A new role of PET/CT for target delineation for radiotherapy treatment planning for head and neck carcinomas

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Abstract

Fluorine-18-fluorodeoxyglucose- positron emission tomography (^{18}F-FDG PET) in head and neck cancer patients is useful for staging, identification of macroscopic disease, detection of invaded lymph nodes and distant metastases, delineation of radiotherapy target volume and assessment of treatment response. This brief review addresses the potential role of PET in radiotherapy planning as compared to MRI and CT scan. Positron emission tomography is considered by radiation oncologists a useful test for the identification of the specific target volume for treatment. In addition, a number of hypoxia-related PET radiopharmaceuticals such as the fluorine-18-fluoromisonidazole (^{18}F-FMISO) and the fluorine-18-fluoroazomycin arabinoside (^{18}F-FAZA) are now available in order to identify hypoxic tumor subvolumes helping to implement new radiotherapy techniques. Magnetic resonance imaging (MRI) has the advantage to discriminate the soft tissue contrast from the tumor, against computerized tomography (CT), but PET/CT scans have the additional advantage to incorporate the metabolic imaging for improving the delineation of variable and hypoxic tumor tissue in the head and neck region. Regardless of the method used for determining the gross tumor volume, clinical examination remains irreplaceable. In conclusion, PET/CT offers complementary information for the delineation of the primary tumor and the corresponding lymph nodes compared to the use of MRI and CT and can support the use of modern radiotherapy techniques, having fewer toxicities.

Introduction

Fluorine-18-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET) has been used in head and neck squamous cell carcinoma (HNSCC) patients for staging, identification of macroscopic cancer disease, for the detection of metastatic lymph nodes, distant metastases and for the assessment of treatment response [1, 2]. Avoiding unnecessary radiation of normal tissues may allow dose escalation in intensity modulated radiation therapy (IMRT). Due to the high radiation dose administered in IMRT, the localization of the primary tumor and of the cervical lymph nodes metastases is quite important [3, 4].

Currently, computed tomography (CT) assisted volume definition remains the gold standard for radiotherapy planning. However, CT scans are limited by soft tissue resolution, dental artifacts and may fail to clearly identify critical normal structures like in the spinal cord, the optic chiasm and optic nerves [5].

On the other hand, magnetic resonance imaging (MRI) helps in the delineation of various organs and offers excellent soft tissue discrimination [6, 7]. However, MRI and PET do not provide electron density data required for dosimetric calculation.

This brief review addresses the promising role of ^{18}F-FDG-PET scan in radiotherapy planning as related with MRI and the CT scan.

Details of the search

Our literature review was based on database search in PubMed/MEDLINE from 2000-May 2012. Terms used were: head and neck cancer, MRI, PET, delineation, contour, radiotherapy and synonyms combined with one or more of the following: radiation, three dimentional conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT), PET-CT, diffusion MRI (DW-MRI). Furthermore, these terms were combined with the respective keywords for each paragraph. Only papers published in English were included.

Applications of ^{18}F-FDG-PET

Research into the biochemistry of PET radioisotopes indicated preferential uptake of particular markers as a function of tumor metabolism with particular metabolic characteristics such as hypoxia and high proliferation ability. Also particular radiopharmaceuticals should penetrate the lipophilic cell membrane of cancer cells easily with fast metabolic clearance but not normal cell membrane [8]. Also particular radiopharmaceuticals should easily penetrate the lipophilic cell membrane of cancer cells with fast metabolic clearance but abnormal cell membrane [8].

The use of ^{18}F-FDG in PET studies is focused on the detection of high proliferative tumors characterized by hypoxic areas [9]. To make use of this latter parameter, other PET radiopharmaceuticals such as the fluorine-18-fluoromisonidazole (^{18}F-FMISO) and the fluorine-18-fluoroazomycin arabinoside (^{18}F-FAZA) are now applied. Furthermore, nitroimidazoles suitable for quantifying hypoxia status in tumors have been used as radiopharmaceuticals for PET, too [10, 11].

The PET/CT may therefore facilitate not only the delineation of the primary tumor and the corresponding lymph nodes metastases in HNSCC patients (Fig. 1) but has specific tumor hypoxia detection abilities.
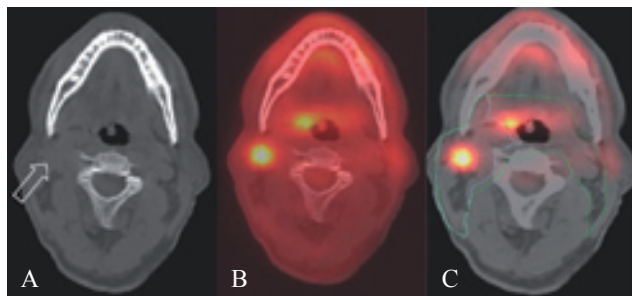

Figure 1. A patient with a tumor of the oropharynx (SUV=7.2) with a positive lymph node (SUV=6.1) at the left submandibular region.

Comparing MRI, CT and PET/CT for the identification of the primary or the unknown tumor

Clinical examination is important to locate the primary cancer tumor followed by diagnostic imaging consisting of CT, MRI and PET. Conventional imaging with CT and/or MRI in detecting the primary tumor have high sensitivities, of 86% and 88% respectively [12] (Fig.2).

When these methods show insufficient detectability, PET may play an important role in tumor delineation. Its sensitivity has been reported to be 93%-100% [13-15].

The potential role of PET in patients with unknown primary tumors is also essential, especially if the tumor is too small or lies in a position difficult to access. Several studies concluded that PET was capable of detecting the unknown primary tumor in about 25% of the cases [16, 17], as confirmed by biopsy [18].

MRI, CT and PET/CT for the detection of lymph-node metastases

In IMRT planning, the detection of the status of regional lymph nodes is very important, because positive lymph nodes are included in high dose target volume. The risk of regional recurrence is high if these lymph nodes are left untreated. However, the elective nodal irradiation in higher doses may not spare normal organs such as the parotid glands, larynx and pharynx [19].

Before the application of PET, the radiological diagnosis of a positive lymph node was only based on its size [20]. We now know that malignant involvement of smaller sized lymph nodes is not uncommon (Fig. 2).
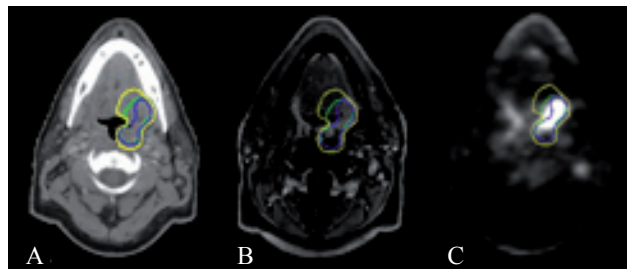

Figure 2. Primary tumor in the head seen on **A**) CT, **B**) MRI and **C**) ^{18}F-FDG PET.

Others, in a meta-analysis of 32 studies with 1236 patients showed that ^{18}F-FDG-PET in staging neck cancer had a sensitivity of 79% and specificity of 86%. In a subanalysis of studies in which ^{18}F-FDG-PET and MRI and CT were used, the sensitivity and specificity of PET was higher than 80% and 86% versus 75% and 79% for MRI and CT, respectively. Therefore, ^{18}F-FDG-PET offers a modest improvement in the diagnosis of head and neck cancer and of its staging [21].

Integrated PET/CT has been shown to have higher accuracy than ^{18}F-FDG-PET alone [22]. Others in 233 patients applied ^{18}F-FDG-PET in addition to conventional imaging staging and concluded that PET imaging alters the stage of the disease based on nodal involvement in 43% of the patients [1].

Tumor and lymph nodes delineation with PET/CT

The increased diagnostic accuracy with PET/CT reduced interobserver variability in target delineation and modified the estimated extension of gross tumor volume (GTV), the clinical target volume (CTV) and the planning target volume (PTV) for both the primary tumor and the regional lymph nodes [23-28]. The aim of a radiotherapist is to increase the radiotherapy dose for target volume and simultaneously decrease the dose in normal tissues.

Others have studied 12 patients by PET/CT and found that the GTV had decreased in four patients and increased in two patients. However, the comparison between the changes of GTV in primary tumor and in lymph nodes was not described [23].

Others, by PET/CT found in 17/21 patients that the GTV delineation was corrected. They performed a separate analysis of the tumor GTV and of the lymph nodes. Increase in the tumor GTV was noticed in 3 and a reduction in 14 patients while nodal delineation was increased in 7 and decreased in 3 of the 21 patients [24].

Others, enrolled 40 patients in order to compare the GTV identified on CT to that obtained from PET. The GTV was changed in 37 of the 40 patients. Thirty of them showed reduction and 7 increase. No comparison was made between the primary tumor and the lymph nodes [25].

Others, in 38 patients compared PET/CT delineation with CT target definition. They showed that the mean total PET/CT based GTV was significantly smaller than that on CT. However this difference was not statistically significant when separate analyses of the CT based and PET/CT based GTV of the primary tumor versus the GTV of nodal disease were performed [26].

Table 1. *Studies comparing CT and/or MRI versus PET/CT for the target delineation concerning head and neck tumors*

References	N	Imaging modalities	CT/MRI/PET-based primary volume	P	CT/MRI/PET-based LN volume	P
[22]	12	CT, PET/CT	2/12 pz with ≥25% increased with PET/CT, 4/12 pz with ≥25% decreased with PET/CT	N/A	Without differentiation from primary tumor	N/A
[23]	21	CT, PET/CT	CT 64.7cm^3 PET /CT 42.8cm^3	0.002	CT 29.9cm^3 PET/CT 37.2cm^3	NS
[24]	40	CT, PET/CT	CT 37.0cm^3 PET/CT 20.3cm^3	N/A	Without differentiation from primary tumor	N/A
[25]	38	CT, PET/CT	CT 34.54cm^3 PET/CT 29.38cm^3	0.046	No data	NS
[26]	29	CT, PET/CT	CT 24cc PET/CT 18cc	0.001	CT 55 suspicious lymph nodes, PET/CT 60 suspicious lymph nodes	NS
[27]	41	CT,MRI,PET	CT/PET 33.9mL CT/MRI 34.9mL	0.39	CT/PET 34.9mL CT/MRI 34.4mL	NS

N: number of patients; N/A, non applied; NS, non significant; P: significance value against PET; pz: patients

A recently published study by PET/CT and CT included 25 patients with HNSCC of whom 20/25 had the primary GTV tumor smaller than the GTV contoured on CT. The difference was statistically significant (P=0.0001). In addition, 60 lymph nodes were identified on PET while only 55 on CT [27].

Other researchers have studied 41 patients and compared the GTV contoured on CT, MRI, PET and on physical examination (PE). For primary tumors, mean GTV was significantly larger when studied by PET/CT than by MRI/CT fusion but without statistical difference (P=0.39, CI=0.62). Qualitative analyses to explain the low CI revealed that the superficial extent of primary disease was often underestimated when GTV was contoured without knowledge of physical examination findings. Similar trends were observed for nodal GTV. Finally, it was concluded that the target volume delineation was not complete without consideration of physical examination [28] (Table 1).

Discussion

The ^{18}F-FDG-PET sensitivity for tumor tissue provides excellent contrast between malignant and the surrounding normal tissues and renders easier the identification of the target volume by the radiation oncologists. Numerous recommendations have been made to obtain consistency of target delineation by collaboration between radiologists and nuclear medicine physicians [18]. Accurate delineation of the GTV is critically important and often achieved by using ^{18}F-FDG-PET, while the boundary between the tumor and the normal tissue can be difficult to define on CT [29].

The application of ^{18}F-FDG-PET in radiotherapy departments has been increased [29, 30], though, the modality has its limitations, mainly there is no objective manner besides optical estimation in order to set the threshold of the ^{18}F-FDG uptake to precisely depict the actual limit between the tumor and normal tissue. More studies on this issue are warranted [31].

Clinical examination and findings

There is often significant variability between Radiation Oncologists regarding the target delineation by MRI and PET/CT. If mucosal disease and the tumor bed are too small their size may be underestimated [16, 17]. The extension of the tumor can be precisely assessed by clinical examination. Regardless of the method used for determining the GTV, clinical examination remains irreplaceable [28]. For example, a clinical examination at the base of the tongue can diagnose cancer extending in the mucosa by palpation, while this diagnosis could be missed by CT and/or ^{18}F-FDG PET/CT [19]. The same has been reported by others with superficial tumor extension to the contralateral side of larynx or the subglottis, which not detected by CT, MRI or PET [30, 28].

Hypoxic tumors identification

The application of ^{18}F-FDG PET in hypoxic tumors was intended to implement an integrated boost in these regions for better tumor control, even though it has been questioned. Comparing the ^{18}F-FDG PET before and during radiotherapy, hypoxia imaging showed significant spatial variability, representing reoxygenation and changes in the locations of tumoral hypoxia [19, 31]. These findings reduce the possibility for using hypoxia imaged subvolumes as targets. Nevertheless, hypoxia-related treatment options are emerging; thus, a number of hypoxia-related PET tracers such as ^{18}F-FMISO and ^{18}F-FAZA are available now in an effort to identify hypoxic tumor subvolumes [8]. Studying

the application of these tracers, it is necessary to image patients at least after 2.5h, because of the slow improvement of the contrast between hypoxic and normal tissues. For ^{18}F-labeled hypoxia tracers, count statistics are of concern because of the necessity to have late-time-point images [32]. Compared to ^{18}F-FMISO, the clearance of ^{18}F-FAZA from blood and from non target tissues is faster and therefore has a higher tumor to background ratio [31]. Before these tracers can be clinically implemented for patient selection, dose escalation or adaptive radiotherapy, additional studies are required.

In conclusion, besides clinical diagnosis, GTV and lymph node metastases can be better diagnosed by PET/CT than by MRI and CT modalities. Studies on hypoxic GTV are also suggesting the importance of using PET/CT with specific tracers.

The authors declare that they have no conflicts of interest.

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Mount Olympus and its only canyon, the Enipea's canyon where the homonymous river runs. Afar one may notice part of the mountain covered with snow.
Mount Olympus gave its name to the city Olympia and to the famous Olympic Games. One of the 7 miracles of ancient Greek world was the golden-ivory statue of Zeus, by Phedias in the Temple of Zeus in Olympia city.

Photo by Dr. Fani Melfou