

RESEARCH ARTICLE

Role of PET/CT in Treatment Planning for Head and Neck Cancer Patients Undergoing Definitive Radiotherapy

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Abstract

Background: In this study, we aimed to investigate the benefits of 18F-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging for staging and radiotherapy planning in patients with head and neck cancer undergoing definitive radiotherapy. **Materials and Methods:** Thirty-seven head and neck cancer patients who had undergone definitive radiotherapy and PET/CT at the Uludag University Medical Faculty Department of Radiation Oncology were investigated in order to determine the role of PET/CT in staging and radiotherapy planning. **Results:** The median age of this patient group of 32 males and 5 females was 57 years (13-84years). The stage remained the same in 18 cases, decreased in 5 cases and increased in 14 cases with PET/CT imaging. Total gross tumor volume (GTV) determined by CT (GTVCT-Total) was increased in 32 cases (86.5%) when compared to total GTV determined by PET/CT (GTVPET/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). No pathological lymph nodes were observed in the remaining five cases with both CT and PET/CT. **Conclusions:** We can conclude that PET/CT can significantly affect both pretreatment staging and assessed target tumor volume in patients with head and neck cancer. We therefore recommend examining such cases with PET/CT before treatment.

Keywords: Head and neck cancer - PET-CT - radiotherapy

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Introduction

Positron emission tomography performed using 18F-deoxyglucose (FDG-PET) is a hybrid method that can yield both functional and anatomic data and has been widely used in the last decade. This method is based on the fact that glucose consumption is increased in tumor cells. (Chapman et al., 2003). FDG PET scans are commonly used for the staging and restaging of various malignancies, such as head and neck, breast, colorectal and gynecological cancers (Kang et al., 2014). Innovations in computer technology have allowed us to combine PET and computed tomography (CT) images i.e. positron emission tomography/computed tomography (PET/CT). PET/CT fused image was obtained, achieved the matching of anatomical and functional details, and may reflect both the biological morphological changes in early detection of disease (Tan et al., 2014).

Radiotherapy (RT) planning computers can use the

PET/CT fusion technique to combine CT and PET images one-to-one. Thus, nodal detection and describing tumor limits has become easier and more accurate with the assessment of matching images. There are several studies indicating that using PET imaging with conventional techniques like x-ray, CT, or MRI can have a significant effect on gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV) (Demir et al., 2009).

In this study, we aimed to investigate the benefits of PET/CT on the staging and radiotherapy planning steps in head and neck cancer patients who had undergone definitive radiotherapy.

Materials and Methods

Thirty-seven head and neck cancer patients who had undergone definitive radiotherapy and routine PET/CT before treatment planning were investigated

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retrospectively in order to determine the role of PET/CT in treatment planning. This group consisted of 32 male and 5 female cases with a median age of 57 years (13-84 years). Primary tumor locations were the nasopharynx in 12 cases, the oropharynx in 7 cases, the hypopharynx in 5 cases and the larynx in 9 cases. Histopathological examination of tumor tissues defined 23 cases as squamous cell carcinoma and non-keratinizing undifferentiated carcinoma in 10 cases. Five cases graded as 3 and 9 cases as grade 4; 23 patients could not be graded.

Definitive radiotherapy was decided on after examining each patient based on clinical findings, physical examination findings, pathology examinations and radiological findings. After the first assessment, a head and neck mask was applied at the treatment position for all patients. Patients with prior PET/CT examinations underwent a CT simulation. Patients without prior PET/CT examination were performed PET/CT simulation after preparing thermoplastic mask. Patients lied down in supine position to device table for CT imaging. Flat carbon fiber treatment table was used in both devices in order to provide the same conditions in both CT and PET/CT. Thermoplastic head and neck mask was prepared for all patients with neck support parts made of foam. Patient's arms were stabilized with shoulder tractors. Tongue depressor was used in patients with tumor localized in mouth floor and 2/3 anterior of the tongue. Center of the scanning area is defined as the overlapping point of horizontal, vertical and longitudinal lasers which are placed in the CT simulation device as the same of the treatment room. Small lead markers were placed to each laser point on the individuals in order to determine reference slice of the CT slices. Topogram images were taken for determining the related area. Head and neck area was imaged by 2 slice multidetector spiral CT with the section thickness of 3 mm.

The routine PET/CT imaging protocol was applied in all cases. PET images with attenuation correction were transferred in DICOM (Digital Imaging and Communications in Medicine) format to the contouring computer at the Uludag University Medical Faculty Department of Radiation Oncology. PET images and CT images were matched using the contouring computer.

Cases were initially staged according to American Joint Committee on Cancer (AJCC) 2010 TNM classification criteria (AJCC, 2010) based on clinical and CT findings. Afterwards, they staged patients based on clinical and PET/CT findings and the two stages were compared. Patients who had undergone neo-adjuvant chemotherapy

were staged based on pre-treatment (on diagnosis) CT and PET/CT findings.

The contouring process was performed by the same radiation oncology specialist. The GTV of the tumor and the GTV of head and neck lymph nodes (LN) were contoured based only on CT images (GTV_{CT} and GTVLN_{CT}, respectively). CT images and PET/CT images were matched using the contouring computer by radiation oncology and nuclear medicine specialists by choosing the image fusion technique. Afterwards, the GTV of the primary tumor and head and neck lymph nodes were contoured by the same radiation oncology and nuclear medicine physicians based on images created by the fusion of PET and CT images (GTV_{PET/CT} and GTVLN_{PET/CT} respectively). Lymph nodes which could not be differentiated by physicians as the primary tumor or metastatic lymph nodes were also included in the GTV_{CT} or GTV_{PET/CT}. Lymph nodes >1 cm were defined as pathological. In the PET/CT images, standardized uptake value (SUV_{max}) ≥2 lymph nodes were included in the GTVLN. GTVs imaged via PET/CT were contoured as a visible area according to the International Commission on Radiation and Measurements (ICRU) 62 (Suit H, 1996).

GTV_{CT} and GTVLN_{CT} determined via CT and GTV_{PET/CT} and GTVLN_{PET/CT} determined via PET/CT were transferred to a treatment planning computer. Data were recorded in cm³ using volume calculating algorithms in the treatment planning system. GTVCT-Total was calculated by adding GTV_{CT} to GTVLN_{CT} and GTV_{PET/CT}-Total was calculated by adding GTV_{PET/CT} to GTVLN_{PET/CT}. The results were recorded in cm³. Mathematical volume changes were calculated.

The SPSS (Statistical Packages for the Social Sciences, IBM) program was used for statistical analysis. The Wilcoxon signed rank-test was used to compare GTV_{PET/CT-Total} and GTV_{CT-Total} with GTV and GTVLN values obtained by CT and PET/CT individually. Pearson correlation analysis was used to compare GTV_{PET/CT-Total} with GTV_{CT-Total}, GTV_{PET/CT} with GTV_{CT} and GTVLN_{PET/CT} with GTVLN_{CT} individually. The McNemar-Bowkertest was used to analyze the stage changes between T_{stage-ct} and T_{stage-pet/ct}, N_{stage-ct} and N_{stage-pet/ct}, M_{stage-ct} and M_{stage-pet/ct}, Total_{stage-ct} and Total_{stage-pet/ct}. The Pearson correlation test was used for correlation analysis. Statistical significance was defined as p<0.05.

Results

Analysis of Stage Alteration. Stage changes were

Table 1. Statistical Analysis of Volume Values

		Median (Min-max)	p*	r	p-value**
GTV	PET/CT	32.71 (3.14-311.23)	<0.001	0.792	<0.001
	CT	55.77 (7.16-390.13)			
GTVLN	PET/CT	7.49 (0-114.46)	0.217	0.777	<0.001
	CT	5.29 (0-126)			
GTVTotal	PET/CT	50.90 (4.80-311.23)	<0.001	0.762	<0.001
	CT	81.98 (7.60-390.13)			

*r:Correlation coefficient *Wilcoxon test **Pearson correlation analysis; GTV: Gross tumor volume; GTVLN:Involved locoregional lymph node volume; GTVLNtotal: Total volume of primary tumor+locoregional lymph nodes; CT: Computed tomography; PET/CT: Positron emission tomography/computed tomography

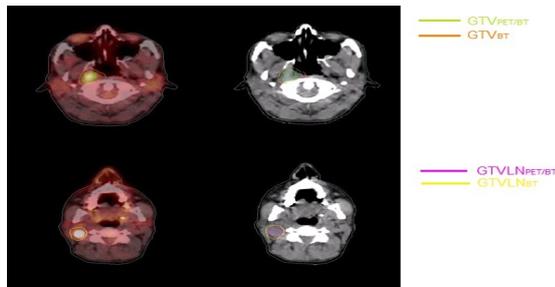


Figure 1. Radiotherapy Planning Volumes Described by Planning CT and PET/CT. GTV: Gross tumor volume; GTVLN: Involved locoregional lymph node volume; CT: Computed tomography; PET/CT: Positron emission tomography/computed tomography

observed with PET/CT in 19 of 37 patients and the treatment plan was changed afterwards. There was no statistically significant difference between $T_{\text{stage-CT}}$ and $T_{\text{stage-PET/CT}}$ ($p=0.306$). However, there was a positive correlation between $T_{\text{stage-CT}}$ and $T_{\text{stage-PET/CT}}$ ($r=0.664$; $p<0.001$). When comparing the T, N and M parameters of the TNM staging system based on CT and PET/CT, the T parameter was increased in 8 cases, decreased in 8 cases and unchanged in the remaining 21 patients with PET/CT imaging. There was no statistically significant difference between $N_{\text{stage-CT}}$ and $N_{\text{stage-PET/CT}}$ ($p=0.197$). However, there was a positive correlation between $N_{\text{stage-CT}}$ and $N_{\text{stage-PET/CT}}$ ($r=0.556$; $p<0.001$). When comparing the PET/CT and CT results, it was observed that the N parameter was decreased in 2 cases, increased in 10 cases and unchanged in the remaining 25 patients. It was also observed that in spite of stage not changes N parameter in nine cases, new LN areas were discovered by PET/CT and added to the treatment plan. Pathological lymph nodes (>1 cm) detected by CT were excluded from the treatment plan in nine cases due to lack of metabolic activity based on the PET/CT data. There was no statistically significant difference between $M_{\text{stage-CT}}$ and $M_{\text{stage-PET/CT}}$ ($p=0.125$). However, there was a positive correlation between $M_{\text{stage-CT}}$ and $M_{\text{stage-PET/CT}}$ ($r=0.543$; $p<0.001$). In four cases (11%), asymptomatic metastatic disease was detected with PET/CT examination findings despite a lack of CT findings. In one case, a lymph node was located at the anterior mediastinum; in two cases bone metastases and in one case bone and lung metastases were detected with PET/CT.

The McNemar-Bowker test could not be applied to $\text{Total}_{\text{stage-PET/CT}}$ since there was no stage 1 case. However, a positive correlation was observed between $\text{Total}_{\text{stage-CT}}$ and $\text{Total}_{\text{stage-PET/CT}}$ ($r=0.424$; $p=0.009$). When PET/CT and CT imaging methods were compared on a stage basis, it was observed that PET/CT did not affect the stage in 18 cases, increased the stage in 14 cases and decreased the stage in 5 cases. The PET/CT method changed the stage in almost half of the cases.

Analysis of Volume Alteration. $\text{GTV}_{\text{CT-Total}}$ was found to be increased in 32 (86.5%) cases and decreased in 5 cases when compared to $\text{GTV}_{\text{PET/CT-Total}}$. $\text{GTV}_{\text{PET/CT}}$ was found to be increased in three cases and decreases 34 cases when compared to GTV_{CT} . GTV and GTVLN volume values were also compared. $\text{GTVLN}_{\text{PET/CT}}$ was found to be increased in 20 cases (54%) and decreased in 12 cases

(32.5%) when compared to GTVLN_{CT} . No pathological lymph nodes were detected in the remaining five cases. A statistically significant difference was observed with the Pearson correlation test when comparing the GTV, GTVLN and GTV Total volumes calculated based on CT and PET/CT imaging methods. The Wilcoxon test showed statically significant difference between GTV and GTV Total while GTVLN was not significantly different (Table 1).

Discussion

Significant changes have happened recently with the increased use of PET/CT, a functional imaging method. It is accepted as a standard method only for staging and radiotherapy of lung cancer for now; however, there are ongoing studies on other cancer types (Kim et al., 2007). In a study of Mutlu H et al. reported that staging with PET CT has better results in terms of survival staging. This superiority leads to survival advantage in patients with locally advanced non small cell lung cancer (Mutlu et al., 2013). It is still not a standard method for head and neck cancers, but has been used widely.

It has been shown that PET/CT is superior to classical methods (CT, MRI and USG) for tumor characterization and may change the treatment methods (Koc et al., 2011).

In a study of De Antonio et. al. it was stated that TNM stage and clinical stage were altered with the PET/CT in 22 % of the cases (Deantonio et al., 2008). Connel et. al conducted a study consisting 76 patients in order to assess the effects of PET/CT on prognosis; and reported TNM stage alteration in 34% of the cases based mostly on N parameter (Connell et al., 2007). Guido et al., also reported that 6 of 38 head and neck cancer patients' stage was altered after PET/CT and they also mentioned that these alterations based on the changes in nodal stage. In this study it was observed that nodal stage was increased in 5 cases and decreased in 1 case with PET/CT. Furthermore; new nodal activity was observed in 9 cases without changing the stage even these lymph nodes were not observed with CT imaging (Guido et al., 2009). In our study T stage was increased in 8 cases, decreased in 8 cases and was not changed in 21 cases ; N stage increased in 10 cases, decreased in 2 cases and was not changed in 25 cases with PET/CT. In 4 cases determined as M0 before; distant metastasis was detected with PET/CT. TNM stage was increased in 14 cases, decreased in 5 cases and was not changed in 18 patients.

In a meta-analysis conducted in order to define the role of PET/CT for detecting distant metastases, it was stated that PET/CT is superior to other imaging methods (Xu et al., 2011). We also observed distant metastases in four cases which we were unable to detect with other imaging methods.

In radiotherapy, it is crucial to contour critical organs and target organs for the treatment plan. The most important reason that PET/CT is a preferred method over others for contouring target volumes is that it can provide better differentiation of tumor tissue from healthy tissue (McGuirt et al., 1995). Comparing target tumor volumes determined by CT and PET/CT images may

result in changing the treatment plan. There are four main methods for GTV contouring using PET/CT, although these methods are not standardized (Paulino et al., 2004; Nestle et al., 2005;).

i) Visual assessment; *ii)* Contouring based on a certain SUVmaxisocontour; *iii)* Contouring based on a certain proportion of the SUVmaxvalue; *iv)* Contouring based on source/basis activity ratio.

Visual assessment is usually used with PET/CT imaging; we also prefer to use the visual method for volume calculation.

Most researchers consider target volume changes described by PET or CT. There are studies reporting both an increase and a decrease in the target volume (Daisne et al., 2004; Heron et al., 2004; Van Baardwijk, 2004; Paulino et al., 2005; Schwartz et al., 2005). In the literature, this change in the GTV is reported as mostly decreasing. Daisne et al. compared the calculated volumes of 19 head and neck cancer patients using CT, MRI and PET/CT and reported that there was no significant difference between the GTV values described by CT and MRI. However, the GTV values calculated using PET were found to be decreased in patients with tumors in the larynx, oropharynx and hypopharynx (Daisne JF et al. 2004). Heron et al. reported that the GTV of primary tumors was decreased in 14 cases and increased in 3 cases (a total of 21 cases) using PET/CT (Heron DE, et al. 2004). In a study by Van Baardwijk et al. consisting 16 patients, comparing $GTV_{PET/CT}$ and GTV_{CT} results, it was found that the $GTV_{PET/CT}$ values were significantly smaller (Van Baardwijk, 2004). Paulino et al. compared $GTV_{PET/CT}$ and GTV_{CT} and reported a 75% decrease in 40 cases (Paulino et al., 2005). In a study by Schwartz et al consisting of 19 cases and in a study by Scarfone et al. consisting of 9 cases, it was reported that there were no significant differences between GTV_{PET} and GTV_{CT} values in both studies (Scarfone et al., 2004; Schwartz et al., 2005). In our study, $GTV_{PET/CT}$ was smaller than GTV_{CT} in 34 (92%) of 37 cases, while GTV_{CT} was smaller than $GTV_{PET/CT}$ in 3 cases.

Heron et al. investigated 21 patients and detected metastatic lymph nodes in 15 cases. They reported that nodal volume parameter was decreased in 3 cases, increased in 9 cases and was unchanged in 3 cases. They also stated that there was no significant difference in terms of nodal involvement areas (Heron DE, et al. 2004). In our study, $GTV_{LN_{PET/CT}}$ was larger in 20 cases (54%) and smaller in 12 cases (32.5%) when compared to $GTV_{LN_{CT}}$. There was no statistically significant difference between $GTV_{LN_{PET/CT}}$ and $GTV_{LN_{CT}}$.

Determining tumor limits based on PET/CT results can be done using several methods which are described above. The most simple and common method is visual assessment. This method requires an experienced nuclear medicine specialist and is totally user dependent.

We state that PET/CT can significantly change both clinical staging and radiotherapy planning referring to both literature data and our study consisting of 37 cases. Therefore, we can assert that PET/CT can provide benefits in radiotherapy planning in patients with locally advanced head and neck cancer.

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