Review Article

Precision Radiotherapy: ^{18}F-FDG PET-based radiotherapy planning in Head and Neck cancers

ABSTRACT

Precision medicine is gaining importance in this era of molecular imaging where the molecular features of a disease can be noninvasively assessed and treated with personalized medicine. This is especially suited for head and neck cancers (HNCa). Early stage HNCa are ideally managed with radiotherapy (RT) or surgery. Head and neck (HN) is a complex region and its tumors respond to RT differently due to dissimilar structures and moving organs such as tongue. Radiation oncologists are always in the process of trying and investigating newer RT techniques in order to achieve precise and targetted therapy to tumour/s. One such innovation is Intensity modulated RT (IMRT) using 3 Dimensional conformal RT (3DCRT). This 3DCRT resizes the radiation beams to match the shape of the tumor. Such focused dose escalation may improve local control in HNCa. Image guided RT in conjunction with IMRT is the most advanced form of RT planning being used these days. Simulation computerized tomography (CT) images are usually incorporated into RT planning module. But limitations of CT such as poor soft tissue contrast than magnetic resonance imaging and inability to clearly define solid / cystic / necrotic areas and viable tumour exist. Functional imaging such as Positron Emission Tomography (PET) has established its superiority over CT in delineating the actual site and extent of HN tumors. A combination of IMRT with BTV (Biological Tumour Volume) may be the most ideal technique to deliver a homogeneous radiation boost to tumour. This review shall discuss PET based RT planning, challenges, practical tips, and how to optimize therapy with the least side effects to the normal surrounding tissues.

Keywords: Biological tumor volume, FDG-PET/CT, gross tumor volume, PET based RT planning

INTRODUCTION

Head and neck cancers (HNCa) account for one-fourth of all male cancers and one-tenth of female cancers in India.[1] This is mainly attributed to the use of tobacco, areca nut, alcohol, etc. Of the HNCa, oral cancers are most common, especially the squamous cell variant. More than 70% of HNCa have locally advanced disease at presentation. Head and neck (HN) region is complex, composed of several dissimilar structures, vessels, and nerves that respond differently to radiation.[2] Accurate planning of radiotherapy (RT) field is, therefore, important. Similarly, HNCa represent a diverse group of histologies and may involve adjacent soft tissue, lymph nodes, or bones that may require different doses of radiation. Structures to be included in a RT field need to be carefully planned based on disease status and multimodality imaging findings. The present method of RT planning using computerized tomography (CT) images invariably involves significant volumes of surrounding normal tissues or critical organs. Two dimensional (2D)

Padma Subramanyam, Shanmuga Sundaram Palaniswamy, Shah Pervez Numani[1]

Department of Nuclear Medicine and Molecular Imaging, Amrita Institute of Medical Sciences and Research Center, Cochin, Kerala, India, [1]Department of Nuclear Medicine, Hamad Medical Corporation Hospitals, Doha, Qatar

Address for correspondence: Dr. Shanmuga Sundaram Palaniswamy,
Department of Nuclear Medicine and Molecular Imaging, Amrita Institute of Medical Sciences and Research Center, Cochin - 682 041, Kerala, India.
E-mail: drpssundaram@gmail.com

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image information derived from conventional X-ray or CT may closely approximate tumor size but never accurate. This can result in limiting the exact radiation dose required to ameliorate the tumor or may lead to excessive dose delivery to surrounding normal tissue. 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG) positron emission tomography (PET) is a functional imaging procedure that clearly demarcates the viable tumor, its margins, and necrotic areas if any. It also highlights locoregional metastatic kymph nodes and distant metastases if any. Semiquantitative PET based software provides 3D information regarding the tumor volume and dose needed to irradiate the disease. Specific PET tracers can additionally identify areas of hypoxia, vascularity, or increased cellular proliferation. Such discordant intratumoral areas (i.e., hypoxic/less vascularity) may need higher radiation than the surrounding tumor. PET defined biological tumour volume (BTVs) can be used to determine any escalation of radiation dose or to predict the additional need of a radiosensitizer or alternative treatment strategies. Image guided RT (IGRT) planning using PET is definitely exciting and holds promise in the management of HNCa with better clinical outcomes.[3,4]

RT planning for HNCa in a PET center needs prior preparation, coordination, and teamwork. Traditionally, RT beams are delivered based on concepts of the anatomically defined gross tumor volume (GTV), planning target volume (PTV), and clinical target volume (CTV). The boundaries of primary tumors can differ significantly from one another in the same patient while using different imaging modalities (PET, CT, or magnetic resonance imaging [MRI]). The definition of the GTV is the single most important step in planning treatment,[5] especially when very high doses (70 Gray, Gy) are delivered to lesions close to radiosensitive vital structures (e.g., brainstem or optic chiasm), and margins are often drawn tightly around the primary tumor. In general, CT and MRI use differences in contrast enhancement, and difference in MR signals to demarcate tumor tissue from normal regions, each having its inherent drawbacks. The tumour delineation on anatomical imaging like CT becomes challenging in two common clinical situations; i.e during postoperative setting, the tumour margins may get confounded due to surrounding edema. The other clinical context is when patient does not undergo a contrast enhanced CT due to patient related issues like high serum creatinine, or post renal transplant recipient status. In contrast to GTV, the new concept of BTV holds promise. BTV is unaffected by these above mentioned factors. The greatest impact of PET apart from RT planning results from changes in nodal status and/or the detection of distant metastasis.[6]

VOLUMES DEFINED IN RADIOTHERAPY PLANNING

Nuclear medicine physicians must understand the various terminologies used in RT planning and how the tumor contouring is undertaken in treatment planning system by radiation oncologists. Volumes that are defined before treatment planning include GTV (Gross Tumour Volume) and CTV (Clinical Target Volume). Those defined during treatment planning process include PTV (Planning Tumour Volume) and organs at risk. The volumes described after treatment planning are the treated volume and irradiated volume [Figure 1].

Gross tumor volume

It is the macroscopic or gross extent of the tumor as determined radiologically and clinically. It may therefore vary in size and extent due to the diagnostic method used. The GTV is obtained by summarizing the area outlined by the radiation oncologist in each CT/MRI/FDG-PET section, multiplied by the thickness of each section.[5]

Clinical target volume

CTV is defined as the tissue volume that contains the GTV and subclinical microscopic malignant lesions. It is derived from the GTV by adding margins around it, to account for subclinical disease extension. It is further classified as CTV-T (for Tumour, if the same dose is prescribed to both GTV and CTV) and CTV-N (for node, if additional volumes with presumed subclinical spread, e.g. regional lymph nodes (if one or more than 1 node, N1,N2 etc).

Planning target volume

It is usually an expansion of the CTV and includes factors such as movement of organs and tissues and setup errors. PTV is a geometrical concept introduced for treatment planning

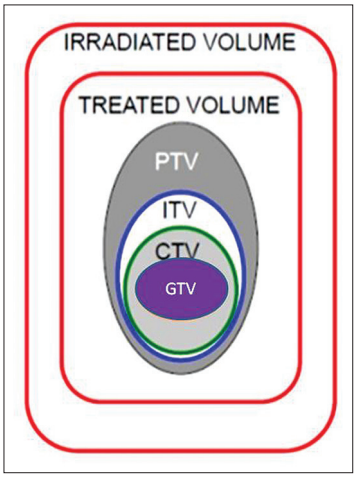

Figure 1: Different radiotherapy planning volumes (terminologies) used with pictorial color code depiction

and is determined by adding margin to the CTV to account for internal target volume (ITV) and patient motion, and the field margins are set to conform to the PTV with allowance for the RT beam penumbra and dose buildup effect.

Biological target volume

BTV is derived from PET-based FDG uptake by viewing the fused PET-CT transaxial slice. It is defined as the isodensity volume of primary tumor when adjusting the different percentages of the maximal standardized uptake value (SUV_{max}) excluding any noise or artifact from surrounding normal tissues, brain and inflammatory/physiological sites of FDG uptake. Fused PET-CT transaxial slice allows the observer to take notice of the high-contrast fused image set for the detection of lesions and at the same time use the CT to define tumor margins [Figure 2].

CHALLENGES IN RADIOTHERAPY PLANNING IN HEAD AND NECK CANCERS

Each RT treatment cycle consists of simulation, planning, delivery, and verification. The minimum requisites for initiating an active program are given below, and it also calls for an efficient execution and management by the nuclear medicine and RT departments collaboratively.

Instrumentation

Conventional RT techniques have given way to high precision-targeted therapy like IMRT.[6] A combination of high-precision RT with BTV contouring may be the most ideal form of RT.[7] IMRT involves numerous radiation beams directed to a specific tumour. Improperly specified dose constraints will result in inferior plans. With this technique, different dose prescriptions (called dose painting) to multiple target sites can be delivered. It also facilitates the boosting of high-radiation doses to the primary tumor and reduces dose delivery to radiation-sensitive tissues.

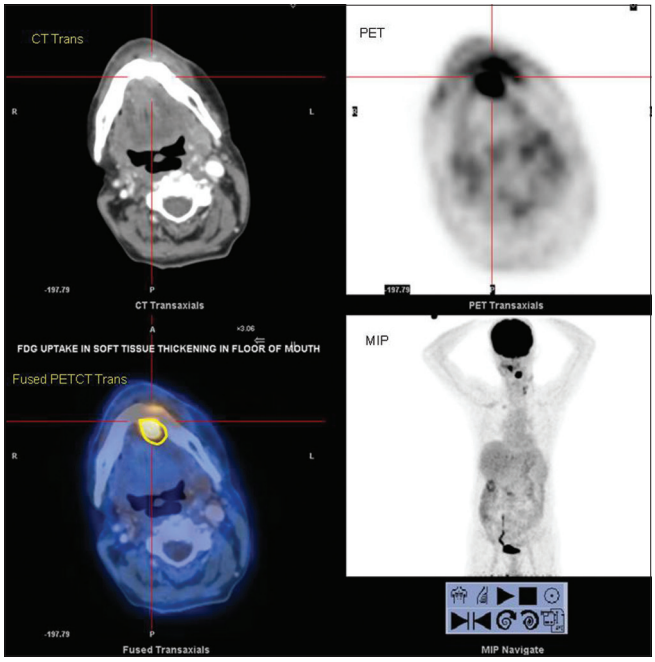

Figure 2: Transaxial PET images in a patient with floor of mouth cancer, CT barely delineating the lesion. PET-based lesion contouring has been depicted in fused image

Tumor volume delineation

A careful comparison of FDG-PET, MRI, and CT scans with the histopathology of resected tumor specimens shows that none of these three imaging modalities is totally accurate.[8] Of these, FDG-PET may be the most accurate in HNCa as it lights up viable tumor tissue.[9] Tumor volume determined by FDG-PET tends to be smaller on average than the volume determined by the other modalities but most closely approximates the true tumor volume.[10] Nevertheless, some tumor regions that are apparent on CT or MRI may not be imaged on PET, and in these cases, an exclusive reliance on PET would potentially lead to geographic miss. Consensus must be reached on the FDG SUV Max cutoff thresholds one must use for contouring.

Hardware requirements for PET based RT planning

Incorporating PET-CT images into the treatment planning process raises challenges in areas of patient immobilization, image registration, and target volume segmentation. CT simulators try to replicate all the stages of the main therapy procedure. It requires a flat table for the patient simulation with 4D infrared patient alignment laser system. The laser markers provide an exact alignment of the patient between imaging table and treatment table. Patient stabilizing equipments such as thermoplastic mask, custom-made neck cushion for a few patients, arm straps to pull shoulders down, bite blocks (to prevent movement of tongue), and bean bags (organ-specific body-contouring material) are essential to immobilize the patient during treatment planning. Therefore, these gadgets need to be prefabricated and made ready for each patient planned for PET-based RT planning. The planning system combines some of the functions of an image-based, 3D treatment planning system and conventional simulator. The simulator software allows import, manipulation, display, and storage of images from CT. Innovations such as 4D CT simulation with PET datasets[10] need additional respiratory gating gadgets to avoid motion artifacts. This allows retrospective gating of the CT simulation data using the patient's breathing cycle. Hence, the radiation oncologist defines the target and its trajectory with respect to changes in normal anatomy and critical structures due to the patient's respiratory excursions, and is highly applicable to liver/lung lesions.

Software requirements for PET-based RT planning

Software systems that support RT planning use image registration and fusion to propagate the dose from 3D treatment images back to a reference (planning) geometry. This enables the detection of anatomic and functional changes that might elicit changes in the treatment plan or prescription, and provide the up-to-date estimates of delivered dose.[11] Image registration and segmentation need specialized software.

IMAGE REGISTRATION IN RADIOTHERAPY PLANNING SYSTEM

PET and CT images are DICOM (Digital Imaging and Communications in Medicine)-formatted images. DICOM is a standard format for transmitting, converting, and associating medical imaging data between medical systems. A patient is

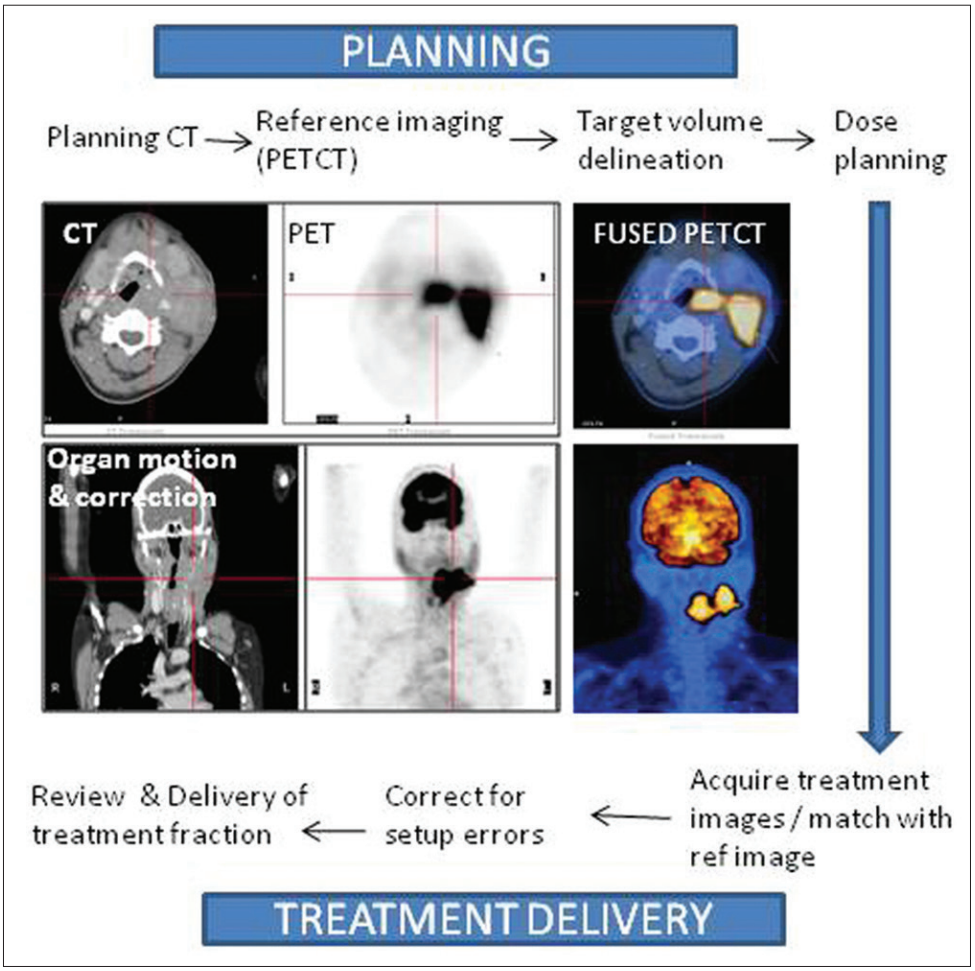

Figure 3: Image registration and steps for incorporating PET-CT images into RT planning system

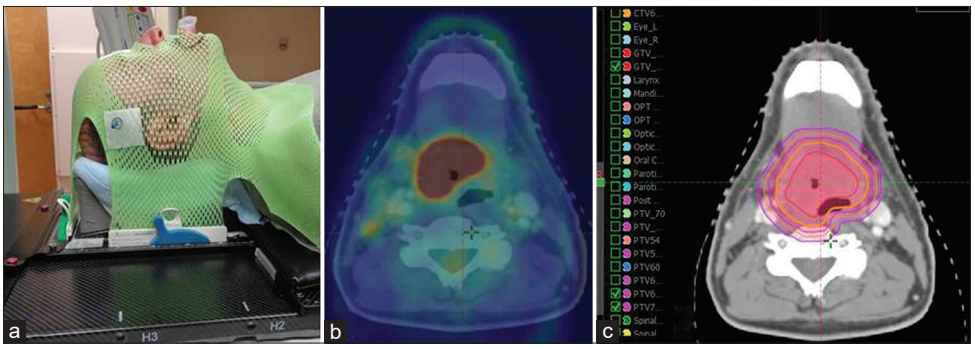

Figure 4: (a) Ideal positioning of PET-based RT planning patient on a flat table covered with a thermoplastic mask and bite block; (b) transaxial PET image showing a large FDG avid lesion involving right tonsillar fossa and posterior aspect of right side of tongue crossing the midline; (c) PET guided GTV contouring of the primary lesion on regional image data sets

usually aligned to the scanner's coordinate system by lasers or other positioning devices. Images acquired from different scanners need to be registered in the same anatomical plane by one of these techniques: manual, landmark-based, surface-based, and volume-based methods. Multimodality images (PET-CT/MR) need to be accurately aligned, checked for organ motion. Once verified and motion corrected, the margins of target lesion/s (as per SUV based threshold specified) is drawn for accurate dose computation. The images may be aligned either by the geometrical features (point-like anatomic features or surfaces) or intensity similarity measures such as mutual information (MI).[12] The image that is being matched is typically called the fixed or target image. The image that is moving its coordinate system to match the fixed image is called the moving or floating image. In this situation, PET image is the moving image and CT is the fixed image. After the lesion/s in PET-CT images are contoured for RT planning, the final images are fed into the RT planning system for dose delivery [Figure 3].

IMAGE (TARGET) SEGMENTATION BASED ON SUV THRESHOLDS

Image segmentation[11] is an important parameter and this can increase the accuracy and reproducibility of target volume delineation. This can be highly variable and calls for an institutional protocol combining teams- nuclear medicine physicians, and radiation oncologists. PET images may be interpreted visually and quantitatively. PET volume segmentation may be based on a selected SUV cutoff or percentage of maximum threshold [Figure 4]. One can use different percentage cutoffs,[13] for example, 40% and 42% maximum intensity thresholding to define the tumor boundary from the fused FDG-PET transaxial images. This method can be implemented for manual contouring as well as automated tumor contouring on PET images. Once the threshold has been fixed and set in any one of the commercially available RT programs in PET workstation, such as PET–Volume Computer-Assisted Reading (PET-VCAR), all lesions above this threshold limit will get highlighted.

ADVANTAGES AND DISADVANTAGES OF PET BASED RT PLANNING

PET can reveal targets that are not well visualized by CT and MRI. FDG identifies areas of viable tumor, especially those with ill-defined margins. SUV (a glycolytic numerical marker) based thresholds for lesion contouring helps in avoiding irradiation to surrounding benign sites of FDG uptake. Visual and quantitative depiction of tumor/metastatic lymph nodes may not be always possible using CT or MRI. Especially in

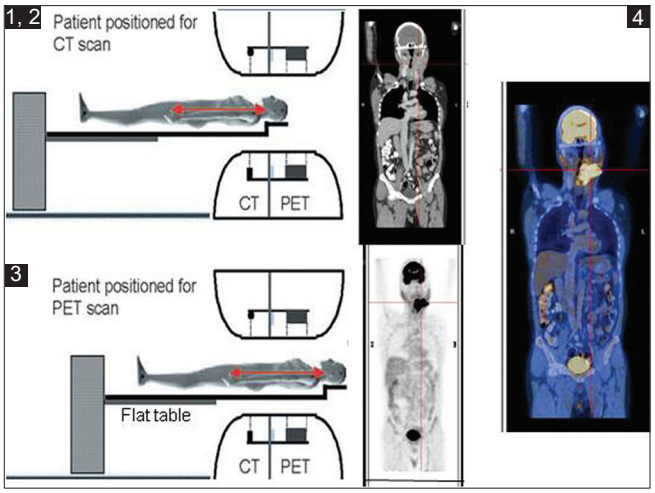

Figure 5: A standard PET-CT patient positioning and acquisition protocol is depicted (1) Following FDG inj and uptake, the patient is positioned for the CT scan a scout image is acquired (10 s). (2) CT imaging is acquired and reconstruction begins (60 s). (3) While CT reconstruction completes, the patient is automatically positioned for the PET imaging. PET attenuation correction factors are computed. Usually 7-8 bed positions are acquired for each patient during wholebody PET acquisition starting from thigh end of the table. For RT planning, an additional regional PET-CT (region of interest) acquisition with flat table is performed. Reconstruction is done for each bed position. 4) Whole body CT, PET and fused PET-CT images are reviewed (cross hair marker denotes the nodal mass in left cervical station) for nodal / metastases evaluation

HNCa, lymph nodal deposits need to be incorporated into the RT field, if detected. In addition, PET provides a possibility that subregions within the tumor can be targeted selectively with higher radiation doses.[14] It reduces the interobserver variability in GTV delineation and identifies parts of the GTV potentially requiring an additional radiation dose. PET using special tracers also additionally allows direct evaluation of tumor cell proliferation, apoptosis, hypoxia, and angiogenesis, which is otherwise not possible by anatomical imaging. However, the use of ^{18}F-FDG PET also bears some disadvantages: the limited spatial resolution, the lack of a standardized method for signal segmentation, and false-positive FDG-PET uptake in sites corresponding to inflammation, trauma etc.

PETCT IMAGING PROCEDURE

Most of the patients referred for PET-based RT planning may have already undergone a variety of conventional imaging and histopathological confirmation of harboring malignancy. Therefore, setting up an initial PET-CT imaging for RT planning is logical. Such scans are called simulation scans because they emulate the treatment position. A diagnostic whole body PET-CT imaging (head to mid-thigh) [Figure 5] is performed in euglycemic status. This is followed by a dedicated regional PET-CT imaging for lesion contouring while patient is placed on a flat table. 0.1 mCi/kg body weight of ^{18}F-FDG is injected through an indwelling IV cannula. Imaging is started 60 min later. CT is completed first followed by PET imaging (imaging starting

from pelvis toward head). PET images are reconstructed to 3.75-mm slice thickness. The CT images are reconstructed to 2.5 mm slice thickness. Once all datasets have been acquired, the simulation PET and CT image sets are sent to the respective workstation for tumor contouring [Figure 4]. Various vendor specific image analysis software packages and dedicated computer workstations are now available for determining tumour volume. (e.g.) PET-VCAR, Advantage Sim Workstation GE PET-CT. This software aids in diagnosing, staging, providing contours for treatment planning and monitoring treatment response. In the past, PET derived tumor contouring was mainly based on the applicator's choice of threshold. Arbitrarily different SUV threshold cutoff values have been tried (e.g., 40% and 50%), depending on the background signals. PET-VCAR performs the task automatically or by manual contouring. It highlights and bookmarks PET-defined regions of interest based on user-defined threshold settings [Figure 4]. The software can be used for visualization and analytical monitoring of disease progression or response to treatment using a multi-examination comparison. The PET-VCAR display option panel allows the user to set the following:

1. The percentage threshold algorithm
2. Fixed threshold algorithm.

Usually, limits for the percentage threshold algorithm are 40%, 42%, and 45% of SUV_{max}. For fixed threshold, it is visually as per SUV_{max} 2.5, 3, 3.5, and 4.

DISCUSSION

The simplest method, which is widely used, is the visual interpretation of the PET images and manual definition of contours as judged by senior nuclear medicine physicians and / or radiation oncologists. Another method is using percentages of the maximum SUV. Published methods are based on a threshold determined as a percentage of the maximum SUV ranging from 15% to 50%.[13] We have used vendor-recommended thresholds of 40% and 42% in our series of 24 early oral cancers patients with good clinical outcome. The reported variability of threshold values for lesions of different volumes indicates that there is no standard value applicable to all patients and that techniques for setting individual thresholds need to be defined and standardized. Although many have used a percentage of the maximum SUV intensity to define a tumor on PET, it has been suggested that this threshold algorithm is inadequate for target volume definition and tends to underestimate target volumes. Only the contoured target will receive the prescribed radiation dose.

24 patients of early oral cancers who underwent PET-based RT planning in our center between 2015 and 2017 were analyzed. Automatic versus manual contouring of target volumes were compared. We found that GTV-PET volumes were higher than the GTV-CT volumes in 22 patients using both methods. This overestimation of GTV PET volumes in our study may be linked to aggressive tumours with ill defined margins. Fixed thresholds of SUVs were assigned. GTVF2 and GTVF3 (fixed SUV thresholds at 3.0 and 3.5 g/ml) correlated well with GTV-CT for the respective lesion. GTVF2 matched the GTV-PET. The mean GTVF2 volume for HNCa was found to be 30.78 ml that is comparable to other studies.[15] Volumes obtained using percentage threshold algorithms showed no statistically significant correlation with the manual contouring techniques.

Paulino *et al*.[15] studied the change in target volume with the addition of PET data. 40 patients with HNCa underwent IMRT planning. GTVs using PET were delineated using a 50% SUV relative to tumor maximum. The median CT-based GTV was 37.2 mL compared with 20.3 mL in the PET-based GTV. The PET-GTV was smaller in 75% of the cases, with the largest difference being a CT-GTV to PET-GTV ratio >5.0 in 7 patients.

Schinagl *et al*.[16] compared five different methods of FDG PET signal segmentation; visual interpretation, 40% and 50% of the maximum tumor signal intensity, fixed SUV of 2.5, and the signal-to-background ratio method in 78 patients with HNCa. Their findings reveal that the volume and shape of the resulting GTV were heavily influenced by the choice of the segmentation tool. Visual interpretation of the PET signal yielded volumes close to those of CT-based GTV delineation, whereas all automated segmentation methods resulted in significantly smaller GTVs than the GTVs based on clinical information and CT alone. Furthermore, in a large percentage of patients (between 29% and 64%, depending on the segmentation tool used), more than 20% of the ^{18}F-FDG PET-based GTV was located outside the GTV based on clinical information and CT. This suggests that tumor could be identified by ^{18}F-FDG PET that was missed using the standard methods of GTV delineation.

Mees *et al*.[17] showed promising results of dose-painting capability of IMRT with hypoxic PET agents. A higher radiation dose can be delivered to tumor subvolumes that may be more radioresistant. FDG-avid regions in the tumor have been shown to be correlated with hypoxia that is associated with tumor radioresistance. Machtay *et al*.[18] studied the potential prognostic significance of pretreatment FDG-PET SUV in squamous cell carcinoma of the HN in 60 patients. They found that higher pretreatment SUVs are associated with worse treatment outcomes, including a worse disease-free survival and a decrease in local control. Similarly, researchers have

investigated the use of PET imaging to define a subvolume for dose escalation.[19]

FDG PET-based BTV dose delivery is easy to perform and ideal in HNCa offering higher cure rates and least side effects. Time, patience, and teamwork are necessary to standardize the institutional PET-based RT planning protocol. By integrating PET-based RT workflows, one can achieve a similar patient position between modalities, reducing error-prone deformable registration. Lesion contouring is possible and transferable, reducing the inaccuracies in RT plans. PET can titrate the dose delivered with respect to adjacent critical structures. Finally, a single imaging workflow can be employed for both PET and RT planning, thereby reducing time, money, and radiation exposure to patients. More importantly PET can change/modify the RT plan if regional or distant metastases are detected. The gold standard for validating a threshold technique for tumor definition would be a comparison with histologic specimens, which is not possible in all cases.

Limitations of PET-based radiotherapy planning

1. PET-defined lesion contouring: One needs to have predefined window and color settings based on the input from the nuclear medicine physician. This will delineate the tumour and its extent with high reproducibility. These manoeuvers are critical in accurate target volume delineation. Automated methods of image contouring have a common inherent weakness, an inability to distinguish between ^{18}F-FDG uptake caused by neoplastic etiology from various common physiological and inflammatory states.
2. Difficulties in determining the exact location of the "edge" of the lesion in 3D spaces. It is important to determine the edges of lesion which is crucial for RT planning. "Edge" appearance is influenced strongly by factors that are directly linked to the size and shape of target volumes.
3. Modifications in PET detector design and electronics: Older versions of PET-CT systems had smaller bore size. making RT planning using PET imaging difficult. Increase in bore size to 70 cm and improvement in electronics of PET scanner (removing statistical fluctuations and erroneous definition of the threshold and cutoff levels) and reconstruction/correction software algorithms have made PET-based tumor contouring a reality.

CONCLUSION

FDG PET-CT is likely to revolutionize radiation treatment planning and tumor response assessment following radiation therapy of many common cancers. Standard anatomical imaging modalities used to select and delineate RT target volumes can be enriched by the information on tumor biology gained by PET-CT. PET volumes are significantly smaller than the other anatomical imaging modalities, allowing highly precise targeted RT to achieve the highest tumoricidal effect. In this review, the promising role of PET-CT in RT planning of HNCa is highlighted. PET-based target volume delineation can optimise and achieve a dose escalating tumoricidal effect especially in patients with tumour heterogeneity.

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Conflicts of interest

There are no conflicts of interest.

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