Original Article

Role of FDG PET/CT Scan in Head and Neck Cancer Patients

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Abstract

Introduction: PET/CT scan has an emerging role in head and neck oncology with a few well-established indications, including: detection of unknown primary tumor site, tumor staging, radiotherapy planning, treatment response assessment and detection of recurrent disease. The purpose of this study is reporting PET/CT findings in head and neck cancer patients to emphasize its role in head and neck oncology.

Material and Methods: In a retrospective study, we reviewed our PET/CT database and found 94 patients with primary head and neck cancer. This is a descriptive report of PET/CT scan findings in head and neck cancer patients referred to Masih Daneshvari hospital, Tehran, Iran, between 2013 and 2016.

Results: The most common primary tumor sites were oral cavity (27%) and nasopharynx (22%). The most common indication for referral was tumor restaging (76%) including treatment response evaluation and differentiation between recurrence and post-treatment fibrosis. In 60% of patients with negative primary tumor site, PET/CT was able to detect evidence of regional or distant metastasis. PET/CT was able to localize the primary tumor site in 66% of patients with unknown primary tumor site. We also had 19 patients with primary head and neck cancer referred for initial staging, demonstrating evidence of metastasis in 66% of all cases.

Conclusion: Most patients are referred for restaging and demonstrate evidence of regional or distant metastasis with significant value for further treatment planning. Providing insurance coverage and familiarizing referring physicians about correct indications of this relatively new diagnostic modality will be to the best interest of head and neck cancer patients in the long run.

Keywords: Head and neck cancers, PET/CT, re-staging, staging

Cite this article as: Bakhshayesh Karam M, Doroudinia A, Safavi Nainee A, Kaghazchi F, Yousefi Koma A, Mehrian P, Agha Hosseini F. Role of FDG PET/CT scan in head and neck cancer patients. *Arch Iran Med.* 2017**; 20(7):** 452 – 458.

Introduction

Head and neck cancers rank amongst the ten most common malignant diseases.[1] Approximately 650,000 new cases of head and neck cancer are diagnosed annually, with 350,000 death reports annually worldwide.[2] They describe a group of tumors that arise in the upper aerodigestive tract including the larynx, pharynx, oral cavity, nasal cavity, and para-nasal sinuses.[3] The vast majority of head and neck malignancies are squamous cell carcinomas (SCC).[4] The choice of therapy in patients with head and neck cancer depends mainly on tumor location, invasion to adjacent structures and presence of distant metastases.[5]

Fluorine-18 fluorodeoxyglucose (18F-FDG) is a radiolabeled analogue of glucose with a cellular uptake mechanism identical to glucose. However, unlike glucose, it does not undergo further intercellular metabolism and is actually trapped inside the cell until complete decay. 18F-FDG is a beta and positron emitter and during intercellular decay, the emitted positrons undergo annihilation with resident electrons. The result of each annihilation is emission of two gamma rays in opposite directions with 511 Kev energy. These gamma rays are detected by PET camera detectors. Therefore, 18F-FDG PET/CT is functional imaging of cellular metabolism and on the final images; areas with higher rate of metabolism demonstrate higher FDG uptake.[6]

Integrated PET/CT has been established as an important diagnostic technique for staging and assessing treatment response in advanced head and neck cancers. It has higher sensitivity than CT or MRI for detection of small lymph nodes.[7] Also, in assessing treatment response, PET/CT has been shown to differentiate early responders from nonresponders.[8]

FDG-PET also identifies aggressive or radiation resistant tumors, as it represents the cumulative effects of multiple adverse tumor characteristics, such as high cell metabolism, proliferation, expression of key oncogenes, and hypoxia[9] depending on the type of PET radiotracer used; however, the most common PET radiotracer is FDG (fluorodeoxyglucose) which reflects tumor metabolic activity as mentioned earlier.

Recently, three dimensional FDG parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been utilized as additional diagnostic and prognostic imaging biomarkers in various human solid tumors[10–12] including head and neck squamous cell carcinomas (HNSCCs).[13–15] The important feature of these FDG PET/CT parameters is that they are continuous variables that are measured quantitatively. Because all the already existing parameters are continuous, it is necessary to

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Accepted for publication: 14 June 2017

establish a cutoff point for their clinical use. However, currently a single optimal cutoff point has not been established, which is a limitation for PET imaging.

The purpose of this study is to initially describe the prevalence and different pathological features of head and neck cancers, evaluated by the PET/CT department of Masih Daneshvari hospital, and then evaluate some FDG-PET parameters in these cases.

Materials and Methods

Patient population

This is a retrospective study performed on 94 patients with primary head and neck malignant neoplasm, referred to Masih Daneshvari hospital, Tehran-Iran between 2013 and 2016. We included all patients with primary head and neck malignancy who underwent FDG-PET/CT imaging in our department from 2013 to 2016. The clinical information recorded included age, gender, primary tumor site, primary tumor pathology, purpose of imaging with 18F-FDG PET/CT, presence of local invasion, presence of distant metastasis and SUVmax (Standard Uptake Value) of primary and metastatic lesions. The study design and protocol were reviewed and approved by the institutional review board (IRB).

18F-FDG PET/CT imaging and interpretation

All PET/CT imaging were acquired using Discovery 690 VCT (GE Healthcare, Milwaukee, USA) that is equipped with 64-slice CT scanner (Light Speed VCT). All patients fasted for at least 4 to 6 hours before 18F-FDG PET scanning and whole-blood glucose concentrations were checked to be less than 150 mg/dL before 18F-FDG administration. Each patient was given 750 mL of oral contrast solution 30 minutes prior to initiation of PET/CT scan to help with uniform distention of bowel loops and improve image interpretation. The oral contrast agent did not contain glucose and included diatrizoatemeglumine and diatrizoate sodium solution 8 mL/500 mL water. No intravenous (IV) contrast was given to the patients. Whole-body image acquisition started about 45 – 60 minutes after intravenous injection of 370 – 555 MBq18F-FDG (4.6 MBq/Kg). The 18F-FDG/CT scanning was performed in spiral mode from the vertex to the proximal thigh and also a separate dedicated head and neck PET/CT was performed subsequently in the arms-down position. The emission scan time per bed position was 2.5 minutes, and eight to ten bed positions were used for whole body imaging; however, the scan time for dedicated head and neck PET was longer, reaching 6 minutes per bed position. The PET data were reconstructed using a standard iterative algorithm with attenuation correction based on the CT scan data. A joint group of one nuclear medicine physician and one radiologist with more than 5 years of experience interpreted the PET/CT images by visual inspection (Subjective) and metabolic activity quantification (Objective) parameters. To quantify metabolic activity in the target lesions, we used Standard Uptake Value (SUV) which is a product of total administered 18F-FDG and its uptake in the selected region of interest (ROI), corrected for patient's weight. All reviewers had access to patient's relevant medical history and medical records from outside facilities if applicable. Foci with increased 18F-FDG uptake in the primary tumor sites, metastatic lymph nodes and distant metastases were evaluated and compared with the background blood pool metabolic activities. Image interpretation was based on visual and semi-quantitative analyses of abnormally increased focal 18F-FDG uptakes but no strict standardized uptake value cutoffs were used. Local, regional, and distant sites were independently assessed and the presence of any primary tumor site, metastatic lymph node or soft tissues in the neck, and distant metastatic sites of each patient were recorded.

Statistical analysis

Continuous variables were expressed as median and range, and categorical variables were expressed as numbers and percentages. All statistical analyses were performed using SPSS software version 11.0 (IBM, Armonk, NY, USA).

Results

Patient characteristics

A total of 94 patients, 57 men and 37 women with a median age of 51 years (range: 4 to 90 years) were included in this study. The patients' characteristics are demonstrated in Table 1.

The primary tumors were most frequently detected in the oral cavity (27%) and the nasopharynx (22%), and the most frequent pathology was squamous cell carcinoma (SCC) with a rate of 44% (Table 2). The most common indication for referral was tumor restaging (80%) including treatment response evaluation and discrimination between recurrence and post-treatment fibrosis.

18F-FDG PET/CT findings

After performing 18F-FDG PET/CT, in 67% of all patients (regardless of the reason for referral), the primary tumor site according to the patient's history was visualized by PET. The most common sites of detected primary tumors were oral cavity (18% of all patients), followed by nasopharynx (14% of all patients), with mean SUV of 8.6 (SD ± 1.2) and 9.6 (SD ± 1.3), respectively.

Moreover, metastatic lesions were detected in 74% of all patients. The most frequent metastatic sites were: Cervical lymph nodes (24% of all patients), Lungs (17% of all patients) and Hilar/Mediastinal lymph nodes (10% of all patients). Other metastatic sites were much less frequent. Mean SUV for each metastatic site was 8.26 (SD = ±1.1).

Totally, 6 patients were referred for PET/CT with metastatic cervical lymphadenopathy and indeterminate primary tumor site or cancer of unknown primary origin (CUP). In 4 patients (66.6%) with cancer of unknown primary origin (CUP), PET/CT was able to localize the exact location of primary tumor site. Of these patients, the primary tumor site was found in nasopharynx in two cases, the primary tumor site was in the submandibular region in one case, and in another case the primary tumor site was in right pyriform sinus. In the other two patients (33.4%), the primary tumor was never identified by PET/CT. Figure 1 demonstrates this patient presenting with extensive right cervical metastatic lymphadenopathy in which PET/CT was able to locate the primary site in the ipsilateral pyriform sinus, not apparent by endoscopy or other conventional imaging modalities. In two other patients, PET/CT was not able to localize the primary tumor site.

Evidence of metastatic lesions was found in 95% of patients with primary head and neck cancer, referred for initial staging and 59% of patients referred for restaging and overall in 66.2% of all patients. The 18F-FDG PET/CT findings are demonstrated in more details in Table 3.

Table 1. Patient characteristics

Characteristics	Number	Percent (%)
Gender		
Female	37	39
Male	57	61
Age (yrs.)		
Mean (range)	51 (4 to 90 yrs.)	
Primary tumor site		
Oral cavity	26	27
Nasopharynx	21	22
Nasal cavity, Paranasal sinus	9	10
Larynx	8	9
Parotid	8	9
Cancer of Unknown Primary origin (CUP)	6	6
Mandible	4	4
Orbit	4	4
Others	8	9
Purpose of study		
Initial Staging	18	20
Restaging	76	80

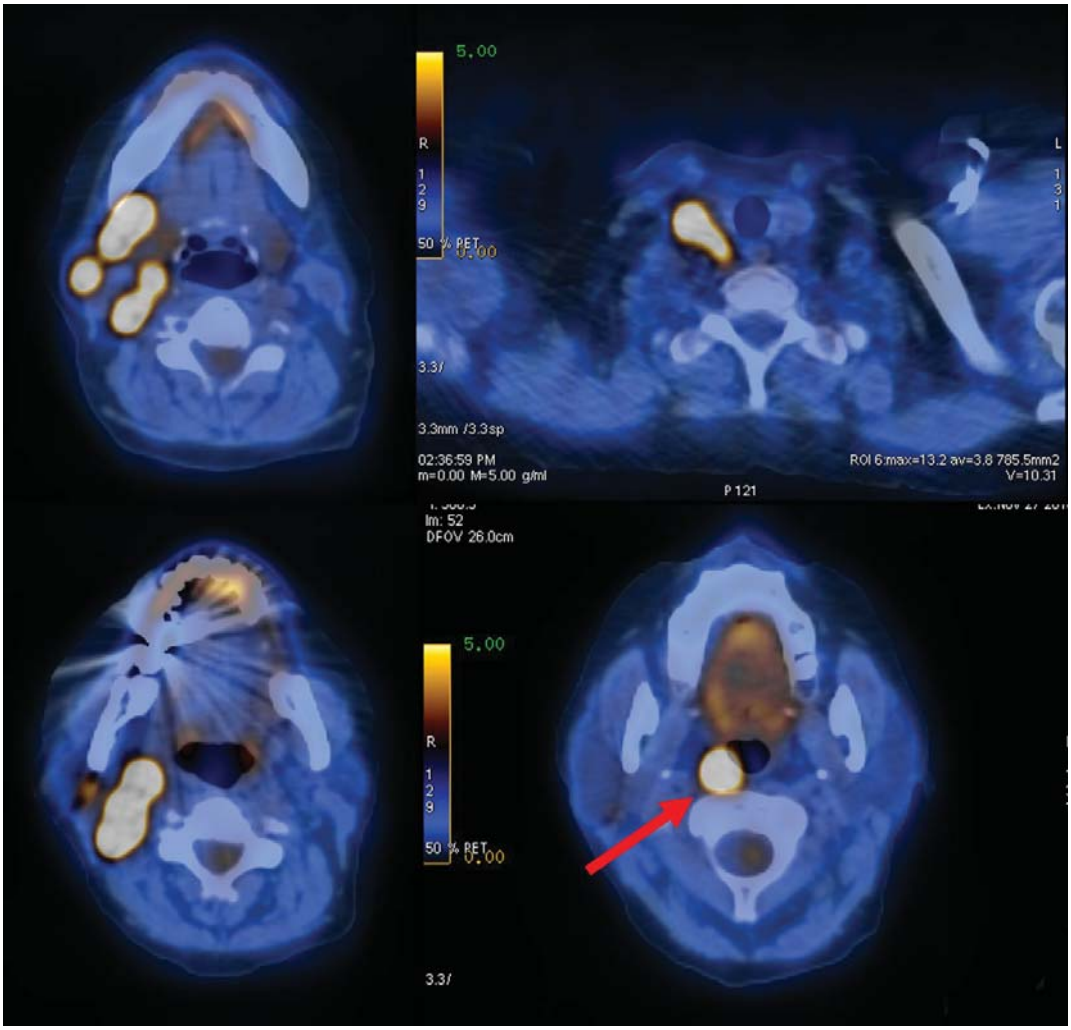

Figure 1. Cancer of unknown primary origin presenting as massive cervical lymphadenopathy

Table 2. Tumor Pathology

Characteristics	Number	Percent (%)
SCC (Squamous cell carcinoma)	42	44
Nasopharyngeal carcinoma	16	17
ACC (Adenoid cystic carcinoma)	7	7
Melanoma	4	4
MEC (Mucoepidermoid carcinoma)	6	6
NHL (Non-Hodgkin lymphoma)	4	4
Others	15	18

Table 3. 18F-FDG PET/CT findings

Findings	Number	Percent (%)
Primary tumor site found in PET/CT		
Oral cavity	17	18
Nasopharynx	13	14
Parotid	6	6
Negative	31	33
Others	27	29
Metastatic sites		
Cervical lymph nodes	29	24
Lung	21	17
Hilar/Mediastinal LN	12	10
Bones	8	7
others	26	11
Negative	25	21

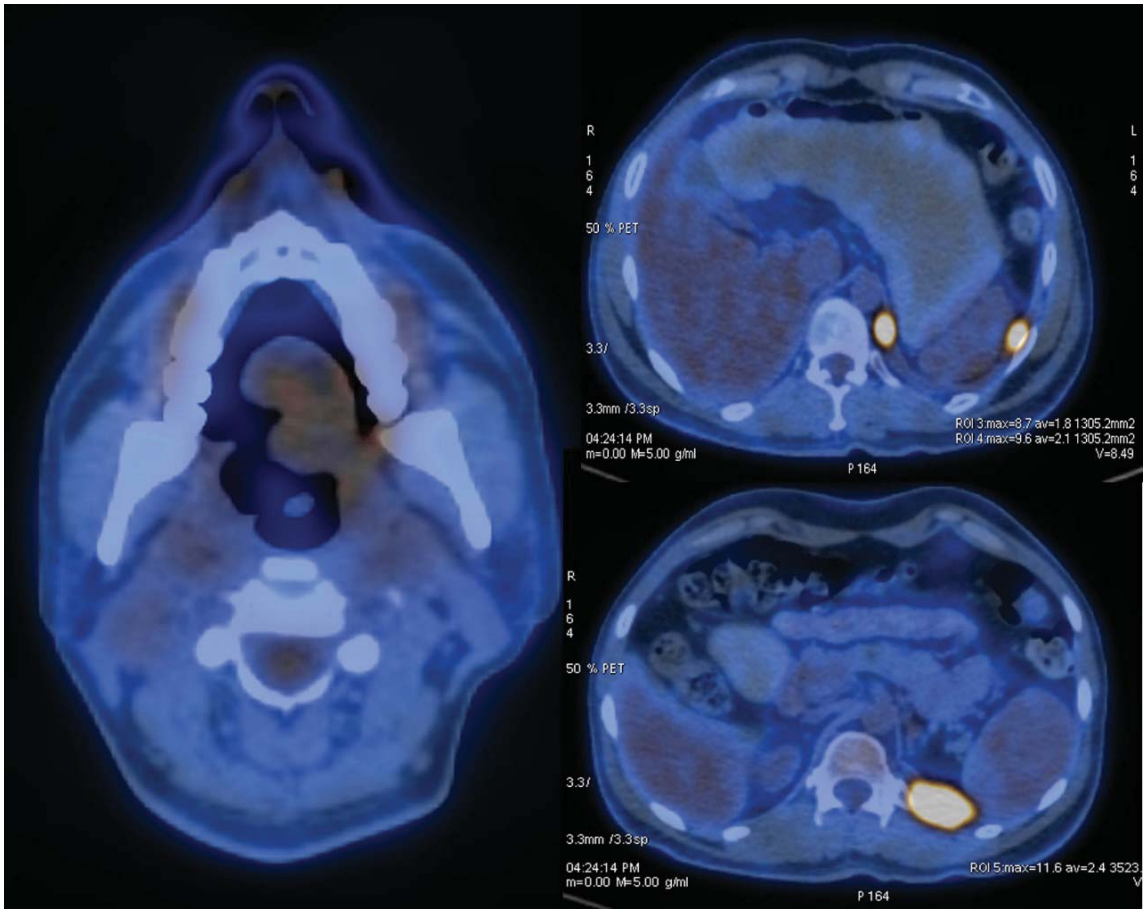

Figure 2. Tongue SCC after partial glossectomy and evidence of distant metastasis in pleura.

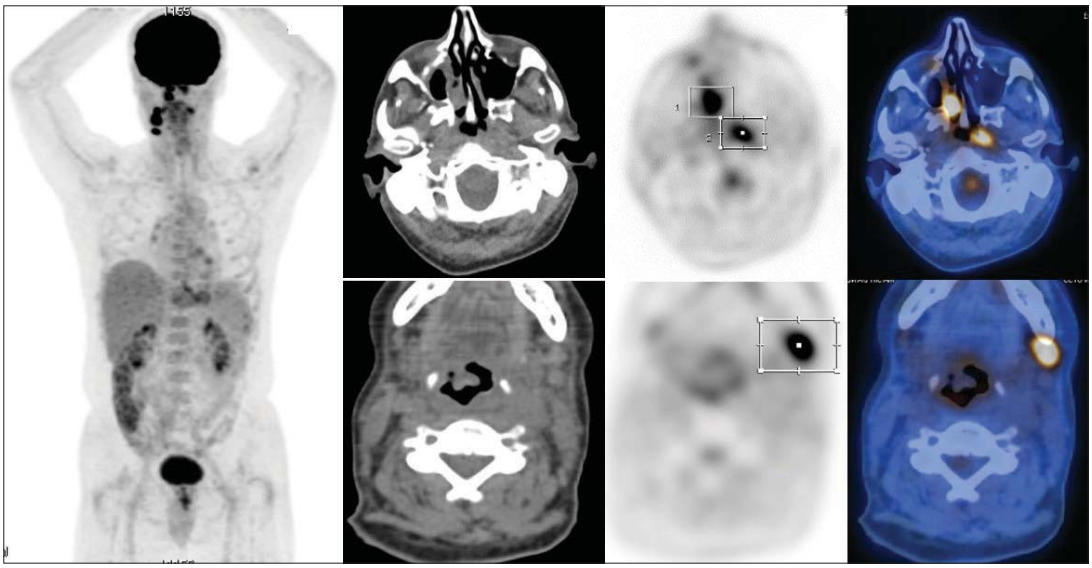

Figure 3. Sinonasal SCC with evidence of metastatic cervical lymphadenopathy

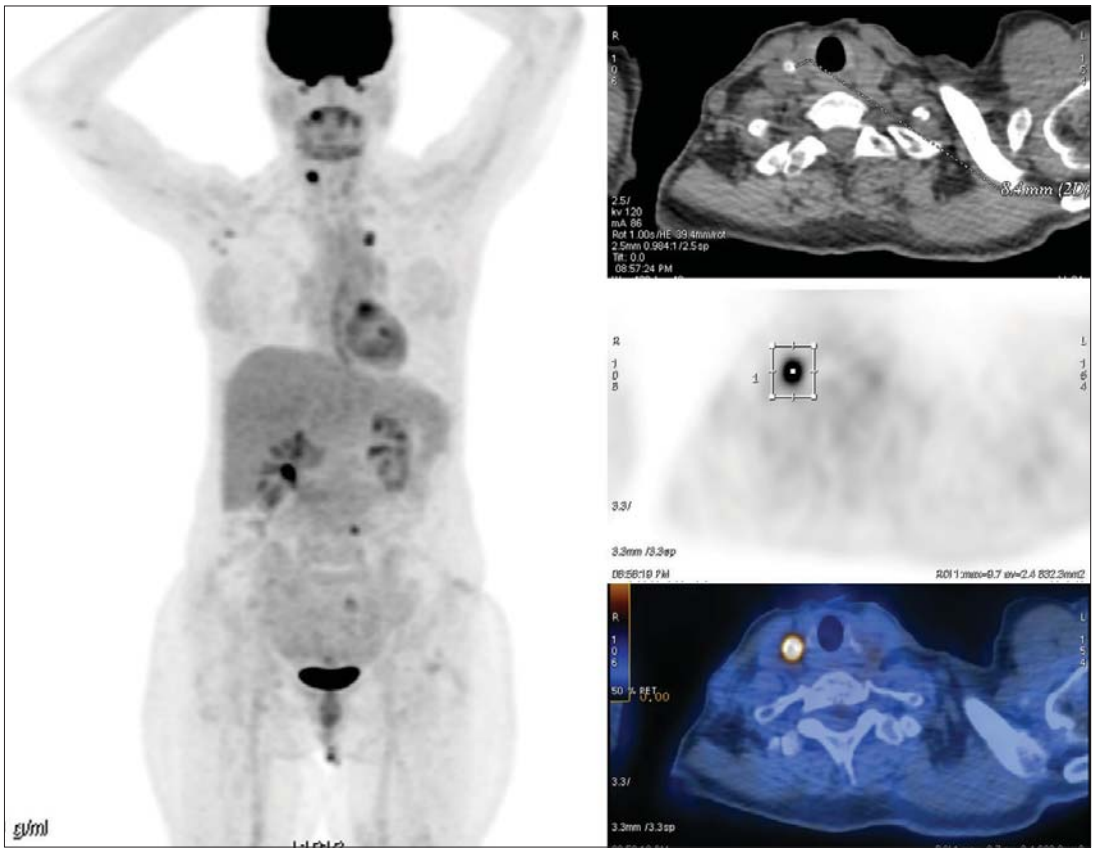

Figure 4. Incidental hypermetabolic thyroid nodule, requiring further evaluation

Figure 2 demonstrates a patient with tongue SCC after partial glossectomy and no evidence of local recurrence, but PET/CT revealed metastatic foci in the left pleura.

We were not able to demonstrate a significant relationship between semi-quantitative metabolic values (SUVmax) and primary or metastatic tumor site.

Discussion

The National Comprehensive Cancer Network (NCCN, 2017) guidelines for follow-up care in head and neck cancer patients recommend post-treatment baseline imaging within 6 months after initial treatment for cancers of the oropharynx,

hypopharynx, larynx, and nasopharynx in patients with T3–4 or N2–3 disease only, and further re-imaging is not recommended except in clinically suspicious patients.[16] However, post-treatment recurrence may occur in patients negative for disease on clinical follow-up (Salaun, et al. 2007).[17] Tissue fibrosis, edema, necrosis, and anatomic changes after radiotherapy and/or surgery can interfere with early detection of residual viable tumor or recurrence by the usual sequential physical and endoscopic examinations of the head and neck (Lell, et al. 2000; Zundel, et al. 2011).[18,19]

The results of our study indicated 18F-FDG PET/CT as a useful tool for restaging and initial staging of head and neck cancers.

We were able to find the primary tumor site in 66% of CUP patients which is almost discordant with the literature. For example, Ossama Hassan, et al. in 2013 performed a meta-analysis and reported that PET/CT detected 30.7% of tumors that were not apparent after conventional workup. In addition, PET/CT scans overall sensitivity, specificity and accuracy were 82.5%, 80.2% and 81.4% respectively.[20] We also demonstrated evidence of distant metastasis in 66.2% of our patients overall which is much higher than the average 10% rate for distant metastasis in head and neck cancer patients according to literature review.[21]

One reason for this discrepancy is the relatively limited number of patients in our study and also the fact that "Masih Daneshvari hospital" is a major referral and tertiary oncologic center in Tehran, Iran and we expect the majority of our patients to have more advanced disease. There is another potential source for bias in our study which is lack of insurance coverage for PET/CT imaging in our country by insurance carriers. Also, since PET/CT is a relatively new diagnostic modality in our country, most referring physicians are not familiar with correct indications to request PET/CT study for their patients.

We were not able to demonstrate a significant relationship between semi-quantitative metabolic values (SUVmax) and primary or metastatic tumor site which is most likely attributed to the wide range of primary tumor pathology we had in our patients (Table 2).

However, for patients with both primary and metastatic disease, usually the value of SUVmax for both primary and metastatic site are close enough and this finding can be helpful to exclude irrelevant focal uptake sites as possible site of distant metastasis. Similar studies have suggested such a correlation between SUV values of primary tumor site and metastatic sites.[22] This finding requires to be further validated in head and neck primary cancers in larger studies.

We believe that our findings can potentially have tremendous effect in overall management planning and prognosis of patients with head and neck cancer. Finding primary tumor site in patients with cancer of unknown primary origin is very important for definitive treatment planning. Also, demonstrating distant metastatic disease in head and neck cancer patients will potentially prevent futile and high risk surgical interventions.[23–25]

Based on available literature review, there are a few well established indications for PET/CT in patients with head and neck cancer which include: Metastatic (M) and lymph node (N) staging in all patients when other imaging modalities are equivocal or when treatment may be significantly modified. Also, PET is recommended for cancers of unknown primary origin and for staging and assessment of recurrent nasopharyngeal carcinoma. Finally, another indication of PET imaging in head and neck cancers is in thyroid cancer patients. PET/CT is most helpful in assessment of recurrent or metastatic disease in treated thyroid cancer patients when thyroglobulin (TG) is rising and there is no evidence of disease on conventional I-131 whole body scan. Another important finding in thyroid PET imaging is incidental finding of hypermetabolic focus in the thyroid which has 30% – 50% chance of malignancy and such an incidental finding is an indication for further evaluation, including thyroid tissue sampling.[26]

Figure 3 demonstrates a Sinonasal SCC case with metastatic cervical lymphadenopathy. Figure 4 is also an incidental hypermetabolic thyroid nodule which requires further evaluation to rule out possible underlying malignancy.

PET/CT is more expensive when used alone in the diagnostic workup of head and neck cancer but results in overall cost saving by reducing the number of futile radical treatments and there is a cost benefit to the use of PET/CT as the diagnostic and staging tool for head and neck cancer patients.[23,27]

Finally, FDG PET/CT has high negative predictive value (NPV) in evaluation of head and neck primary tumor sites.[28] According to literature review, PET/CT also has high NPV for node negativity in HNSCC. This may obviate the need for elective neck dissection in N0 HNSCC patients. It is suggested to perform pre-operative PET/CT imaging of other tumor primaries or draining lymphatic basins in the patients staged N0 clinically.[26] Further studies are necessary regarding the role of 18F-FDG PET/CT in surveillance of head and neck cancer patients.

In conclusion, 18F-FDG PET/CT is a useful tool for staging and restaging head and neck cancers and can detect regional recurrence, distant metastases and possible second primary tumors with high sensitivity and specificity. It can be also utilized for detection of primary sites in cancers with unknown primary origin. Interpretation of PET/CT should be performed together with clinical findings and the results of other imaging modalities and pathology reports. Diagnosis of distant metastases and second primary tumors are the domain of PET/CT imaging in head and neck cancers. Additionally, PET/CT has high negative predictive value in restaging of the primary tumor site. Finally, PET/CT is cost-effective and improves treatment results in advanced head and neck cancers.

Providing insurance coverage and familiarizing referring physicians about correct indications of this relatively new diagnostic modality will be to the best interest of head and neck oncology patients in the long run.

Acknowledgments

We appreciate all the help and support we received to conduct this study from Masih Daneshvari hospital authorities and PET/CT department administration.We did not have any funding or financial support for this research.

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