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

Sonay Arslan¹, Candan Demiroz Abakay², Feyza Sen³, Ali Altay², Tayyar Akpınar³, Ahmet Siyar Ekinci⁴, Onur Esbah⁴*, Nuri Uslu¹, Kezban Esra Kekilli⁵, Lutfi Ozkan²

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 (13-84 years). 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

Asian Pac J Cancer Prev, 15 (24), 10899-10903

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.

¹Department of Radiation Oncology, ²Department of Medical Oncology, Diyarbakır Gazi Yusufçuk Education and Research Hospital, Diyarbakır. ³Department of Radiation Oncology, ⁴Department of Nuclear Medicine, Uludag University, Faculty of Medicine, ⁵Department of Radiation Oncology, Bursa Ali Osman Sonmez Oncology Hospital, Bursa, Turkey  *For correspondence: onurilyasoglu131202@yahoo.com
son Arslan et al
Asian Pacific Journal of Cancer Prevention, Vol 15, 2014
CT
PET/CT-Total
max
stage-ct
node volume; GTVLTOTAL: Total volume of primary tumor+locoregional lymph nodes; CT: Computed tomography; PET/CT: Positron emission tomography/computed tomography
*r:Correlation coefficient *Wilcoxon test  **Pearson correlation analysis; GTV: Gross tumor volume; GTVLN:Involved locoregional lymph node volume; GTVTotal: Total volume of primary tumor+locoregional lymph nodes; CT: Computed tomography; PET/CT: Positron emission tomography/computed tomography

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 the 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 differentiates 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 GTV LN PET/CT determined via CT and GTV PET/CT and GTVLNPET/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. GTVTotal was calculated by adding GTV CT to GTVLN CT and GTV PET/CT. Total was calculated by adding GTV PET/CT to GTVLNPET/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 GTV LN values obtained by CT and PET/CT individually. Pearson correlation analysis was used to compare GTV PET/CT-Total with GTV CT-Total* GTV CT with GTV LN PET/CT-Total with GTV LN CT individually. The McNemar-Bowkertest was used to analyze the stage changes between T-stage and T-stage-pet/ct* N-stage and N-stage-pet/ct* M-stage and M-stage-pet/ct* Total stage 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 CT | 32.71 (3.14-311.23) | <0.001 | 0.792 | <0.001 |
| CT        | 55.77 (7.16-390.13) |       |      |           |
| GTV LN PET/CT CT | 7.49 (0-114.46) | 0.217 | 0.777 | <0.001 |
| CT        | 5.29 (0-126) |       |      |           |
| GTV Total PET/CT CT | 50.90 (4.80-311.23) | <0.001 | 0.762 | <0.001 |
| CT        | 81.98 (7.60-390.13) |       |      |           |
observed with PET/CT in 19 of 37 patients and the treatment plan was changed afterwards. There was no statistically significant difference between T_{stage-CT} and T_{stage-PET/CT} (p=0.306). However, there was a positive correlation between T_{stage-CT} and T_{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_{stage-CT} and N_{stage-PET/CT} (p=0.197). However, there was a positive correlation between N_{stage-CT} and N_{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_{stage-CT} and M_{stage-PET/CT} (p=0.125). However, there was a positive correlation between M_{stage-CT} and M_{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 Total_{stage-PET/CT} since there was no stage 1 case. However, a positive correlation was observed between Total_{stage-CT} and Total_{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. GTV Total volumes determined by CT and PET/CT images may show statistically 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 SUVmax isocountour; iii) Contouring based on a certain proportion of the SUVmax value; 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 calculated using PET were found to be decreased in patients with tumors in the larynx, oropharynx and hypopharynx (Daisne 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 et al., 2004). In a study by Van Baardwijk et al. consisting of 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 Scarton et al. consisting of 31 cases, it was reported that there were no significant differences between GTVPET and GTV_{CT} values in both studies (Scarton 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 et al., 2004). In our study, GTV_{LN PPPET/CT} was larger in 20 cases (54%) and smaller in 12 cases (32.5%) when compared to GTV_{LN PCT}. There was no statistically significant difference between GTV_{LN PPET/CT} and GTV_{LN PCT}.

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.

References

American Joint Committee On Cancer (2010). AJCC Cancer Staging Manual Seventh Edition. Springer.

Chapman Jd, Bradley Jd, Eary Jf, et al (2003). Molecular (Functional) imaging for radiotherapy applications: an RTOG symposium. Int J Radiat Oncol Biol Phys, 55, 294-301.

Connell CA, Corry J, Milner AD, et al (2007). Head Neck. Clinical impact of, and prognostic stratification by, F-18 FDG PET/CT in head and neck mucosal squamous cell carcinoma. Head Neck, 29, 986-95.

Daisne JF, Duprez T, Weynand B, et al (2004). Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. Radiology, 233, 93-100.

Deantonio L, Beldi B, Gambero G, et al (2008). FDG-PET/CT imaging for staging and radiotherapy treatment planning of head and neck carcinoma. Radiation Oncology, 3, 29.

Demir B, Okutan M, Demir M (2009). Positron emision tomografi ve radyoterapi tedavi planlaman. Turk Onkoloji Dergisi, 24, 88-97.

Guido A, Fuccio L, Rombi B, et al (2009). Combined 18F-Fdg-Pet/Ct Imaging In Radiotherapy Target Delineation For Head-And-Neck Cancer. Int J Radiation Oncology Biol Phys., 73,759-63.

Heron DE, Andrade RS, Flickinger J, et al (2004). Hybrid PET–CT simulation for radiation treatment planning in head-and-neck cancers: a brief technical report. Int J Radiat Oncol Biol Phys., 60, 1419-24.

Kang PM, Seo WI, Lee SS, et al (2014). Incidental abnormal fdg uptake in the prostate on 18-fluoro- 2-deoxyglucose positron emission tomography-computed tomography scans. Asian Pac J Cancer Prev, 15, 8699-703.

Kim SY, Roh JL, Yeo NK, et al (2014). Combined 18F-fluordeoxyglucose-positron emission tomography and computed tomography as a primary screening method for detecting second primary cancers and distant metastases in patients with head and neck cancer. Ann Oncol, 18, 1698-703.

Koc ZP, Balci TA (2011). Bas ve boyun tumorlerinde positron emisyon tomografi/bilgisayarlı tomografi (PET/CT). Fırat Tip Dergisi, 16, 194-8.

McGuirt WF, Williams DW III, Keyes JW Jr, et al (1995). A comparative diagnostic study of head and neck nodal metastases using positron emission tomography. Laryngoscope, 105, 373-75.

Mutlu H, Buyukcelik A, Erden A, et al (2013). Staging with PET-CT in patients with locally advanced non small cell lung cancer is superior to conventional staging methods in terms of survival. Asian Pac J Cancer Prev, 14, 3743-6.

Nestle U, Kremp S, Schaefer-Schuler A, et al (2005). Comparison of different methods for delineation of 18F-FDG PET-positive tissue for target volume definition in radiotherapy of patients with non-Small cell lung cancer. J Nucl Med, 46, 1342-48.

Paulino AC, Johnstone PA (2004). FDG-PET in radiotherapy treatment planning: Pandora’s box? Int J Radiat Oncol Biol Phys, 59, 4-5.

Paulino AC, Koshy M, Howell R, et al (2005). Comparison of CTand FDG–PET-defined gross tumor volume in intensitymodulated radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys, 61, 1385-92.

Scarton C, Lavevy WC, Cmelak AJ, et al (2004). Prospective feasibility trial of radiotherapy target definition for head and neck cancer using 3-dimensional PET and CT imaging. J Nucl Med, 45, 543-52.
Role of PET/CT in Treatment Planning of Head and Neck Cancer Patients Undergoing Definitive Radiotherapy

Schwartz DL, Ford E, Rajendran J, et al (2005). FDG–PET/CT imaging for preradiotherapy staging of head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys*, 61, 129-36

Suit H (1996): Assessment of the Impact of Local Control on Clinical Outcome. In, Meyer JL, Purdy JA: Frontiers of Radiationtherapy and Oncology (3-D Conformal Radiotherapy: A new era in the irradiation of cancer). Basel: Karger, 17.

Tan R, Yao SZ, Huang ZQ, et al (2014). Combination of FDG PET/CT and contrast-enhanced MSCT in detecting lymph node metastasis of esophageal cancer. *Asian Pac J Cancer Prev*, 15, 7719-24

Xu GZ, Guan DJ, He ZY (2011). (18) FDG-PET/CT for detecting distant metastases and second primary cancers in patients with head and neck cancer. A meta-analysis. *Oral Oncol*, 47, 560-65.

Van Baardwijk A (2004). Comparison of clinical target volume in PET–CT and CT-scan based treatment planning in patients in patients with head and neck cancer. *ESTRO*, 23, 177.