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Original Article

To Assess the Clinical Impact of 18F-FDG PET/CT in Non-Treated Cases of Squamous Cell Carcinoma of Head and Neck Presenting with Clinically and/or Radiologically N0 Status

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ABSTRACT

Background: *The most common sites are the oral cavity, pharynx and larynx and 85% to 95% neoplasms of the head and neck are SCCHN. The preservation of function, especially as it relates to speech, swallowing, and mastication, as well as cosmetic considerations, are considered essentials for determining the most effective management paradigm for SCCHN. The most common known imaging modalities in clinical use are CT and MRI imaging, despite their suboptimal sensitivity and specificity for the detection of distant metastases. The aim of present study is to establish the impact of ^{18}F-FDG PET/CT in clinically and/or radiologically negative neck in the assessment of cervical lymph nodes.* ***Materials & Methods:*** *The present study was conducted in the Department of Nuclear Medicine and PET CT, Sudhamayi Hospitals and Clinics, Cochin, Kerala over a period of about one and half years. The study group comprised of untreated patients of both sexes with age ranging from 20 to 81 years referred to our department with an established tissue diagnosis of SCCHN for ^{18}F-FDG-PET/CT Whole Body scan for evaluation of disease status and staging. 8 -10 mCi of ^{18}F-Flouro-Deoxy-Glucose (^{18}F-FDG) was injected I.V. in euglycemic status. Time of injection was noted along with pre-injection and post injection counts. Whole body PET/CT images (head to mid-thigh) were acquired after 45 min to 60 min post injection. Data including age, sex, endoscopy (direct / indirect) findings, neck lymph nodes level by clinical examination and radiological finding, FNAC/histopathology report of the primary and /or lymph nodes and conventional imaging (CT/MRI when available) findings was recorded. SPSS software was used for analysis.* ***Results:*** *At presentation, in 32.4% (n-12) of patients no nodes were palpable. Ipsilateral (single / multiple levels) lymph nodes were present in 48.7% of the patients (n-18). Bilateral involvement was seen in 18.9% (n-7) of the cases. Patient with FDG non avid necrotic lymph node was staged N0 on PET/CT but clinically had N2c disease was excluded from further analysis. There was no change in the overall stage or management of this patient.* ***Conclusion****: ^{18}F-FDG PET/CT can accurately predict N stage better than clinical / conventional imaging leading to change in nodal staging and thus overall staging of patients. Thus it acts as a valuable tool in determining the exact nodal spread of squamous cell carcinoma and thus establishing the exact treatment plan.*

Key words: *Downstaging, Euglycemic, nodal, Squamous cell carcinoma*

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INTRODUCTION

Head and neck cancer is a broad term that encompasses epithelial malignancies that arise in the paranasal sinuses, nasal cavity, oral cavity, pharynx and larynx. Almost all of these epithelial malignancies are squamous cell carcinomas of the head and neck (SCCHN) with most common sites being the oral cavity, pharynx and larynx.[1,2] The most important risk factors are tobacco and alcohol consumption[1] and are implicated in 75% of all SCCHN and have a multiplicative combined effect.[3] Treatment decision in SCCHN are often complicated, involving many specialists, including head and neck surgeons, medical and radiation oncologists, radiologists, plastic surgeons and dentists. Primary tumour site, stage and resectability, and patient factors - including swallowing and airway considerations,

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desire for organ preservation and co-morbid illnesses – are used to guide appropriate management.[4] The preservation of function, especially as it relates to speech, swallowing, and mastication, as well as cosmetic considerations, are considered essentials for determining the most effective management paradigm for SCCHN. This is particularly true for oral cavity, oropharyngeal, and laryngeal carcinomas.[5] Thus, precise prediction of the extent of the primary tumors, cervical node status, and distant metastatic spread is important for treatment planning and prognosis. Patients with known distant metastases can possibly be spared the toxicities of aggressive and often unnecessary loco-regional therapy.[6]

Regional nodal metastases are highly prevalent in the SCCHN, with more than 50% of patients presenting with lymph nodal metastases. Tumors involving the nasopharynx, oropharynx, oral cavity, hypopharynx, and the supraglottic larynx are most likely to have metastatic spread.[7]

Regardless of the tumour histological subtype, the presence of regional lymph nodal metastases currently stands as the most important prognostic factor, negatively influencing the average 5 year survival by as much as 40% to 50%.[8] Nodal status also determines the crucial management issues related to the extent of surgery, the estimated gross tumour volume for radiotherapy and the selection of patient subset who are eligible for combined therapy.

The incidence of occult nodal metastases varies with the site, size and depth of invasion of the primary tumour. Considering an overall 20% to 30% risk of occult metastases and 50% chance of extra-capsular spread in those patients with clinically node negative (cN0) neck, preoperative staging is usually hampered by the relatively high false-negative or false-positive results when imaging is involved as a result of the relatively low prevalence of N+ disease.[9]

There is data documenting that the detectability threshold of occult metastases is below the spatial and contrast resolution of available imaging modalities including CT, MR imaging and[18] F-FDG-PET/CT.[10] On histopathological examination, most cN0 cervical metastatic disease measures between 2 and 4 mm. One study clearly documented that[18] F-FDG-PET failed to identify nodal disease in 25% of patients with histologically proven lymph nodal metastases when the size of these nodes was less than 3 mm.

The management of clinically and radiologically negative neck is still controversial, although most centres favour either an elective neck dissection for staging and/or postoperative radiation for cancer sites with an expected rate of nodal metastases that exceed 20%. Given that only one-third of cN0 patients harbour occult neck disease, most patients undergo elective neck dissection whose benefits may not sufficient to outweigh its risks.[11]

Role of [18] F-FDG-PET and [18] F-FDG PET/CT has been evaluated in the initial staging of head and neck carcinomas in a number of studies and is extremely useful in the situations where anatomic imaging is equivocal and the disease cannot be assessed by direct visualization.[12-17] Also, PET/CT is extremely useful in the detection of cervical lymph nodal metastases not identified by other imaging modalities.[14]

The aim of present study is to establish the clinical impact of ^{18}F-FDG PET/CT in non-treated SCCHN patients presenting with clinically and/or radiologically negative cervical lymph nodes.

METHODS

The present study was conducted in the Department of Nuclear Medicine and PET CT, Amrita Institute of Medical Sciences, Cochin, Kerala, India in association with the Departments of Head and Neck Surgery, Medical Oncology, Surgical Oncology and Radiation Oncology beginning in November 2011 and till May 2013. Institutional ethical committee clearance was obtained. The study group comprised of non-treated patients of both sexes referred to our department with an established tissue diagnosis of SCCHN for ^{18}F-FDG-PET/CT Whole Body scan for evaluation of disease status and staging. Patients who had received any previous treatment or any history of previous malignancy were not included in the study. Informed consent was obtained from patient after informing about the entire procedure. A set of instructions were given to the patient a day before the appointment and on the day of appointment they were repeated.

Detailed history was obtained before the ^{18}F-FDG-PET/CT scan and used along with patient data extracted from our hospital information system prior the ^{18}F-FDG-PET/CT study. Data included age, sex, endoscopy (direct / indirect) findings, neck lymph nodes level by clinical examination and radiological finding, FNAC/histopathology report of the primary and /or lymph nodes and conventional imaging (CECT/MRI) findings. 7th edition (2010) of American Joint Committee on Cancer (AJCC) was used for staging criteria. Patients were divided in two groups: Group A: Conventional imaging done and Group B: Conventional Imaging not done. 8 -10 mCi of ^{18}F-Flouro-Deoxy-Glucose (^{18}F-FDG) was injected I.V. in euglycemic status. Time of injection was noted along with pre-injection and post-injection counts. Whole body PET/CT images (head to mid-thigh) were acquired after 45 min to 60 min post injection. Oral & IV contrast was given for CT part of the study in patient with normal renal function status. As and when required, dual point imaging (2-3 hours post injection of FDG) or imaging with hands down was also performed.

Data sets were reconstructed using iterative reconstruction technique. Image fusion was performed using co-ordinate based fusion software and subsequently reviewed on ADWPET workstation that provided multi-planar reformatted images and displayed PET images, CT images, and PET/CT fused images. Data was interpreted by visual inspection of the images as well as by semi-quantitative analysis in the form of standardized uptake values (SUV max in gm/ml),

RESULTS

A total of 37 patients were referred for ^{18}F-FDG PET/CT scan during the above mentioned period - 33 males (89.2%) and 4 females (10.8%). The mean age of presentation for males was 57.5 years and for the females was 55 years. Oropharynx was the most common site of primary tumour, seen in 40% of cases (n-15).

At presentation, in 32.4% (n-12) of patients no nodes were palpable. Ipsilateral (single / multiple levels) lymph nodes were present in 48.7% of the patients (n-18). Bilateral involvement was seen in 18.9% (n-7) of the cases.

Table 1 elaborates the Pre PET/CT N staging at presentation (excluding Nasopharynx) according to 7th edition of AJCC staging guidelines 2010 for 32 patients.

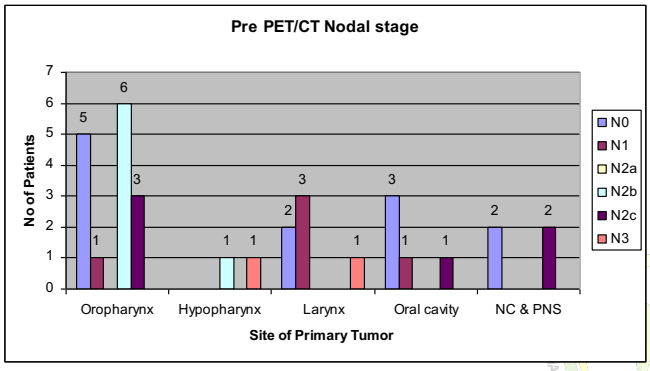
Most common pre-PET/CT nodal staging (N), by the way of clinical examination and CT scan neck in 32 patients

(excluding 5 patients with nasopharyngeal malignancy), was N0 (37.5%). All patients with nasopharyngeal carcinoma presented with lymph nodal metastases. Respective nodal stage for each primary site (excluding nasopharynx) at presentation is shown in Graph 1.

Table 1: Pre PET/CT N staging at presentation (excluding Nasopharynx) according to 7th edition of AJCC staging guidelines 2010 for 32 patients

N0	12 (37.5 %)
N1	05 (15.6 %)
N2a	00 (0.0 %)
N2b	07 (21.9 %)
N2c	06 (18.8 %)
N3	02 (06.2 %)

Graph 1: Nodal stage for each primary site (excluding nasopharynx)



Impact of PET/CT on various nodal stations according to the 7th edition of AJCC 2010 is shown in Table 2 and Table 3 and Graph 2 for all 37 patients and for all subsets of malignancy in our study group.

Table 2: Post PET/CT N stage changes in 37 pts

Primary Tumor site (n-37)	No change (n-22)	Upstage (n-11)	Downstage (n-3)	Overall stage changed
Nasopharynx (n – 5)	2	1	2	1 (DS)
Oropharynx (n – 14 + 1*)	7	6	1	3 (US) 1 (DS)
Hypopharynx (n – 2)	2	-	-	-
Larynx (n – 6)	4	2	-	2 (US)
Oral cavity (n – 5)	3	2	-	-
Nasal Cavity & Paranasal sinuses (n – 4)	4	-	-	-

(*) 1 pt had FDG non avid necrotic lymph node;
US – upstaged, DS - downstaged

One patient of oropharyngeal cancer and one of carcinoma of oral cavity in Group B were detected of positive nodes after initially being negative. Upstaging was seen in a total of 11 patients. Downstaging was seen in 3 patients whereas 22 patients demonstrated no change.

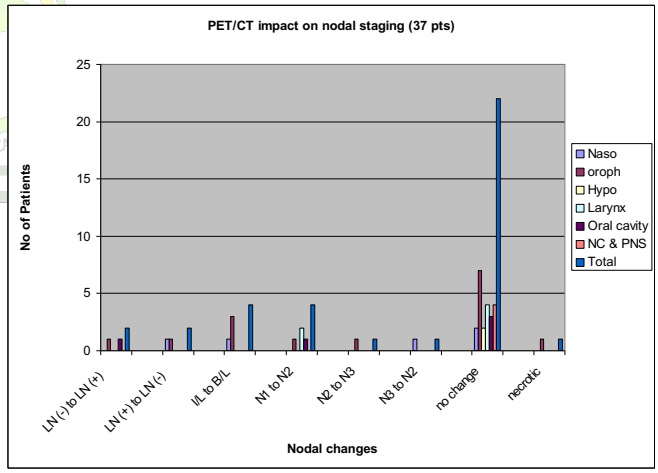
Table 4 shows the Nodal stations as per 7th Edition of AJCC and number of patients in each station after PET/CT. Among 37 patients there were 13 patients with N0 nodal stage after PET/CT scan. Outcome of these 13 patients with N0 nodal stage is given in Table 5.

Patient with FDG non avid necrotic lymph node was staged N0 on PET/CT but clinically had N2c disease was excluded from further analysis. There was no change in the overall stage or management of this patient.

For the remaining 8 patients with N0 disease, follow-up data was available for a median period of 7 months (range 3 -12 months) showing presence or absence of disease.

Table 3: PET/CT impact on various nodal stations

	Naso-pharynx (n-5)	Oro-pharynx (n-15)	Hypo-Pharynx (n-2)	Larynx (n-6)	Oral Cavity (n-5)	NC & PNS (n-4)
LN (-) to LN (+)	-	1 Group B	-	-	1 Group B	-
LN (+) to LN (-)	1 Group A	1 Group B	-	-	-	-
I/L to B/L (includes Naso N2 & N2c)	1 Group A	3 Group A, A, B	-	-	-	-
N1 to N2 (excluding Naso N2)	NA	1 Group B	-	2 Group A, A	1 Group A	-
N2 to N3	-	1 Group A	-	-	-	-
N3 to N2	1 Group B	-	-	-	-	-
No change	2	7	2	4	3	4
Necrotic	-	1	-	-	-	-



Graph 2: PET/CT impact on various nodal stations

DISCUSSION

37 patients were referred for ^{18}F-FDG PET/CT scan during the study period - 33 males and 4 females had overall mean and median age of 57.2 and 63 years respectively. Male predominance with median age of presentation in early 60s has been reported in the cancer statistics review done by Ries LAG et al[17] and Parkin DM et al.[18] More than 50% of patients of SCCHN at presentation have regional lymph nodal metastases.[19] 25/37 patients (67.6%) presented with lymph nodal metastases, inclusive of ipsilateral and bilateral nodes distribution. Presentation with ipsilateral lymph nodal metastases was more common than bilateral lymph nodal metastases (48.7% v/s 18.9%), similar to the pattern reported by Prestwich RJ et al[20] (63.6% v/s 25.5%). However, incidence of bilateral lymph nodal metastases was higher when compared to the reported incidence of 10% by Jereeczek-Fossa BA et al.[21]

Table 4: Nodal stations as per 7th Edition of AJCC and number of patients in each station after PET/CT

NODAL STATION	No of patients (n-37)
N0*	13
N1 (nasopharynx)	--
N1 (all other tumors)	03
N2a	01
N2b	05
Bilateral (N2 for nasopharynx and N2c for all others)	11 Nasopharynx – 3 Others – 8
N3 (nasopharynx & all others)	04

(*) includes 1 patient with necrotic lymph node

Table 5: Outcome of patients with N0 nodal stage (n-13)

OUTCOME	No of Patients
No evidence of disease	04
Disease present (residual – 2* / Progressive - 3)	05
Lost to follow-up after Rx completion	02
Pt Death (1-at end of Rx completion & 2- post op day 1)	02

(*) includes 1 patient with necrotic lymph node

According to the 7th edition of AJCC 2010 (excluding 5 patients with nasopharyngeal malignancy which are staged separately), N0 was the most common nodal station in 12 out of 32 patients (37.5%) at presentation.

After PET/CT scan, as per AJCC 2010, lymph nodal metastases were seen in 24 patients of our study population and 13 had N0 disease. Discordance in the level of nodal involvement between PET/CT and clinical examination and/or conventional imaging was observed in 14 patients (37.8%), similar to the incidence reported by Prestwich RJ et al [20] who had an incidence of 40% (n-22/55). Of these 14 patients, 11 were upstaged (78.6%) and 3 were downstaged (21.4%) patients. Similar results were also reported by Prestwich RJ et al. i.e. upstage of 72.7% patients (n-16) and downstage of 27.3% patients (n-6).

Among those 14 patients, final stage was upstaged in 5 and downstaged in 2 patients and out of these 5 patients; conventional imaging had been done in 3 patients. Thus, PET/CT accurately predicted N stage better than conventional imaging leading to overall stage change in 13% of patients (a total of 23 conventional imaging procedures were done for nodal staging). Similar results have also been mentioned by the numerous studies in the literature [21-24] that N staging is improved by 15% to 20% with the use of PET/CT as it identifies nodal disease not otherwise detected on conventional imaging.

The maximum impact on nodal changes was seen in patients with oropharyngeal malignancy (n-7), where nodal staging was upstaged in 6 patients and downstaged in 1. Of these 7 patients, there was an overall stage in 4 patients – upstaging in 3 and downstaging in 1. In our study, PET/CT detected bilateral FDG avid lymph nodes in 4 out of 37 patients (10.8%) when clinically and/or on conventional imaging there was no evidence to suggest involvement of contralateral group of lymph nodes. Prestwich RJ et al. also had almost same results (9.1%). PET/CT detected lymph nodal metastases in 2 out of 37 patients (5.4%) with no palpable lymph nodes on clinical examination; an observation similar to Prestwich RJ et al. However, Jeong HS et al[25] reported that PET/CT had 20% more accuracy over physical examination for predicting pathological nodal involvement. This discordance may be due to different population under study, time of clinical presentation or sample size.

The major limitation of our study was the smaller sample size with shorter duration of clinical follow-up. Also, conventional imaging investigations were not available in all the patients to make head to head comparison with PET/CT.

CONCLUSION

^{18}F-FDG PET/CT can accurately predict N stage better than clinical / conventional imaging leading to change in nodal staging and thus overall staging of patients. Thus it acts as a valuable tool in determining the exact nodal spread of squamous cell carcinoma and thus establishing the exact treatment plan.

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