is the relatively poor spatial resolution of PET images (of the order of 4 mm) that is not acceptable for precise dose delivery associated with desired dose – escalation approaches in radiotherapy. Whilst the CT and MRI provide an overall spatial uncertainty of the order of 2 mm, the spatial resolution of the current commercially available PET/CT systems is more than double [90]. However, extensive research and development is currently under way aiming to improve the spatial resolution of PET images concentrating on different aspects of the image acquisition and reconstruction: partial volume effect, [91] depth of interaction,[92] scanner bed wobbling, [93] resolution modeling, [94] etc. Some time ago Siemens announced the introduction of a new HI-REZ PET/CT system that uses measured point spread function (PSF) matrix throughout the field of view (FOV) of the PET scanner to de-convolve the PET slice onto a 2 mm spatial resolution image. Clinical confirmation of this exciting advancement in PET technology is thus imminent. If proven, this will allow not only nuclear medicine doctors to better visualize and localize increased radiopharmaceutical uptakes, but also the radiation oncologist to pinpoint better certain physiological activities needed for incorporation of biologically specific sub-volumes into the BPTV.

The second problem to address before painting the target volumes as suggested in Figure 3 is a clear understanding of the quantitative PET information. Integration of quantitative PET information and underlying tumor physiology would involve precise co-registration between immunohistopathological and PET images. This in turn would allow development of tumor models that identify BTVs
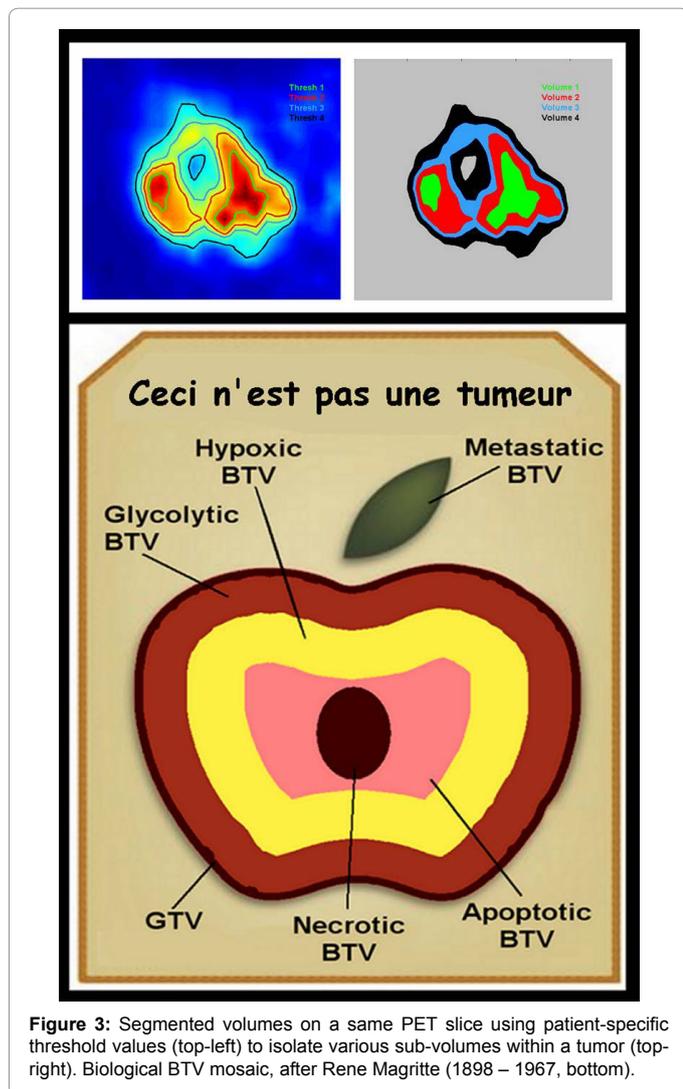
Figure 3: Segmented volumes on a same PET slice using patient-specific threshold values (top-left) to isolate various sub-volumes within a tumor (top-right). Biological BTV mosaic, after Rene Magritte (1898 – 1967, bottom).

based on characteristics influencing radio-response and mapping these interlocking BTVs might be achieved by using different radiopharmaceuticals. Systematic pre-clinical studies are needed to establish thresholding measures for every radiopharmaceutical intended for use in the future and to isolate and define specific biological processes within the scanned object (proliferation, glycolysis, hypoxia, necrosis) that could be of importance in attaining the ultimate goal of applying PET imaging data radiotherapy treatment planning. These are the physiological processes that could be of importance for the radiotherapy treatment planning, scoped with either only one (FDG) or multiple radiopharmaceuticals (such as FMISO) [95]. It should be remembered that the single intensity value for a given voxel is based on the catabolic activity of more than 10^5 cells and it is unrealistic to expect that the domains of the sub-volumes with different physiological characteristics will be defined by sharp boundaries within the tumor volume. Even if it would be possible to define certain target sub-volumes within the pre-defined GTV, these will be characterized by the relatively greater abundance of a certain type of cell or metabolic condition but this does not imply exclusion of other biological situations co-existing within the same volume. In effect each sub-volume so defined would represent a statistical sample of various possible biological entities. For example, the volume labeled as Hypoxic

would only contain regions lacking oxygen in excess to other possible cellular phenotypes (necrosis, apoptosis, proliferation, etc). In contrast, the sub-volume labeled as Glycolytic will certainly incorporate areas lacking oxygen particularly in poorly vascularized regions.

Thirdly, once a clear thresholding relation between the underlying physiology and quantitative PET signals for a given histology and particular radiopharmaceutical is established, it has to be found a correlation between tumor specific physiological process and the radiation dose that will lead to a better tumor control. These correlations are expected to become dose painting rules in the biological tailored planning target volumes.

Finally, the future BPTV should not be expected to be a static object. In lung cancer patients, as well as other cancer sites severely affected by the respiratory motion (liver, esophagus, etc), 4D PET/CT should be sought of as the prerogative for an accurate both anatomical and functional pin-pointing tool [55-57,96,97]. In conjunction with beam delivery systems equipped with Real-time Position Management (RPM) option, 4D PET/CT might open a door for dose escalation protocols [92-97].

Conclusions

This article reviews the feasibility and limitations of FDG-based PET/CT data on target volume delineation in radiotherapy treatment planning. Direct correlation of GTV_CT to GTV_PET is not only contradictory due to different nature (anatomy vs. physiology) of the two imaging modalities, but also suffers from poor correlation between the two image data sets expressed in terms of large statistical variations in the GTV ratios. Although the comparison of the PET-based volumes to the CT-based volumes is largely repeated in the current literature, replacing the GTV_CT (as defined in the ICRU 50 and ICRU 62 reports) by the GTV_PET does not seem to be the way the functional imaging should be introduced in the radiation treatment planning process. With the information available today, it seems that definition of the GTV should still be based on anatomical imaging modalities followed by the BTV definitions (as subsets of the GTV) based on functional imaging modalities. Deeper insight into the tumor and normal tissue physiology, together with the nature of the radiopharmaceutical used must be taken into account for both quantitative PET signal interpretation and its incorporation into the treatment planning process.

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