The Role of 18-FDG Positron Emission Tomography (FDG-PET) in Detecting Post-Radiotherapy Loco Regional Relapse/Residual Disease in Nasopharyngeal Cancer

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ABSTRACT

Background: Post-radiotherapy nasopharyngeal changes represent a diagnostic dilemma. Early detection of persistent or recurrent disease may be translated to better cure rate if salvage therapy is implemented. Neither clinical exam nor current radiological anatomical studies (CT/MRI) can differentiate between benign post therapy changes and recurrence. PET scan is a functional study capable of identifying viable tumors as areas of increased radiotracer uptake.

Methods: Fifty-five patients underwent 18-FDG PET scans post radiation therapy for nasopharyngeal carcinoma at King Faisal Specialist Hospital and Research Centre. We compared the 18-FDG PET scan with the clinical, radiological and pathological findings.

Results: Clinical examination and CT of the head and neck showed post-treatment abnormality in the nasopharynx in 40 patients. Among these, 28 patients had asymmetry in the CT scan. Three out of the 28 patients had positive PET scan. Out of the 12 patients with positive primary disease in the CT scan, 3 had negative PET scan which was also confirmed by biopsy in 2 patients. Eleven patients had positive PET scan in the primary site; this was pathologically confirmed to be recurrent disease in 5 patients. In 2 patients repeat PET scan was converted to negative. The remaining 4 patients did not have biopsy due to the presence of concurrent distant disease. None of the patients with negative PET scan in the neck exhibit recurrence or persistent neck disease to the day of reporting the study. PET scan showed persistent higher sensitivity, specificity, positive and negative predictive values at both the primary site and the neck region than the CT did.

Conclusion: PET scan is a useful tool in differentiating between post radiotherapy fibrosis and recurrent nasopharyngeal cancer.

Key Words: Nasopharyngeal cancer – FDG/PET – Post therapy changes.

INTRODUCTION

The therapeutic outcome of recurrent nasopharyngeal cancer is strongly influenced by the early depiction of recurrence. The present anatomical studies such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), provide unparalleled morphological details based on tissue density, location and structure. However, none of these studies can differentiate between tumor and reactive or fibrotic tissue [1,2]. Post therapy fibrosis represents a clinical dilemma, since it is difficult with both clinical and radiological tools to exclude harboring malignancy. Early detection of relapse/residual disease and prompt introduction of salvage therapy (radiosurgery or brachytherapy) was shown to give excellent tumor control [3-5]. The current diagnostic limitations may lead to either under-treatment or overtreatment [6]. Early studies confirmed the PET value in differentiating between recurrent brain tumors and post radiation treatment (RT) necrosis/fibrosis [7-9]. FDG-PET is a unique functional imaging modality that shows the cellular metabolic activity in vivo. Positron-emission tomography (PET) has been in existence since the 1960. FDG (2-[18F] fluoro-2-deoxy-D-glucose) is a glucose analog which is taken up in viable cells by the same pathway. However, unlike glucose, once trapped inside the cell, further metabolism is blocked. The rate of FDG uptake in tumor cells was shown to be greater than normal cells [10,11].
The role of FDG-PET is evolving in the detection of active malignant disease and cancer staging. PET was shown to be particularly useful in cancer esophagus, breast, lungs, lymphoma, metastatic disease and others (colorectal and cervical carcinoma) [12-17]. Many studies have documented the high accuracy of FDG-PET for staging, detection of relapse, tailoring RT fields, evaluation of response to therapy and prediction of outcome.

The aim of the current study is to validate the accuracy of FDG-PET scan in post-radiotherapy treatment for nasopharyngeal cancer.

PATIENTS AND METHODS

Patients:

A total of 55 patients with the diagnosis of nasopharyngeal cancer were seen at the combined head and neck cancer clinic at King Faisal Specialist Hospital and Research Center. There were 36 males and 19 females and their ages ranged from 13 to 80 years (median of 41 years). All patients had histologically confirmed squamous cell carcinoma of the nasopharynx (90% undifferentiated and 10% non-keratinizing). All patients underwent computed tomography (CT) of the head and neck. All except one were staged in accordance with the AJCC, 1997 staging system which was as follows: T1: 3 patients (5.6%), T2: 10 patients (18.5%), T3: 23 patients (42.6%), T4: 18 patients (33.3%), N0: 12 patients (22%), N1: 7 patients (13%), N2: 14 patients (26%) and N3: 21 patients (39%).

FDG-PET scanning:

The PET scan was carried out by injecting 370 MBq (10 mCi) 18-FDG after a 6-hour fast. Imaging was initiated 30-45 minutes later, using an ECAT EXACT 47 scanner (Siemens, Hoffman Estates). This three-ring system with a 16.2 cm field of view produces 47 contiguous image planes with plane spacing 3.375 mm, and having an in plane resolution of 6.7 mm. A whole body technique was used, whereby images were obtained in sequential bed position and joined into a single display. Whole body images were obtained (10-15 minutes in each bed position), processed and reconstructed using a 0.4 Hann filter. Transmission scanning was performed immediately post-emission, using external rotating germanium-68 rod sources. Attenuation correction was occasionally performed. PET scan was performed 2-217 months (median 16 months) post-radiotherapy.

Head and neck CT scanning:

CT head and neck examinations were obtained using high resolution spiral CT scan. Intravenous injection of contrast medium was used and both axial and coronal cuts were obtained. The criteria to call the CT positive in the primary site were similar to what was reported in the literature [18].

Diagnostic CT/MR imaging and PET scans were read independently by two nuclear medicine expert radiologists and a head and neck radiologist. The data was collected and compared with clinical results and histological diagnosis.

Statistical methods:

To statistically assess the performance of the CT and PET scans in detecting residual/recurrent disease, sensitivity, specificity, positive and negative predictive values were calculated for the entire patient population for a lesion- and study-based analysis using the standard definitions [19]. Fisher’s Exact and Cohen’s Kappa tests were employed to measure the agreement between the CT and PET scans findings and to assess its correlation to the gold standard (positive biopsy or proved disease progression during follow-up) [20]. The statistical analysis was performed using the SPSS version 15 software and a p-value <0.05 was considered statistically significant.

RESULTS

Primary disease:

The data were collected retrospectively; hence biopsy was not routinely done. Out of the 55 patients who underwent post radiotherapy FDG-PET scan, only 16 patients (29%) underwent biopsies from the primary site. FDG-PET scan was reported positive, negative or questionable in 11, 41 and 3 patients, (20%, 74.5% and 5.5%) respectively. None of the patients who had negative PET scan showed evidence of recurrent or persistent disease either on biopsy or on follow-up. PET scan results correlated significantly with the relapse rate (Fisher exact test p-value = 0.00028). Among the 11 patients who had positive PET scan, 5 had positive biopsy. In two patients who had positive PET scan 8 and 10 weeks post therapy, the study
was converted to negative when PET was repeated 3 months later. The remaining 4 patients with positive primary PET scan did not have biopsy due to the presence of distant metastases. The PET scan sensitivity, specificity, positive and negative predictive value was: 100%, 95%, 81.8% and 100% respectively. In 3 patients, the PET scan findings were questionable (faint uptake), however they were reported as in favor of inflammatory process. None of these patients showed relapse in the primary site. Fig. (1) shows axial PET image with faint uptake at the nasopharyngeal region and the corresponding CT axial image with nasopharyngeal fullness.

The CT scan of the primary site was interpreted as asymmetry, positive (definite contrast-enhancing mass) and negative in 28, 12 and 11 patients, (51%, 22% and 20%) respectively. Four patients did not have post-treatment CT scan. Among the patients with CT asymmetry, only 3 had positive PET scan; two of them were false positive due to short timing of the PET study after therapy Fig. (2).

None of the patients who had CT asymmetry and negative PET scan relapsed in the primary site. Among the 12 patients who had positive CT, 8 had positive PET scan and confirmed relapse either by biopsy or evidence of disease progression on follow-up Fig. (3). Three patients had negative PET scan and negative biopsies. One patient who had weak radiotracer uptake on PET scan reported as questionable, did not show disease progression on further follow-up. None of the 11 patients with negative CT scan had positive PET scan. On follow-up, there was no evidence of recurrence in this group of patients. The sensitivity, specificity, positive and negative predictive value of CT scan of the primary site to diagnose local recurrence was: 100%, 73%, 66.7% and 100%, respectively. There was a significant association between the findings of CT scan of the primary site and local recurrence \( (p\text{-value} = 0.00001) \). Furthermore, a significant correlation between the CT scans of the primary site and PET results (Fisher exact test, \( p\text{-value} = 0.0000009 \)).

**Nodal disease:**

Post-treatment, FDG-PET scan was positive for neck nodal disease in 10 patients. Histopathology confirmation was obtained in 7 patients. One patient did not have biopsy because of presence of distant metastases. Two patients had false positive scans, probably because PET was done shortly after therapy. The repeat PET scans were negative in both patients. None of the patients with negative PET scan developed neck failure on follow-up.

On the other hand, post-therapy CT scan was positive for neck nodal disease in 17 patients. Of these, only 8 had positive biopsy or evidence of progression during follow up. One patient out of the 34 patients with negative CT scan had positive PET scan and was confirmed positive on biopsy. The sensitivity, specificity, positive and negative predictive values of the PET scan to identify neck-nodal relapse was: 100%, 95.7%, 80% and 100%, respectively and was: 89%, 79%, 47% and 97% for the CT neck results, in the same order. There was a good agreement between post therapy neck CT scan and the PET outcome (Cohen’s Kappa 0.38, significantly different from zero, \( p\text{-value} = 0.0039 \)).
DISCUSSION

Nasopharyngeal cancer is the most common head and neck cancer and represents 35% of all head and neck cancer diagnosed annually in Saudi Arabia [21]. Radiation therapy-induced changes (edema, inflammation, necrosis and fibrosis) are limiting factors that challenge the sensitivity of CT or MRI in the diagnosis of residual/recurrent nasopharyngeal carcinoma. Not all asymmetries of the nasopharyngeal mucosal outline, mass lesions and abnormal enhancements in the CT scans are signs of tumor recurrence [1].

The current anatomical diagnostic studies such as CT and MRI lack the differentiation between reactive changes and malignancy and may sometimes confuse fibrosis with recurrent cancer. As a consequence, tumor size at the primary site can be over-estimated [13]. The functional studies such as positron emission tomography carry a great potential to differentiate between malignant and non-malignant process. It improves detection of pathology based on metabolic activity rather than size. However, the drawback of this technology is that it is also positive in certain non-malignant conditions such as inflammation and infection [1,22-24].

Several studies reported on FDG-PET sensitivity and specificity in the staging of nasopharyngeal carcinoma [18,25-28]. Some others evaluated the efficacy of FDG-PET in the diagnosis of residual/recurrent disease [1,29-34]. Kao et al reported 100% sensitivity, 96% specificity and 97% accuracy for FDG-PET in 36 patients with nasopharyngeal cancer [31]. Keyes et al found FDG-PET scan to be extremely effective and reliable in the post-therapy setting in head and neck cancer [26], with a sensitivity and specificity of 80% and 81% respectively, compared with 58% and 100% for CT [35]. Our results are in good concurrence with Kao’s results and a bit inferior to Keyes’s ones. The later study involved patients with oral cavity and laryngeal...
In the current study, we reported a significantly higher specificity and positive predictive value for the PET scan than for the CT scan of the primary site (95% and 81.8% Vs. 73% and 66.7%). The sensitivity and the positive predictive value of the CT scan were even worse on assessing the regional relapse at the neck region (89% and 47% respectively). Our results concur with Kao, et al. and other studies in the superiority of the FDG-PET scan to CT scan for distinguishing recurrent/persistent tumor from post therapy changes [1,18,30,35,36]. Based on our results, the high false positive rate of the CT scan in follow-up of patients (33% at primary site and 53% at the neck), makes it an unsuitable tool in routine follow-up unless supplemented with biopsy. Despite the inaccuracy of CT scan in terms of false positive findings in the follow-up of patients with nasopharyngeal cancer, in our study no false negative result was encountered at the primary site, a finding which differed from what was reported elsewhere [30].

A critical review of somewhat conflicting data done by Schechter, et al. [36], indicated that PDG-PET had little additional value to physical examination and conventional imaging studies, supplemented by biopsy when appropriate, for the detection of subclinical nodal metastases, unknown primaries, or disease in the chest and head and neck cancer. This review however confirmed the role of PDG-PET in differentiating residual or recurrent disease from treatment-induced normal tissue changes. The authors conclude that PET can contribute to timely institution of early salvage therapy and obviate the need for unnecessary biopsies of irradiated tissues, which may aggravate radiation injury and/or an already existing necrotic ulcer.

In a more recent systemic review [1] comparing FDG/PET, CT and MRI in detecting recurrent nasopharyngeal carcinoma, FDG/PET had significantly better sensitivity and specificity than CT and MRI. It has been emphasized that time-to scan should be selected carefully. Initial increased FDG uptake was observed very early after irradiation which may have been caused by post therapy inflammatory changes. Subsequently, FDG uptake in the tumor decreased within 3 to 4 months. Time-to scan was reported as one of the most important factors for the high sensitivity and specificity of PET [1,18,30].

In the current study, patients used to be assessed clinically 6 weeks after end of radiation therapy. CT scan of the head and neck with and without contrast was routinely done 2 weeks later. PET scan takes another 2 weeks to be done, which makes time-to scan about 2.5 months. This may explain the false positive results encountered in 2 of our patients (18%). Appropriate selection, referral and timing of PET scans in defined clinical situations along with the knowledge of the potential pitfall errors, can lead to a reduction of interpretation errors, and minimize the number of false positive studies.

Our study was based on visual analysis and hence 3 patients’ results were questionable. A quantitative evaluation of PET might be more accurate in differentiating benign from malignant processes [30,37]. Other major limitation of FDG/PET is the lack of anatomic details, which hinders localization and characterization of increased FDG uptake [1].

Recently, the use of combined PET/CT imaging appears to be promising and of higher accuracy than conventional PET, particularly in the head and neck region and opens a new era in PET-CT-based radiation therapy planning for primary and recurrent tumors [38-40].

The PET/CT facility has been recently introduced at KFSH, after completion of the current study. We are currently establishing at KFSH, a protocol to incorporate PET/CT for staging, radiation therapy planning and follow-up of patients with nasopharyngeal cancers.

Conclusion:

PET is an excellent functional study to differentiate post-therapy changes from recurrent or persistent disease in nasopharyngeal cancer. FDG-PET scan is proven to be superior to CT scan in detecting post therapy recurrent/persistent disease. PET can contribute to the timely institution of salvage therapy while avoiding unnecessary biopsies of irradiated tissues.
REFERENCES


