Review article:

Use of FDG-PET/CT for Biological Target Volume Definition in Head and Neck Cancer

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Recieved on:Nov.2017 - accepted on Jan.2017

ABSTRACT

Most of patients with head and neck cancers (HNC) need curative radiotherapy either as radical treatment or in the postoperative adjuvant setting. Accurate target definition is paramount to ensure a good outcome of radiotherapy. Pretreatment Computed Tomography (CT) is regularly performed for radiation therapy planning, which both guides dose calculation and aids accurately contouring the tumor volume. Nevertheless, when using CT, the low resolution of soft-tissue and the dental artifacts may render the primary tumor identification difficult. The interobserver inconsistency on the definition of the radiation target volume is additionally a generally perceived issue. With the increase of the frequency of HNC treatment by Intensity-modulated radiotherapy (IMRT), the accurate target volume delineation performed by using Fluorodeoxy-D-glucose positron emission tomography combined to CT (FDG-PET/CT) had become even more significant. Nevertheless, the ideal technique for precisely deciding the exact margins and form of the biologic tumor volume (BTV) remains challenging. FDG-PET/CT can define BTVs either for escalation of dose or alternative treatment strategies. Debatable issues still exist on the role of FDG PET/CT during radiotherapy treatment. Moreover, some new PET tracers, other than FDG, have been investigated for imaging specific biologic tumor characteristics in HNC. The purpose of this narrative review is to discuss the use of FDG-PET/CT for BTV definition before and during delivery of radiotherapy for HNC with attention to PET tracers other than FDG.

Key words: FDG-PET/CT, biologic target volume, head and neck cancer, radiotherapy planning.

الملخص:

يحتاج معظم المرضى الذين يعانون من سرطان الرأس والرقبة العلاج الإشعاعي إما كعلاج جذري أو كعلاج مساعد بعد العمليات الجراحية. إن تعريف الهدف الدقيق في العلاج الإشعاعي هو أمر بالغ الأهمية لضمان نتائج جيدة من العلاج. يتم إجراء التصوير المقطعي قبل العلاج بانتظام وذلك من أجل تخطيط العلاج الإشعاعي، حيث يساعد في حساب الجرعة الإشعاعية ويسهم بدقة حساب حجم الورم. ومع ذلك، فعند استخدام التصوير المقطعي ، فانخفاض الدقة التصويرية للأنسجة الرخوة والإضافات المعدنية للأسنان تجعل من الصعب تحديد الورم الأساسي. كما أن عدم الاتساق بين المقيمين في تعريف حجم الهدف الإشعاعي هو مسألة معروفة عموما.

مع زيادة وتيرة علاج سرطانات الرأس والرقبة عن طريق العلاج الإشعاعي معدل كثافة (IMRT)، فتعيين حجم هدف العلاج الإشعاعي بدقة باستخدام التصوير المقطعي المدمج مع التصوير البوزيتروني باستخدام نظائر الفلوروديوكسي- دي- الجلوكوز أصبح أكثر أهمية , ومع ذلك، فإن الأسلوب المثالي لتحديد هوامش والشكل الدقيق لحجم الورم البيولوجي لا يزال تحديا قائما.

يمكن للتصوير المقطعي المدمج مع التصوير البوزيتروني باستخدام نظائر الفلوروديوكسي- دي- الجلوكوز أن يحدد حجم الورم البيولوجي إما لغرض تصعيد الجرعة الإشعاعية أو لإيجاد استراتيجيات العلاج البديلة. لا تزال هناك قضايا قابلة للنقاش حول دور التصوير المقطعي المدمج مع التصوير البوزيتروني خلال العلاج الإشعاعي. وعلاوة على ذلك، يتم التحقق من بعض نظائر التتبع الجديدة، خلاف الفلوروديوكسي- دي- الجلوكوز ، لتصوير خصائص الورم البيولوجية في أورام الرأس والرقبة .

والغرض من هذا الاستعراض هو مناقشة استخدام التصوير المقطعي المدمج مع التصوير البوزيتروني باستخدام نظائر الفلوروديوكسي- دي- الجلوكوز لتعريف حجم الورم البيولوجي قبل وأثناء العلاج الإشعاعي لأورام الرأس والرقبة مع إلقاء الضوء على نظائر التتبع بخلاف الفلوروديوكسي- دي- الجلوكوز.

Introduction

Head and neck cancer (HNC) is the sixth most common type of cancer, representing about 6% of all cases and accounting for an estimated 650,000 new cancer cases and 350,000 cancer deaths worldwide each year [1-3]. Patients needing curative radiotherapy, either as radical therapy or in postsurgical adjuvant setting, constitute 74% of the all patients with HNCs. The results of a phase III trial illustrate that there is an overall decrease of 20% in survival rate among patients who did not adhere to recognized organizational standards during their radiation therapy protocols [4]. Thus, the adherence to accepted radiation therapy protocols affects their intended positive outcomes [5].

Imprecision in tumor target definition is recognized as a common source of radiation therapy error [6]. Intensity-modulated radiotherapy (IMRT)use is on the rise during HNC as it allows for the delivery of high radiation doses with steep dose gradients sparing critically important adjacent tissues, [7,8]. Accurate target delineation is essential for ensuring a good outcome of IMRT. Imaging plays a central role in defining the targets for radiation therapy, which is routinely planned on the basis of a single pretreatment Computed Tomography (CT) scan, thus providing the required electron density maps for dose calculation and accurate geometric contouring [9].

CT data contribute to radiotherapy planning based upon the definition of a number of target volumes defined by the International Commission on Radiation Units and Measurements (ICRU) Report 62 [10]. Grossly palpable or visible disease identified and delineated on axial CT images, is defined as a Gross Tumor Volume (GTV). It is spatially expanded depending upon natural history of disease, patterns of spread, and probability of microscopic disease being present in apparently normal surrounding tissues. The GTV is spatially expanded further to create the planning target volume (PTV), to account for setup errors related to patient and organ motions. The boundary between GTV and PTV is variable and depends on site, technique and institutional practice.

Moreover, the radiation oncologist needs to define target volumes surrounding normal structures as organs-at-risk (OARs) on axial CT images. However, the low resolution of soft-tissue and dental artifacts may complicate the identification of primary tumor when using CT. Interobserver inconsistency of radiation target volume definition is a widely known issue. In laryngeal cancer for example, target definition using only CT leads to significant inter- and intraobserver variations in delineation of the GTV [11].

Grouping both imaging modalities, Positron Emission Tomography (PET) and CT, together in one scanner machine allows the addition of functional data into anatomical images. Fluorodeoxy-D-glucose PET combined to CT (FDG-PET/CT) has become an important diagnostic tool for HNC evaluation, and is applied in various clinical settings, ranging from the detection and staging to tumor response assessment and

post-therapy follow-up [9,12].With the simultaneous introduction of IMRT and the advances in radiation therapy techniques, the accurate target volume delineation performed by using FDG-PET/CT has become a major area of interest. However, the optimal method for accurately determining the exact margins and shape of the BTV remains challenging.

With greater access to PET / CT imaging modality, radiation oncologist has begun to consider a modification of the conventional notion of standardized administration dose for PTV. On the other hand, the idea of biological focusing on and dose mapping has turned attractive.

FDG, a glucose analog, is the most commonly used radiotracer. There are potential favorable benefits of utilizing FDG for target volume outlining. It might aid to diminish the interobserver inconstancy in GTV, help in reducing the measure of GTV, and aid in perceiving the tumor range or the lymph nodes missed by CT or MRI, and confine the distinctive GTV elements conceivably needing extra radiation dosage. Be that as it may, the utilization of FDG-PET/CT likewise bears a few inconveniences: the constrained spatial determination, and the absence of an institutionalized technique for signal segmentation, and false-positive perceived caused by inflammation. A variety of novel alternative tracers to image specific biologic tumor characteristics are under investigation [13].

The correct definition and the detailed specifications of BTV remains a pending query. Since the introduce of the PET/CT scanners target delineation in radiation therapy planning using FDG-PET/CT scans is still controversial. The purpose of this review is to discuss the use of FDG PET/CT for BTV definition before and during delivery of radiotherapy for HNC with attention to PET tracers other than FDG. Consequently,

For that purposes and after presenting the adopted research methodology, we will evaluate the two topics of (a) Target volume definition and (b) Novel PET/CT tracers. They include the consecutive subsections of : Thresholding methods for target outlining, Clinical implications, Dose escalation with PET/CT based GTV and Adaptive dose planning based on mid-therapy PET/CT, for (a); and Targeting hypoxia and Imaging proliferation, for (b).

Methodology

In order to fulfill the requirements of this narrative review, aiming to establish clinical significance of the possibility of contouring biological target volume using [18]FDG-PET/CT before and during radiotherapy treatment, especially for HNC patients, we carried out a thorough research of the bibliography in Pubmed, Google Scholar and Web of Science databases. We included unique articles disseminated during the last decade to date. The inquiry methodology utilized two mixes of Watchwords: (a) “FDG-PET/CT” AND “head and neck cancer” and (b) “Biological Target Volume Definition” AND “head and neck cancer”, and an aggregate of 155, 7 and 303 articles were found, from previously cited databases.

We evaluated every one of the titles and modified works(excluding redundant articles), surveys, publications, letters to the editorial manager, case reports, works including low statistical sampling (number of patients with cancer), non-clinical examinations and additionally include potential for PET/MRI multimodality.

A sum of 70 articles were incorporated and classified by sections and subsections as follows: Thresholding methods for target outlining [20], Clinical implications [12], Dose escalation with PET/CT based GTV [9], Adaptive dose planning based on mid-therapy PET/CT [14], Novel PET/CT Tracers [1], Targeting hypoxia [19] and Imaging proliferation [16].

Target volume definition

Thresholding methods for target outlining

At the level of target definition and in addition to the decision of appropriate treatment techniques, the fusion of functional imaging data into the radiation planning procedure is understood to open a pathway into new era of radiation oncology based on molecular imaging.

Integrating functional imaging into radiation therapy planning provides a specific level of functional articulation bringing the prospect for quantitative analysis of functional imaging, yielding an upper hand over anatomical imaging modalities (CT, MRI) [14,15]. There are different means to contouring the volume of the target within PET/CT images, different methods have been reported, ranging from a manual qualitative visual method to automated quantitative or semi-quantitative thresholding methods. It is challenging to identify lesion edges in noisy PET data. One of the primary regions of ambiguity is the characterization of the target 'edge'. Distinctive strategies have been established for that reason. From which we refer to the following: (1) Visual analysis, which is mainly administrator reliant and is prone to window-level settings and interpretation contrasts [16-18]. (2) Iso-contouring in light of a set standardized uptake value (SUV). (3) Set limit of max tumor signal intensity (40 or 50%) [19,20].

A noteworthy downside of utilizing the SUV is that it is mainly affected by contrast recovery and noise characteristics that shift with reconstructive conventions and choice of scanners. Thusly, different strategies have been introduced, for example, the iterative background subtracted relative-limit utilizing watershed algorithm and hierarchical clustering in which the ideal relative-edge relies upon the tumor size not the signal-to-background ratio (SBR) (SBR) [21,22] and the variable threshold in view of flexible SBR [23].

One an examination on 78 patients, planning methods were evaluated and it was observed that volume and shape of GTV was impacted by the segmentation technique of choice (figure 1) [24]. Applying the visual strategy, it was discovered that volumes are near CT-characterized GTV while every single automated volume were reduced. In the same report fixed SUV strategy was not successful to classify the GTV and more than fifth of PET-based GTV were off the clinical/CT-based GTV, however it is uncertain

if this symbolizes a false positive as a result of peri-tumoral inflammation. Furthermore, another examination demonstrates that SUV (SUVmax) and SBR techniques delivered a comparable GTV volume more practically identical to tumor volumes than CT or MRI. Nevertheless, none of the three techniques was successful to recognize superficial tumor expansion because of an absence of correct spatial determination [23]. While, gradient-based segmentation algorithm appeared to be more exact than the SBR, none of these systems is broadly accessible off institutes where they were originally produced [21].

When comparing functional volumes delineated by specific SUV cutoff and gradient percentage of the SUVmax, **Moule et al.** [25] have discovered that the technique was not able to distinguish amid the tumor and background uptake above 36 Gy and the outlined volumes was relative to the dose conveyed. **Schinagl et al.** [26] on a study on 12 patients with head and neck cancer reported that the segmentation tools using the primary tumor as reference correlated poorly with pathology. PETSUV was unsatisfactory in 35% of the patients due to merging of the contours of adjacent nodes. They recommended an automated segmentation method for purposes of reproducibility and inter-institutional comparison. **Perez-Romasanta et al.** [27] reported on a cohort of 19 patients (39 lesions)with a histological diagnosis of head and neck cancer who would undergo definitive concurrent radio-chemotherapy or radical radiotherapy with intensity-modulated radiotherapy technique (IMRT). Contouring on PET images was accomplished through standardized uptake value (SUV)-threshold definition. The threshold value was adapted to R(S/B). They concluded the methods that rely mainly on SUV(max) for thresholding, as the RS/B method, are very sensitive to partial volume effects and may provide unreliable results when applied on small lesions.

Visual interpretation by skilled experts remain the most accurate delineation technique, and there is no agreement regarding the optimal contouring method. Due to the lack of proper validated automatic segmentation tools, the visual definition (delineation) of the tumor target remains the most useful approach which is based on expert visual interpretations by radiologists and nuclear medicine physicians and on knowledge of the likely patterns of disease infiltration within strict SUV scale limits and with particular windowing protocols [28].

On the wake of the rapid expansion of multimodalities and hybrid imaging, a question arise of whether the GTV should be defined based on single imaging modality or on several modalities and was addressed by some studies; in one such investigation, 41 patients with oropharyngeal carcinoma , GTVs were defined on the basis of findings at separate CT, MR imaging, FDG PET, and physical examination (GTVREF) and then compared to those from a combination of CT and MR imaging (GTVCTMR) and CT and FDG PET (GTVCTPET) [28]. The GTVREF was significantly larger than GTVCT-

PET and GTVCTMR for primary tumors and a poor concordance was observed. The qualitative analysis demonstrated that the underestimation of mucosal disease when contouring mainly caused such discrepancy.

The lack of concordance found between various imaging modalities in this and other studies [28-30, 24] suggests that using all imaging modalities along with physical examination was the safest approach when defining a target.

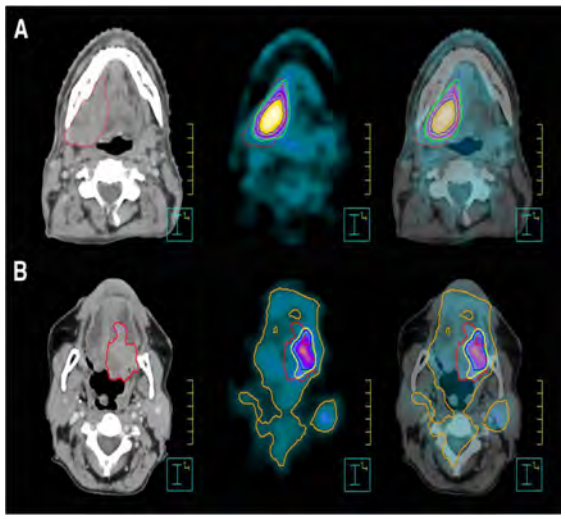


Figure (1):CT (left),^{18}F-FDG PET (center), and combined ^{18}F-FDG PET/CT (right) patient with T4N2M0 carcinoma of oral cavity/ base of tongue, for A/B. Red color corresponds to GTV delineated on CT (absolute volumes equal to 47.5 cm^3 /16.9 cm^3 for A/B) ; green color corresponds to PET-based GTVs got by visual observation (absolute volumes equal to 43.8 cm^3 /6.9 cm^{3}for A/B); orange color corresponds to GTVs acquired by applying isocontour of SUV of 2.5 (absolute volumes equal 32.6 cm^{3}for A; this technique was unsuccessful in B as a result of consideration of substantial ranges with typical background); yellow and dark blue colors correspond to GTV with fixed threshold of 40% and 50%, respectively, of maximum signal intensity (absolute volumes equal to 20.1 cm^3 /15.5 cm^3 and 14.9 cm^3 /7.1 cm^{3}for A/B); light blue color corresponds to GTV with versatile threshold in light of signal-to-background proportion (absolute volumes equal 15.7 cm^3 / 6.8 cm^{3}for A/B). [24].

Clinical implications

There have been various investigations demonstrating the impact of PET/CT on the definition of GTV and PTV. From those, we refer to an earlier study, noting the conceivable change in the GTV when utilizing the FDG-PET data for the treatment planning, by **Ciernik et al.** [19]. In the study, the team explored 39 cases with solid tumors, imaged with CT and FDG-PET with an incorporated PET/CT scanner. Treatment planning were based on combined images from both imaging modalities. CT data were used at first for volume outlining; PET data were incorporated at a later stage as an overlay, later, to outline the target volume. Two independent specialists both noticed the expansion of GTV by at least 25%, as a result of PET imaging in 17% of head and neck tumor cases [2/12]. Generally, 56% [22/39] of cases showed that utilizing metabolic imaging can cause a substantial change in GTV delineation. Furthermore, the study pointed that PET might be valuable to choose candidates with genuine restricted tumors and that PET/CT uncovered far off metastases for 16% of cases, hence changing the treatment arrangement from curative to palliative.

Nishioka et al. [16] investigated the advantages of joining the FDG-PET data into treatment planning by considering 21 candidates having head and neck carcinoma and they concluded that there were no visible change caused by image co-registration for 89% of cases, as far as GTV volumes for primary tumors. Clearer CTV and GTV identification on the co-registered images prompt

better normal tissue preservation. In particular parotid gland was preserved in 79% of patients whose upper neck areas were tumor-free. Besides, no attempt was carried on the study to change the size of primary tumor by thresholding methods. **Chatterjee et al.,** [31] explored the differences in GTV and CTV definitions for the primary and nodal volumes when FDG PET/CT was used as compared with contrast enhanced CT (CECT) in 20 patients with oropharyngeal cancer. PET/CT gross tumor volumes were smaller than CECT volumes (mean ± standard deviation: 25.16 cm(3) ± 35.8 versus 36.56 cm(3) ± 44.14; $P < 0.015$) for the primary tumor. There were no significant differences in gross tumor volume for T1/T2 disease, although differences in gross tumor volumes for advanced disease (T3/T4) were significant. The nodal target volumes (mean ± standard deviation: CECT versus PET/CT 32.48 cm(3) ± 36.63 versus 32.21 cm(3) ± 37.09; $P > 0.86$) were not statistically different.

Wang et al. [32] and **Paulino et al.(20)** have examined the utilization of PET/CT guided IMRT for the treatment of HNC. The advantage of utilizing IMRT is that it enables a high dosage of radiation to be conveyed to the PTV while limiting the exposure of neighboring vital tissues. In the study of Wang et al., on 28 patients initial CT based staging changed in 57 % as a result of PET/CT. In14 of 16 studied cases, they found that the volume analysis using PET/CT differ fundamentally in relation to those outlined from the CT alone, for which CT alone was not sufficient to distinguish primary tumors for 8 patients. Moreover, 16 of 28 patients who were followed for over half a year did not have any evidence of recurrence. An aggregate of 40 patients with squamous cell carcinoma emerging in the head and neck have been investigated by **Paulino et al.** utilizing the IMRT method. They found that about 25% of candidates were subjected to PET/CT–GTV under-dose when the CT–GTV was utilized for IMRT protocol. In any case, these finding are not definite, as it is well known that GTV outlining in the head and neck can be troublesome in light of the fact that specific normal tissues can favor FDG (tonsils, base of tongue, thyroid and parotid glands). Another study by **Arslan et al. (33)**, reported on 37 HNC patients treated with definitive radiotherapy. GTV determined by CT (GTVCT-Total) was increased in 32 cases (86.5%) when compared to total GTV determined by PET/CT (GT VPET/CT-Total). The GTV of the primary tumor determined by PET/CT (GTVPET/CT) was larger in 3 cases and smaller in 34 cases compared to that determined by CT (GTVCT). The GTV of lymph nodes determined by PET/CT (GTVLNPET/CT) was larger in 20 cases (54%) and smaller in 12 cases (32.5%) when compared to GTV values determined by CT (GTVLNCT).

From these discussed historic cohort studies, so far on contrasting PET versus CT based GTVs, the correct impact of the modification of the target volume consequences is not well understood. In addition, inadequate number of prospective studies observed. Up to this point, many studies [24,34,35] concluded that

the normal routine with regards to contrasting the GTV_CT with the GTV_PET isn't direct and special attention should be addressed with the speculative representations of the outcomes. The intrinsic variances between CT and PET imaging and the poor association between the images of the two modalities articulated in terms of a large statistical variation in the GTV ratios, can be attributed to such complexity. However, there are two clinical features of FDG-based PET incorporation into radiotherapy treatment planning that might be noted. At the level of the addition and/or omission of the proximal nodes into CTV for head-and-neck cancer cases, PET imaging gives confined indicative data whereas nodes identification by PET are being delineated from the CT informational index. PET imaging can likewise move radiotherapy treatment from curative to palliative should the functional imaging uncovers metastasis. Till now, there are insufficient dosimetric analyses to investigate contrasting dose volume of carried radiotherapy utilizing CT and PET-based GTV. Clinical and phantom based examinations, did not confirm the most fit approach of consolidating PET information into the radiation treatment procedures, as pointed out by Devic and Kolarova et al. [14,15, 36].

Dose escalation with PET/CT based GTV

Several clinical studies were performed to evaluate the feasibility of using dose escalation to a PET-based GTV contouring and the effectiveness of PET for radiation therapy planning in general [37-40]. Dose gradations can be assigned to an area outlined using PET or, otherwise, on the basis of voxel intensity according to "dose painting by numbers" [41].

Dose painting by numbers, assumes that a target can be defined by voxels with intensity values, but not necessary indicating whether voxels are inside or outside the target. The feasibility study of applying the dose escalation to an FDG PET–avid GTV with dose painting by numbers instead of GTV contouring was carried out elsewhere [42]. Their examination reasoned that PET-characterized BTVs are an appealing focus for dosage escalation, because of the imperfect result for the greater part of patients with HNC. Where, the needed radiotherapy dose to exceed the radioresistance in target volume is unspecified. Radiobiological simulations may foresee such dosages; however, existing treatment calculations in the head and neck are as of now approaching tolerance dose. Of notice are two disseminated clinical studies assessing the result of18F-FDG-PET-based treatment employing dose escalation method. Madani et al. [43] revealed a stage 1 trial dose escalation plan of 25 and 30 Gy conveyed along 10 fractions followed by 22 fractions of 2.16 Gy utilizing IMRT, for an aggregate dosage of 72.5 or 77.5 Gy. They contemplated 23 and 18 candidates selected at dosage level 1 and 2, respectively. For four of nine examined patients, the site of relapse was inside the 18F-FDG-PET-contoured area (figure 2), despite the fact that dosages were accomplished and toxicity were experienced. In a later report, a similar research team has distributed the outcome of a phase 1 trial of DPBN conveying a mean dose

of 80.9 Gy to the high dosage CTV, for seven examined cases, and a mean dosage of 85.9 Gy to the GTV, for 14 considered cases, at 32 fractions.[42].The initial 10 fractions included a voxel intensity based (DPBN) IMRT plan utilizing a pattern of ^{18}F-FDG-PET scan, for every patient. Using a similar imaging method (^{18}F-FDG-PET) for fractions 11-20 and the rest of the fractions were carried out by applying a uniform dose IMRT, they perceived that the radiation exposed volume of normal tissue and target was decreased, especially while escalating dose to GTV. Madani et al. [39] had not reported any grade 4toxicitytaking note that just 9 of 21 patients, got corresponding chemotherapy, follow-up have indicated mucosal ulcers as the dosage restricting toxicity. For a period of 4 to10 months following the treatment, six examined cases had mucosal ulcers where five of them were seen at dose level II (mean aggregate dose of 85.9 Gy to the GTV). Therefore establishing dose level I (mean aggregate dose of 80.9 Gy to the high CTV) as the upper tolerance dose in the study and the significance of longer-term aftercare and follow-up in these investigations.

Optimization in term of balancing dose escalation (fraction dose, total dose) effectiveness versus patient safety (toxicity)and the added advantage of PET/CT tumor volume delineation should be addressed further in clinical research.

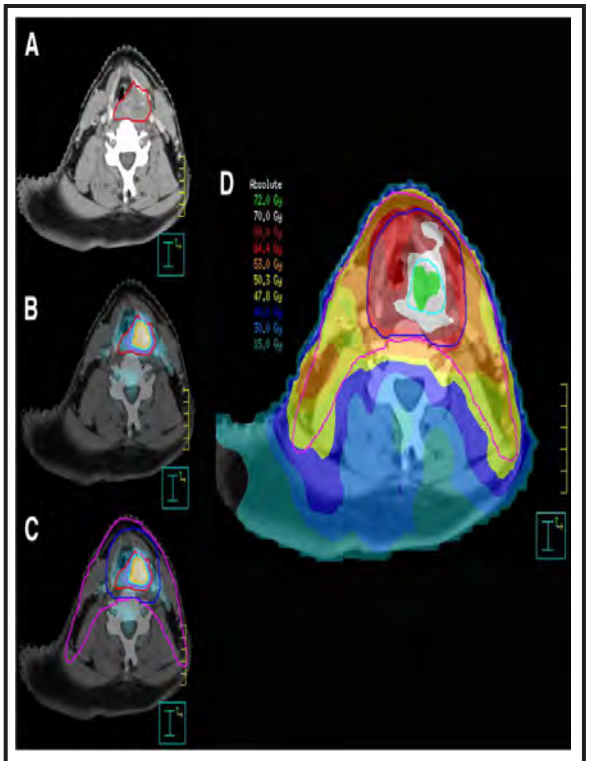


Figure (2): Patient with T3N2M0 hypopharyngeal carcinoma imaged with CT (A), compared to 18F-FDG PET combination images (B and C) and the corresponding measured dose (D). Red/light blue color refers to GTV portrayed on CT, GTV_{CT}, and ^{18}F-FDG PET utilizing adaptive threshold based on signal-to-background ratio, GTV_{SBR}, (absolute volume of 39.0/13.1 cm^3). Moreover shown are target volume to 50.3, 68.0 and 72.0 Gy for pink, dark and light blue colors, respectively. Sub volume of GTV_{CT} has received a dose of 72.0 Gy due to added integrated IMRT boost of 4.0 Gy.[43].

Adaptive dose planning based on mid-therapy PET/CT

The compromise between disease control and toxicity in head and neck cancer in both chemotherapy and radiation therapy is subtle. Cure rates remain unsatisfactory, while intensity and toxicity of treatment have been described as "pushed to what must be the limits of human tolerance" [44,45]. In attempts to optimize the therapeutic ratio for individual patients, personalizing treatment is gaining

interest. The alteration of radiation delivery, during the therapy course, based on changes in the normal and tumor tissues, can be considered as a mean to achieve such personalized treatment. CT scan is typically utilized –pretreatment- for radiation therapy planning to delineate the target volume and any organs at risk. Treatment usually proceeds without taking into account the anatomic changes arising during the course of fractionated dose delivery. **Geets et al** [46] observed a reduction of 51% and 48% in the clinical and in the planned target volumes, respectively, after a partial radiation therapy treatment course of 45Gy. In a later study of patients with laryngopharyngeal cancer receiving chemo-radiation therapy [47], PET-based and CT-based primary tumor GTVs were found to decrease at a mean rate of 3.2% and 3.9% per treatment day, respectively, while nodal GTVs decreased at a rate of 2.2% per treatment day. In addition, spatial shifts were noted in the GTV. Furthermore, geometric shifts in the position of the primary tumor during treatment differed between PET and CT-defined GTVs. Thus, it is suggested that anatomic (CT) and the functional (PET) imaging modalities provide complementary information during treatment (figure 3).

Adaptive radiation therapy delivers an advantage by means of improving the therapeutic ratio i.e. minimizing the overall dose to normal tissues and focusing therapeutic dose at tumor tissues, and presents a clinical challenge. Of great interest is the characterization of therapy regiment alteration relied to tumor based on changes observed on images. The usefulness of integrated biologic and functional imaging techniques is concretized by tumor sub volumes identification (eg, radiation-resistant hypoxic regions) as candidates for dose escalation [48]. The non-uniform radiation delivery can be guided by biologic characterization of tumor and neighboring tissues at functional imaging. **Geets et al.** [46], in a study examining10 patients encountering pharyngolaryngeal SCC and treated with CRT and subjected to various imaging modalities (MRI, CT and ^{18}F-FDG-PET during the course of treatment (at baseline and after mean recommended doses of 14, 25, 35, and 45 Gy)), demonstrated that the early reaction observation over the treatment can aid the modification or the adjustment of the overall procedure. Utilizing a technique based on the gradient to outline GTVs on ^{18}F-FDG-PET, throughout radiotherapy regimen. GTVs were considerably diminished, yet stay less than those characterized with MRI and CT ($P< 0.001$) for all cases. In contrast to pre-treatment CT based volume contouring a gradual decrease of the irradiated volume by 15% to 40% was observed.. In addition, they observed that just high dose volumes (≥V90) were affected by this adaptive approach with additional sparing of organs at risk (OAR). **Hentschel et al.** [49] investigated serial ^{18}F-FDG-PET scans at three times during CRT on 37 patients contrasting changes in SUV with baseline. They noted that a 50 % drop in SUVmax after 10 to 20 Gy radiation dose delivery, for the studied case, was predictive of two years OS (88% versus 38%,P= 0.02),

"and a below median volume of disease defined on baseline PET was also predictive of two year OS (83% versus 34%,P= 0.02)."

Key challenges present in the use of functional imaging to guide adaptive radiotherapy treatment. Proper selection of imaging technique is an issue with few data to support one choice of one modality over the other, reproducibility of imaging characteristics critical for modifying dose delivery is another issue, **Bittner et al.** [50] and **Lin et al.** [51] demonstrated significant difference in hypoxic sub-volumes identified on successive 18F-fluoromisonidazole (FMISO) PET scans obtained before treatment. Moreover, the optimal timing for radiology imaging evaluation during the course of treatment is un-known. Decreasing tumor uptake and increasing the nonspecific background activity, limit the utility of obtained PET images in the course of fractionated radiation therapy [13,42,46,47]. Also, the impact of concurrent chemotherapy on changes during treatment process is uncertain and the optimal tumor contours method is not well-understood. On the other hand, the decrease of tumor to background uptakes ratio makes it difficult to use automated tools related to the threshold SUV. The maximal SUV of tumor imaged with FDG-PET, decrease progressively and the volume defined by the threshold SUV is unchanged during the radiation treatment course, as found by **Moule et al.** [52]. The possibility of moving beyond the simple delivery of homogeneous dose to an anatomically defined treatment volume, becomes possible thanks to the inclusion of functional imaging into the treatment planning process. Thus, the adaptive planning of the radiotherapy treatment protocols based on functional imaging is a relatively new area of investigation, and it remains in the realm of research. Nevertheless, we cannot imagine that radiation therapy will continue to be delivered exclusively on the basis of a single pretreatment imaging assessment of the tumor.

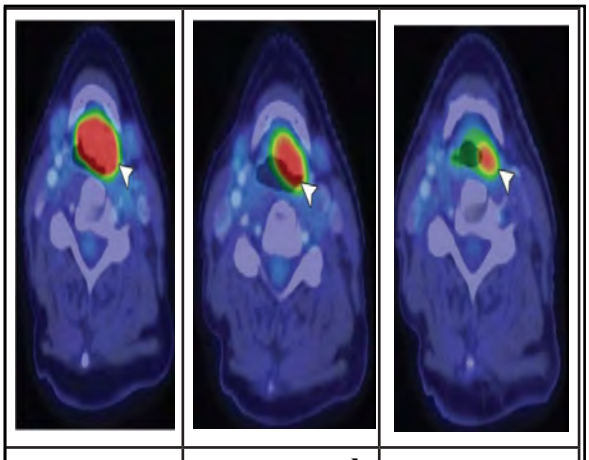


Figure (3): Adaptive therapy planning in a 68-year-old man with a supraglottic SCC (T2N2bM0) treated with chemoradiation therapy (70 Gy in 35 fractions over 7 weeks, two cycles of cisplatin 100 mg/m2 per day in weeks 1 and 5). (a) Axial fused PET/CT image obtained before the start of therapy shows marked metabolic activity (SUVmax, 22.2) in the tumor (arrowhead). (b) Axial fused PET/CT image obtained after 11 fractions of radiation therapy shows a reduction in tumor size and metabolic activity (SUVmax, 9.7). (c) Axial fused PET/CT image, obtained after 21 fractions of radiation therapy, shows continued reduction in tumor size and metabolic activity (SUVmax, 7.9)(9).

Novel Pet/Ct Tracers

FDG is not a tumor-specific tracer and accumulation in benign lesions, such as

regions of inflammation, causes false-positive results with consecutively low specificity. Therefore, novel alternative tracers with higher specificity are under investigation for the non-invasive imaging of cellular processes such as hypoxia and proliferation [45].

Targeting hypoxia

As concluded in the work of **(53),** hypoxia is an established indicator of poor prognosis for patients with head and neck cancers. It leads to radiation resistance in tumor cells. **Hall et al.,** [54] found that the needed cell-killing dose, in hypoxic conditions, reach the three time value of those in normoxic conditions. Hypoxia imaging provides relevant information for treatment planning in HNC. It enables dose escalation in hypoxic tumor tissue while sparing non hypoxic surrounding tissue (figure 4). This contributes to a reduction of post radiation side effects and consecutive improvement of the quality of life in these patients in spite of intensified radiation dose. Yet the main requirement of hypoxia imaging remains dose adjustment for IMRT. The assessment of tumor hypoxia can be carried out by a number of invasive techniques. They include the polarographic oxygen electrodes and the immunohistochemical staining of pathologic specimens. Additionally, from the many existing number of PET tracers, allowing the noninvasive visualization of hypoxia, we cite the mostly investigated one, FMISO, that has been used for the assessment of HNC [55-58]. It has been used for hypoxic BTV definition, in the form of 18F-FMISO, during a study aiming to demonstrate the potential to dose-escalate to sub volumes **(59,60).** Moreover, **Lee et al.** [61] delivered a dose of 70Gy to the gross tumor volume (GTV; the range of18F-FMISO uptake inside the^{18}F-FDG-PET/CT GTV) and a dose of 84 Gy to the hypoxic GTV, for ten cases without surpassing ordinary tissue tolerance. They found that the hypoxic GTV dose of 105Gy was feasible for one of two patients sparing normal tissue. On the other hand, **Thorwarth et al.** [59] studied 13 candidates and analyzed the dosage painting by numbers (DPBN) in contrast to IMRT plan keeping up iso-toxicity, observing an increase of tumor control probability from 0.552 to 0.702 by dose escalation to a to a contoured 18F-FMISO hypoxic volume. The sequential time variability constraint of the 18F-FMISO imaging makes difficult clinical studies with dose escalation to 18F-FMISO-defined volumes

Moreover, **Nehmeh et al.** [62] have shown that a voxel by voxel investigation of putative hypoxic regions, for patients undertaken two benchmark ^{18}F-FMISO scans along 3 separated days, uncovered a solid association over the two time points in under 50% of patients. Delivering a higher target-to-background signal ratio, the hypoxia-specific PET agent Fluorine 18 fluoroazomycinarabinoside (FAZA) clears the blood more rapidly than FMISO [63,64]. Moreover, **Grönroos et al.** [65] showed theoretically that theFluorine 18 fluoroerythronitroimidazole (FETNIM) is a more potent indicator of hypoxia than FMISO, owing to its greater hydrophilia and better pharmacokinetics. To define the optimal

time point for the integration of hypoxia (18)F-FAZA-PET/CT information into radiotherapy treatment planning to benefit from hypoxia modification or dose escalation treatment, **Bollineni et al.** (66) reported that instead of using the FAZA-BL scan as the basis for the dose escalation, FAZA at the second week of chemo-radiotherapy is most suitable and might provide a more reliable basis for the integration of ^{18}F-FAZA-PET/CT information into radiotherapy treatment planning forhypoxia-directed dose escalation strategies. Appearing to be promising hypoxia-specific radiotracers, FAZA and FETNIM required in depth investigation, especially in direct comparison with FMISO.On the other hand, using numerous Cu isotopes (60/61/62/64) as a form of Cu-diacetyl-bis(N4-methylthiosemicarbazone) (Cu-ATSM) can be considered as a PET tracer for imaging hypoxia. The 64Cu isotope was considered as a non-invasive marker of tumor hypoxia due to its ideal physical properties and great formation yield (67). For hypoxic and normoxic cells, the [Cu(II)-ATSM] complex is diminished by intracellular thiols bringing about an unsteady complex [Cu(I)-ATSM], which is in turn re-oxidized to a more stable state [Cu(II)-ATSM] that diffuses out of cells in normoxic cells. While, in hypoxic cells it separates gradually and irreversibly caught by intracellular copper chaperone proteins. In rat models, Lewis et al. (68) have shown the association between 60Cu-ATSM and tumor pO2 and **Chao et al.** (69) have demonstrated that the dissemination of60Cu-ATSM inside the GTV of patients with HNC was heterogeneous and planned delivery of 80 Gy into 35 fractions to the ATSM-avid tumor sub-volume and the delivery of 70 Gy into 35 intervals to the GTV without compromising normal tissue dose tolerance. **Grassi et al.** (70), reported in HNC patients, F-FDG and Cu-ATSM provided similar results about delineation of BTV.

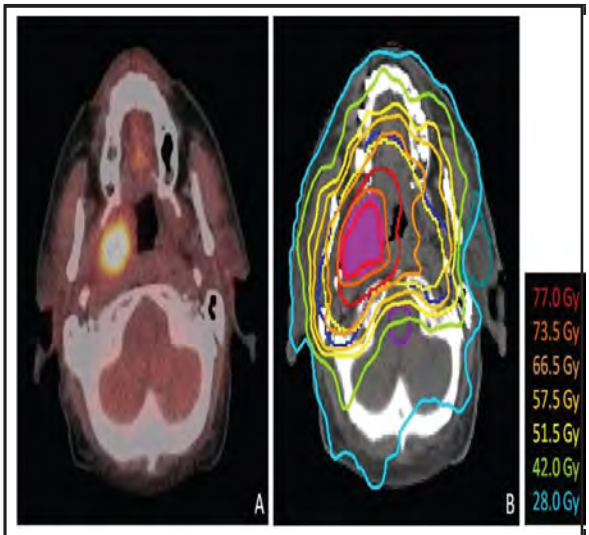


Figure (4): A. [18F]-FMISO PET/CT acquired 4h pi. A hypoxic volume was delineated based on this image by applying a 40% threshold relative to the maximum SUV. This contour was then registered to the RT planning CT and prescribed with 110% of the conventional dose (77 Gy). B. Corresponding slice of the RT planning CT with the FMISO PET based hypoxic target volume overlaid in pink. Resulting IMRT dose distribution of a homogeneous dose escalation by 10% is shown. Regions of interest: PTV70 (red), PTV60 (yellow), PTV54 (blue), left parotid gland (dark green), brain stem (purple). (71).

In summary, no appropriate hypoxia-agent for PET can be favored most, each agent has its advantages and disadvantages and may be better suited for evaluating particular tumor types than others, allowing for extra studies to be investigated for such purpose.

Imaging proliferation

Both chemotherapy and radio-therapy treatment can cause the rate of cellular proliferation in responding tumors and consequently the tumor size to decrease [72], on the other hand continued and accelerated cell reproduction is an indication of treatment failure [73]. Developing imaging strategies is crucial to identify tumor cell repopulation for early response assessment and to delineate these areas as targets for dose escalation. Unlike FDG, the FLT-PET is the most widely used to assess cellular proliferation [74,75] and allows the detection of cellular division as it is taken only the actively dividing and not surrounding inflammatory cells. FLT uptake can be used for early monitoring of cellular response to radiation treatment in HNC tumors [73,76].

Studies had shown that FLT can provide an advantage of assessing early tumor response to therapy in HNC patients with good reproducibility of SUV measurements and with changes in uptake observed prior to changes in tumor volume [76-78].

As illustrated by **Troost et al.** [76],it is technically feasible to delineate areas with high cell proliferation for dose escalation. However, the use of FLT is not histologically validated. **Linecker et al** [79] concluded that the FLT uptake and the Ki-67 index are not correlated, after a study of 19 patients with head and neck SCCs. Due to its uptake by the germinal centers of reactive lymph nodes, leading to a low positive predictive value, the FLT cannot yield a clear differentiation between beignet and malignant abnormal cervical lymph node [80]. The ultimate need of further research is obvious concerning the establishment of the FLT in the assessment of early treatment response and the adaptive radiation therapy planning.

Furthermore, the accelerated repopulation along the radiotherapy for HNC can unfavorably influences result. Besides, the advancement of PET tracers for DNA synthesis imaging may provide better specificity than ^{18}F-FDG-PET which is additionally taken up by peri-tumoral inflammatory cells. The tracer 3′-Deoxy-3′-18F-fluorothymidine (18F-FLT) mirrors the activity of thymidine kinase 1, a key enzyme in DNA synthesis and is taken up by dividing tumor cells however not by terminally separated resistant reaction cells [81]. **Troost et al.**[59] examined 10 patients with HNC (two of them have gotten corresponding chemotherapy) and investigated the role of such tracer in early reaction evaluation to radiotherapy, as shown in figure 5. They imaged patients utilizing 18F-FLT-PET/CT, before and along the second and fourth weeks of the radiotherapy course, where in the fourth week they noted a substantial lessening in CT-based GTV, contouring not perceived at earlier phase of the treatment and major changes in SUVmean and SUVmax on 18F-FLT images as early as one-week post radiotherapy and a further decrease before the fourth week of treatment.. Utilizing a subjective fixed SUVmax limit of 80%, permitting the tumor sub-volume to be outlined in the first and second ^{18}F-FLT PET scan, the feasibility of dosage escalation was illustrated. Whereas, the expected repopulation hap-

pening after a month of radiation treatment were not reflected on the uptake of ^{18}F-FLT PET along the radiation delivery for patients with HNC. Moreover, the feasibility study of Fuzzy Locally Adaptive Bayesian algorithm (FLAB) as the ideal segmentation strategy for the proliferative volume for repeated FLT PET/CT along chemo-radiotherapy, for patients with HNC, was carried out by **Arens et al.** [82]. Also, there are some studies demonstrating the uptake reduction of 18F-FLT PET relative to the radiation delivery duration, for Squamous Cell Carcinoma (SCC) of the esophagus case study. **Yue et al.** [83] on the other hand, noted a raise in the uptake of ^{18}F-FLT PET after treatment breaks mirroring the acceleration of the repopulation process.

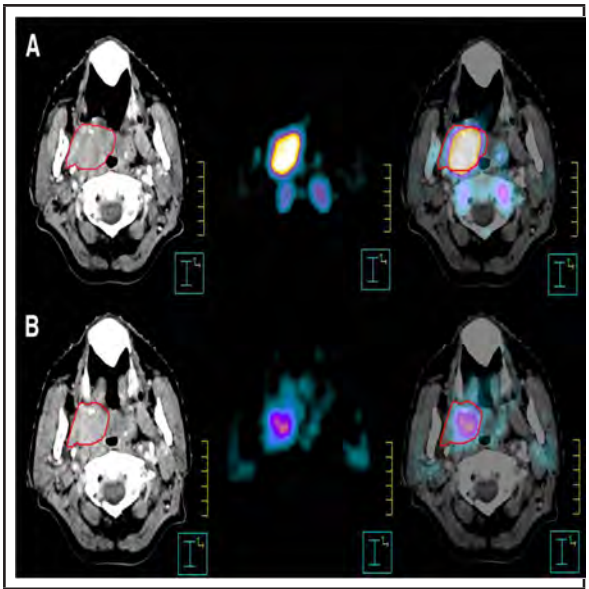


Figure (5):CT (left),^{18}F-FLT PET (center), and combined ^{18}F-FLT PET and CT (right) patient with T3N0M0 oropharyngeal carcinoma before and after 8 fractions of 2 Gy radiation treatment for (A) and (B), respectively. Red color corresponds to GTV based on CT imaging modality. As observed, there is an considerable decrease in18F-FLT PET signal intensity compared to the small reduction of GTV on CT.**(76).**

As hypoxic tumor volume eventually decreases during the course of treatment, further studies are needed to investigate best practice to integrate methods of adapting treatment regimen delivery. Proliferation imaging play a vital role in monitoring specific tumor reactions, and hence the effectiveness of the therapy procedure, post radiation therapy mostly when treating below tumoricidal threshold dose.

Conclusion

FDG use is rapidly increasing as tracer in PET functional imaging due to both its high sensitivity and specificity in cancer imaging, emerging new tracers might in the near future play a bigger role in cancer management but not likely replace FDG soon. Limitation in regulations and lengthy clinical trials along economic feasibility is still a hindrance in the path of adopting such novel tracers clinically. Clinical examination together with CT remains the optimal standard for target volume definition in the planning of radiotherapy for HNC. PET/CT provides unique and complementary information about target volume which may increase the precision of radiotherapy planning. To what extent this improves the treatment outcomes for patient with HNC is unclear and will require further research.

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