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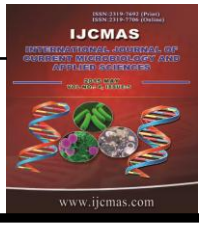

Original Research Article

Comparative evaluation of oral cancer staging using PET-CT vs. CECT

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Keywords

Oral cancer, Positron emission tomography, Computed tomography

A B S T R A C T

The present study tries to establish the utility of PET/CT in staging squamous cell carcinoma of oral cavity. Objective :To evaluate the effectiveness of PET/CT scanning in staging oral cancer in view of the exact delineation of the primary tumor and metastatic disease. Cross sectional study. Setting and design: Central government Tertiary care centre. 50 cases of oral carcinoma were included in the study. PET/CT imaging was done for all the patients. The PET/CT imaging was reported by a Nuclear Medicine expert and the CECT Imaging by a radiologist separately. Patients underwent wide local excision and lymph node dissection with or without reconstruction and post operative radiotherapy according to the stage. Each level of node resected were labeled and sent separately. The specimens were examined by histopathologist. The findings of CECT and PET/CT were expressed as sensitivity, specificity, positive predictive value and negative predictive value with post operative histopathology report as gold standard. Chi-Square Test, Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 17.0 for Windows). Results: For assessing primary tumor, PET/CT had sensitivity, specificity,PPV and NPV of 72.6%, 89.03%, 80.23 % and 84.14 % respectively, CECT showed 62.38%, 70.21%, 61.81% and 70.71% respectively. For assessing nodal status, PET/CT had sensitivity, specificity, PPV and NPV of 79.54 %, 90.8 %, 53.8 % and 97.05 % respectively and CECT showed 61.1%, 84.7%, 35.06% and 94.21% respectively. The comparison was statistically significant with p value < 0.01. Assessment by PET/CT changed the treatment in only 5 patients (10%). PET/CT has higher sensitivity, specificity, PPV and NPV compared to CECT. It should be done in all cases with advanced oral cancer for better disease staging and treatment planning.

Introduction

According to the World Health Report 2004[1], cancer accounted for 7.1 million deaths in 2003 and it is estimated that the overall number of new cases will rise by 50% in the next 20 years [2]. Oral cancer is common in men in developing countries. There were 2, 74,300 new cases and 1, 45, 500 deaths worldwide in 2002, of which two-thirds took place in developing countries [3]. Oral cancer is the most common form of cancer and of cancer-related death in men in India. In India, the age standardized incidence rate of oral cancer is 12.6 per 100 000 population. . It has been estimated that 43% of cancer deaths worldwide are due to tobacco, unhealthy diet, physical inactivity and infections [4]. Despite many advances in surgical techniques, technology, radiation therapy, and chemotherapy, survival rates have not improved significantly in decades. Accurate evaluation prior to treatment helps to guide surgical extent or radiation field and minimize loco-regional treatment failure. The presence of distant metastases at the initial evaluation will influence the prognosis and thus treatment selection. Under staging the disease would lead to inadequate treatment and over staging would lead to subjecting the patient to unnecessary treatment burdens. Imaging modalities like computerized tomography and magnetic resonance imaging are conventionally used for assessment of oral cancer. Positron emission tomography is a new functional imaging modality which detects the tumor activity. Whole body 18F-fluorodeoxyglucose (FDG)-Positron emission tomography can be used as a functional tumor detection modality in conjunction with or separate from anatomic imaging (CT and MRI). This modality has been used in various centers worldwide for staging of the tumor, detecting residual or recurrent lesions and for evaluation of neck secondary with occult primary. However, positron emission tomography is costly compared to other modalities and performing them for all cases of oral malignancy are often questioned. Our study tries to identify the advantages of PET/CT over CECT in terms of efficacy and utility.

Materials and Methods

50 cases of untreated oral cancer between the age of 20 to 75 years who presented to the outdoor patient departments of Otolaryngology and Head and Neck surgery and Radiation oncology of our institute were included in the study. Patients with hypersensitivity to F-18 FDG and other contrast materials, systemic diseases like uncontrolled diabetes mellitus, pulmonary tuberculosis were excluded from the study. All patients underwent thorough clinical examination regarding the size and extent of the primary lesion and nodal status in ENT outpatient department. Biopsy from the primary lesion and fine needle aspiration cytology was taken under local anesthesia. All routine hematological and biochemical investigations were done.

The patients were then referred for PET/CT scanning to the department of nuclear medicine. Patients were fasting for at least 4 hours before the study. Blood glucose levels were checked on arrival. Patients with blood glucose levels of less than 150 mg/dl were included. Patients were given 10 mCu of FDG intravenously and 90 ml of intravenous iodinated contrast material (Omnipaque) at a concentration of 30mg/ml at a rate of 3 – 5 ml/sec followed by 30 ml saline flush at 3-5 ml/sec after 60 minutes. Contrast Enhanced Computed Tomography was done 45 to 60 seconds after contrast administration. Image slices were reconstructed with a thickness of 1.25 mm. Following this, PET imaging was

done. Images were acquired 60 minutes after intravenous administration of 10 mCu of FDG.The data of CECT and PET/CT were obtained separately from the database and reported by a radiologist and nuclear medicine physician respectively. Both of them were blinded for the study. The patients were discussed in the tumor board of the institute and accordingly planned for surgery. Intra operatively the exact location, size and extent of the tumor was recorded and each levels of neck nodes were labeled separately and sent for histopathology. For primary tumor evaluation, size of the tumor and the ability of imaging modality to detect involvement of specific subsites were compared with intra operative findings and histopathological report. The subsites were floor of mouth, skin, bone, retromolar trigone and gingivobuccal or gingivolabial sulcus for carcinoma alveolus, involvement of lip, upper and lower gingivobuccal or gingivolabial sulcus , skin and retromolar trigone for carcinoma of buccal mucosa and involvement of floor of mouth , deep muscles of tongue, alveolus, base of tongue and crossing over to midline for carcinoma of tongue. For neck nodes, the ability of the imaging modality to detect nodal metastasis was compared to the histopathology which was taken as gold standard. If the imaging modalities detected any distant metastasis, they were confirmed using image guided needle aspiration cytology. Further the TNM staging of the tumor as per clinical, CECT and PET/CT was compared with that of histopathology ie pTNM.

Results and observations

Out of the 50 patients, 41 were males and 9 were females. The mean age for the whole study cohort was 48.5 years. (Range 23 to 72 years) . The study included equal number of carcinoma of tongue and lip or buccal mucosa patients i.e. 18 each and 14 patients of carcinoma alveolus. History of smoking was present in 25 patients (50 %) with average Pack years of 11 years and15 (42.8%) consumed alcohol. History of tobacco chewing in the form of Gutka and Zarda was elicited in 18 patients.

PET/CT detected the primary tumor in all 50 cases. The average maximum Standardized Uptake Value for primary tumor was 11.3(3.0 – 22.3) and for nodal metastasis was 5.9(2.5 – 14.3). There was no difference in the SUV max values in non irradiated patients and post irradiated patients whose average SUV max was 12.9. The average SUV in carcinoma tongue was 11.5(Fig 1), for carcinoma alveolus was 14.5(Fig 2), for lip and buccal mucosa was 7.8(fig 3) and for verrucous carcinoma was 4.8. As per PET/CT 28 patients were staged as T4, 7 patients as T3, 14 patients as T2 , and 1 patient as T1. PET/CT showed evidence of lymph node metastasis in 63 levels out of which 44 levels were confirmed by post operative histopathology. Lymph node metastasis in 10 levels identified by histopathology was missed by PET/CT. Majority of patients had N0 stage neck disease (22/50) i.e. 44% patients , followed by N2b stage (15/50) i.e. 30%, followed by N1 (10/50) i.e. 20% and N2c stage (3/50) i.e. 6 %. 31 patients had stage IV disease i.e. 62%, 8 patients had stage III disease i.e. 16%, 10 patients had stage II disease i.e. 20% and 1 patient had stage I disease i.e. 2%.

CECT failed to detect the primary lesion in 4 patients. As per CECT 27 patients were staged as T4, 11 patients as T3 and 8 patients as T2. CECT showed evidence of lymph node metastasis in 77 levels out of which only 27 levels were confirmed by histopathology. Lymph node metastasis in 17 levels as identified by post operative histopathology was missed by CECT.

Majority of patients had nodal disease of the stage N2b ie 38%, followed by N0 ie 32%, followed by N1 ie 26% and N2c ie 4%. As per CECT, 33 patients had stage 4 disease i.e. 66%, 9 had stage 3 disease i.e. 18%, 4 had stage 2 disease i.e. 8% and 4 had stage 0 disease i.e. 8%.

For assessing primary tumor, PET/CT had sensitivity, specificity, positive predictive value and negative predictive value of 72.6%, 89.03%, 80.23 % and 84.14 % respectively as compared to CECT which showed 62.38%, 70.21%, 61.81% and 70.71% respectively. For assessing nodal status, PET/CT had sensitivity, specificity, positive predictive value and negative predictive value of 79.54 %, 90.8 %, 53.8 % and 97.05 % respectively as compared to CECT which showed 61.1%, 84.7%, 35.06% and 94.21% respectively. The results were statistically evaluated with Chi-Square test and were found to be significant with a p value of < 0.001.

This study shows a definite advantage of PET/CT as compared to CECT in terms of sensitivity, specificity, positive predictive value and negative predictive value which was statistically proven to be significant. Our results are comparable to the results of other studies which have been done on this subject. As per his study, Zimny et al[5] described the sensitivity, specificity, and accuracy of PET/CT in tumor detection as 77%, 82% and 79%, respectively. Martino et al[6] reported that FDG-PET had a sensitivity of 95% and specificity of 92% in the initial detection of head and neck tumors. PET/CT could detect the primary tumor in all cases whereas CECT alone failed to detect the primary in 4 cases in our study. PET/CT was able to detect involvement of bone in most of the cases of carcinoma alveolus. Superficial buccal mucosa lesions were easily identified by PET/CT, however failed to be detected with CECT alone due to poor enhancement. However, deep muscle involvement in cases of carcinoma of tongue was missed by PET/CT, probable due to the lack of soft tissue delineation of computed tomography. In such cases PET fused with MRI would have been a better option. All the 4 cases of verrucous carcinoma were detected using PET/CT. They showed low uptake values (average SUV 4.8) and lack of uptake in the nodes thus suggesting a less aggressive nature of this variant and absence of nodal metastasis due to sub epidermal plugging of tumor cells. PET/CT also accurately identified the primary tumor in the 4 post irradiated patients. The uptake values in these patients were comparable to non-irradiated patients . CECT alone could not detect the primary lesion in 4 of the patients, out of which one was of stage 1 and 3 were of stage 2. This could be most probably due to superficial mucosal lesion or absence of peri tumoral edema and inflammation in such patients. 2 patients had to undergo repeat PET/CT due to rapid tumor progression. Both these patients showed high uptake values in initial scanning which indicated high tumor activity and aggressiveness. Another patient who had PET/CT for buccal mucosa lesion showed a mild uptake (SUV 3.5). However this patient was lost to follow up for 4 months due to personal reasons. But when the patient presented the lesion was of the same size indicating that the tumor aggressiveness is directly related to SUV value. This fact was further supported by the fact that buccal mucosa carcinoma which are comparatively less aggressive tumors had a lower uptake value (average SUV 7.8) compared to the more aggressive carcinoma alveolus and tongue (average SUV 14.5 and 11.5 respectively). This would help the surgeon in planning surgery for such patients in terms of timing of surgery and extent of surgical resection. Those patients

with higher uptake value should be operated at the earliest with a more radical approach while excising the tumor. This is again in confirmation with the study by Christoff et al[7] who concluded that high SUVmax was significantly associated with shortened overall survival after 36 ($p = 0.026$) and 60 months ($p = 0.02$). Subsequent multi-variate Cox regression analysis including SUVmax, age, gender and UICC stage as co-variables determined that, high SUVmax was the only predictor of inferior overall survival after 60 months ($p = 0.035$).

35 out of 44 lymph node groups involved by the disease were detected by PET/CT (Fig 4). Out of 65 lymph node levels detected to have increased uptake in PET/CT, 30 levels were not proven to have disease histopathologically. This is evident by the low positive predictive value of PET/CT in our study for assessing the nodal metastasis. 22 patients who were staged as N0 by PET/CT were confirmed by histopathology which shows the high negative predictive value . 4 of these patients did not undergo any neck dissection and were kept under follow up. None of these patients have developed recurrence till date, maximum follow up being 3 years. 15 patients of 27 histopathologically proven N0 neck were of carcinoma buccal mucosa which proves the low aggressive nature of the tumor at this site.4 patients belonged to stage 4 and 4 patients were in stage 3. This indicates that, PET/CT would help in guiding the surgeon in making decision regarding whether to do prophylactic neck dissection or keep patients under follow up in case of N0 neck in early oral cavity lesions. Those patients who show no uptake in the neck nodes on PET/CT can be kept under close follow up. However, further studies with long term follow up would be required to prove this. All patients with skip metastasis were accurately identified by PET/CT. Similarly 2 patients with bilateral neck metastasis were also identified by PET/CT. As per the study by Kim et al[8], FDG PET/CT was significantly more sensitive and accurate than CT/MRI in the ipsilateral (88% vs. 70%, $P < 0.01$ and 93% vs. 89%, $P < 0.01$, respectively) and contra lateral (52% vs. 36%, $P < 0.01$ and 91% vs. 90%, $P = 0.039$, respectively) neck.

Table.1 Showing TNM staging comparison (original)

STAGE	CLINICAL	PET	CECT	PATHOLOGICAL
0	0	0	4	0
I	1	1	0	1
II	11	10	4	11
III	11	8	9	7
IV	27	31	33	31

Figure.1 showing CECT and PET/CT of a patient with squamous cell carcinoma tongue

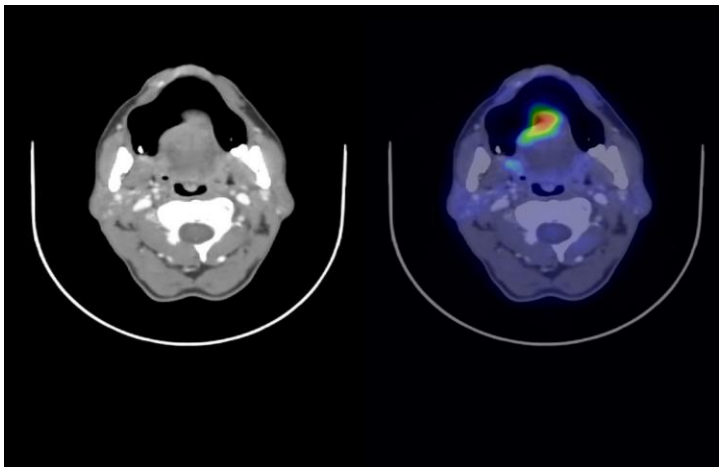


Figure.2 showing CECT and PET/CT of a patient with squomous cell carcinoma of alveolus

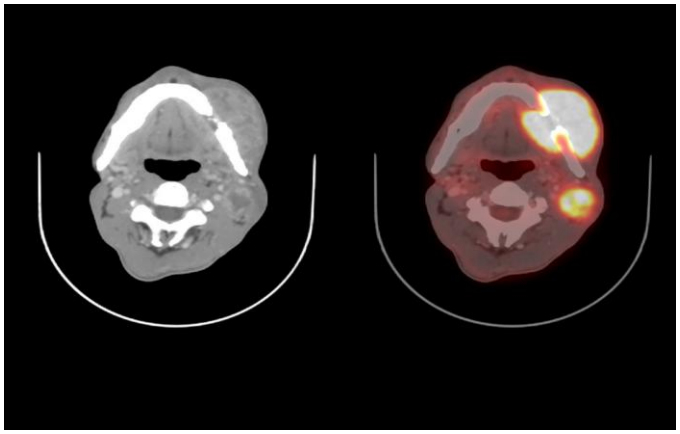


Figure.3 showing CECT and PET/CT of a patient with squamous cell carcinoma buccal mucosa

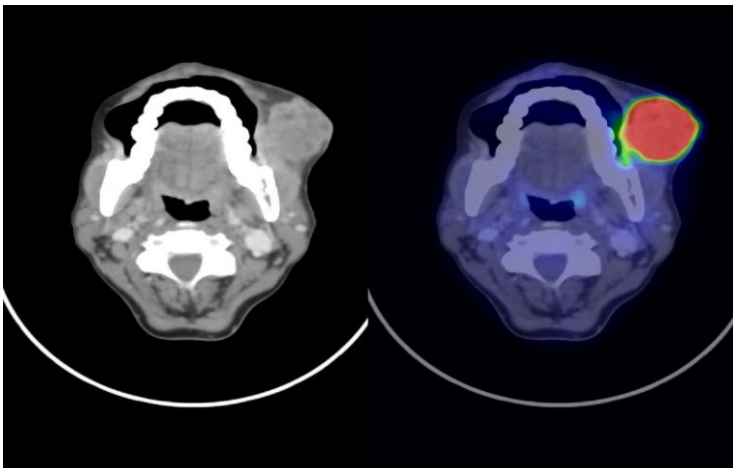
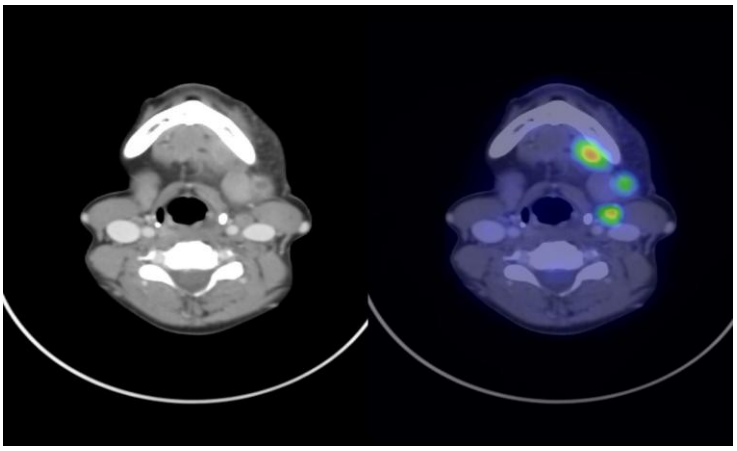


Figure.4 showing CECT and PET/CT of a patient with nodal metastasis



Distant metastasis was identified by PET/CT in 2 patients. One patient showed uptake in the pubic bone, but could not be histopathologically proven as the lesion was too small to be assessed using guided biopsy. Another patient had uptake in the mediastinal lymph node with SUV 4.3. Both these patients were advised post operative chemoradiation therapy following surgery. The staging as per PET/CT was the most accurate compared to clinical and CECT, considering pathological staging as the gold standard. As per PET/CT only one patient of stage II was over staged to stage III. The staging was accurate in all the other patients (table 1). The treatment plan was changed only in 4 patients (8%) , where one patient underwent bilateral neck dissection , one total thyroidectomy for papillary carcinoma thyroid and two patients received post operative chemoradiation.

Positron emission tomography/computed tomography has higher sensitivity, specificity, positive predictive value and negative predictive value compared to contrast enhanced computed tomography for assessing primary oral cavity malignancy. However , its impact on treatment is still low so as to advise it for all stages of oral cancer. For advanced stage disease PET/CT should be performed as there are higher chances for nodal metastasis and distant metastasis. For early stage disease PET/CT would help in taking decision regarding elective neck dissection and observation in patients with N0 neck. The SUV values of the tumor are an indirect evidence of tumor activity and aggressiveness and would help the surgeon for planning the extent of resection and neck dissection.

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