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Original article

Comparison of PET/CT with conventional imaging modalities (USG, CECT) in evaluation of N0 neck in head and neck squamous cell carcinoma

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ABSTRACT

Background: Evaluation of a clinically N0 neck is mandatory in cases of squamous cell carcinoma of head and neck region in order to determine the need to address the neck. The study was designed to compare the accuracy of PET/CT scan with that of USG and CECT Neck in assessing clinically N0 neck in cases of squamous cell carcinoma of upper aerodigestive tract.

Methods: Single center, prospective, study over a 2 year period. All Cases of squamous cell carcinoma of upper aerodigestive tract with no palpable neck lymphadenopathy and who were scheduled for surgery were evaluated with USG, CECT and 18F-FDG PET/CT, of the neck. Post operative histopathology was correlated with pre-operative nodal status. Statistical analysis was done using the chi square test.

Results: In the 49 patients enrolled, 51 neck sides underwent dissections. Sensitivity of USG, CECT and PET-CT was 4.76%, 23.80% and 71.43% respectively while the specificity was 93.33%, 93.33% and 96.67% respectively. The positive predictive value (PPV) calculated for USG, CECT and PET-CT was 33.33%, 71%, 93.5% respectively while the negative predictive value (NPV) 58.33%, 63.63% and 82.85% respectively.

Conclusions: In N0 neck in head and neck squamous cell carcinoma, though FDG-PET-CT is more accurate than either USG or CECT in staging of the neck, it is not accurate enough to alter the current treatment paradigm.

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Introduction

The presence of cervical nodal metastasis is one of the most important prognostic factors in head and neck squamous cell carcinoma (SCC). However, the proper management of oral SCC patients with a clinically negative neck remains controversial. Indeed, it has been reported that incidence of clinically occult metastases in the neck can be as high as 30–50% depending on sub-site and stage of the primary tumor.¹ Such patients usually undergo an elective neck treatment, either neck dissection or radiotherapy. The disadvantage of this strategy is that most patients do not harbor metastases, and therefore, they may be subjected to additional costs and the morbidity of unnecessary treatment.² Treatment policies can be determined by considering the probability of nodal metastases. Elective neck treatment is thought to be indicated if the risk of occult metastasis is judged to be greater than 15%–20%. Currently, ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) are usually used for pre-operative assessment of the primary tumor and cervical status. These imaging techniques are comparable to each other in detecting cervical metastasis and may detect some occult nodal metastases missed by physical examination.^{3,4} Several studies have been published about [18F]FDG PET for the evaluation of clinically negative neck in oral SCC patients.^{5–8} However, the results and clinical implications of these studies are diverse. While some authors suggest that [18F]FDG PET might be a promising diagnostic aid in the evaluation of clinically negative necks,^{4–6} others have claimed that it might not be useful.^{9,10} The dilemma would be even more severe, if we consider the well documented fallacy in interpretation of FDG-PET in setting of chronic granulomatous infection. We present a study which evaluates FDG-PET/CT in comparison to conventional imaging (CT and USG) in settings of a country with high prevalence of tuberculosis and other chronic granulomatous infections. To the best of authors' knowledge this is the largest series being reported from Indian subcontinent.

Subjects and methods

Patients

The institutional review board of our hospital approved this study, and written informed consent was obtained from all enrolled subjects. The inclusion criteria were a primary in the head or neck region which had been histologically proven to be SCC but had no palpable lymph node in the neck, had received no prior treatment to the head or neck region, and having been scheduled for surgery. Those patients with other severe medical co-morbidities, known distant metastasis, some sort of treatment already taken outside or second primary tumors were excluded. Patients' characteristics in terms of primary sub-site and T stage are as per Table 1. Preoperative evaluation was accomplished within 2 weeks before surgery. All patients were studied using USG, CECT and 18FDG PET/CT, of the neck.

Table 1 – Patient characteristics.

Variable	No. of patients
Age (years)	
Range	42–82
Mean	59.45
Sex	
Male	37
Female	12
T stage	
T1	14
T2	17
T3	10
T4	8
Primary Sites	
Buccal mucosa	17
Alveolus	8
Lip	6
Tongue	5
Floor of mouth	5
Retromolar trigone	4
Larynx	2
Gingivo buccal sulcus	1
Hard palate	1

Imaging USG

Ultrasound of the neck was carried out by a set of radiologists with varying experience. A high resolution 10 MHz 8 L linear probe (Logic3Pro, WiproGE Healthcare Ltd) was used for the purpose.

CT

CT examination of the head and neck was performed after intravenous administration of iodinated contrast material (Omnipaque 300 [iohexol]; 9800 scanner (GE Healthcare), dose 120cc, injection rate 03 ml/s by pressure injector and scan delay: 18 s).

Scanning range was individually adapted. The axial images were obtained parallel to the body of the mandible from the skull base to the supraclavicular fossa with a 5-mm-thick contiguous section. Coronal reconstructions were done with 3-mm-thick contiguous slices in both soft tissue and bone windows.

[18F]FDG PET-CT

All studies were conducted using a dedicated full ring Lutetium Ortho-silicate (LSO) crystal PET/CT scanner (Biograph 2, Siemens Medical Systems, Erlangen, Germany). Non-enhanced CT images were acquired at 130 kV and 90 mA (mean) with a section width of 5 mm. CT based attenuation correction was done for PET images and reconstruction done using iterative reconstruction algorithm. The PET/CT protocol included patient fasting for minimum 6 h and confirmation of blood glucose levels below 140 mg/dl before intravenous injection of 370 MBq (10 mCi) of FDG. Whole body PET/CT scan (skull base to mid-thighs) was done 1 h after FDG injection.

Image interpretation and analysis

For correlative analysis of nodal staging of USG, CECT, [18F]FDG PET/CT and histopathologic examination, the neck was

divided into levels based on the imaging-based nodal classification.¹¹ Two experienced nuclear medicine physicians interpreted the [18F]FDG PET studies individually by visual inspection. They had no knowledge of the CECT findings. They evaluated foci of increased FDG uptake with reference to background tissue uptake (the neck muscles), and scored the FDG uptake on a 5-point scale as follows: 0 = no abnormal uptake, 1 = benign, 2 = probably benign, 3 = probably malignant, and 4 = definitely malignant. Scores of 3 and 4 were considered to be positive results for tumor involvement. A checklist of the distributions of the primary tumors and their metastatic node were recorded accordingly. Any initial difference of opinion was resolved by consensus. CT was interpreted in a blinded fashion by two radiologists, and any disagreement was resolved by consensus. The radiologists compiled the same checklist, using the same 5-point scale. Nodes were considered metastatic if their shortest axial diameter was 11 mm in the jugulodigastric region or 10 mm in other cervical regions, if central necrosis or an irregular border was present, or if there was a cluster of three or more nodes of borderline size.

Surgical procedure and histology

Neck dissection was planned by our head and neck surgical team based on the imaging results. Supraomohyoid neck dissection (levels I, II, and III) was performed in patients with a negative neck. Nodes harvested were subjected to frozen section analysis and extended supraomohyoid neck dissection (levels I to IV) or modified radical neck dissection (levels I to V) was performed in those patients with more than one involved node or extracapsular nodal spread. Bilateral neck dissection was performed in patients with the primary tumor crossing the midline or with probably metastatic nodes in the contralateral neck. The specimens were labeled by the surgeons in such a way that reference could be made to the schema used in the interpretation of the [18F]FDG PET and CT studies. Lymph nodes were dissected from the specimens and stained with hematoxylin and eosin for histologic analysis.

Statistical analysis

Sensitivity and specificity of USG and CECT was compared against that of PET/CT using Chi square test.

Results

From January 2007 to December 2008, a total of 50 patients with primary tumor in oral cavity and no clinically palpable nodes were assessed. Patients characteristics are as per Table 1. One patient, of hard palate primary, did not undergo any neck dissection and was not included in the final analysis. The rest 49 cases were prospectively recruited into the study. In clinically negative neck, USG, CECT and PET-CT reported 3, 7 and 17 neck sides respectively as positive. All of our patients underwent primary tumor resection and neck dissection. Of 49 patients, 26 underwent level I to III dissection, 21 underwent level I to IV or V dissection, and the remaining two underwent bilateral level I to V dissection. Hence, in all, 51

Table 2 – Comparison of USG, CT and PET in terms of true positive and false negative rates for N0 neck.

Variable	Necks pathologically positive	%	Sensitivity
USG finding			
Positive (n = 3)	1	33.3	4.76%
Negative (n = 48)	20	41.66	
CT finding			
Positive (n = 7)	5	71.4	23.8%
Negative (n = 44)	16	36.36	
PET finding			
Positive (n = 17)	15	88.23	71.43%
Negative (n = 34)	6	14.7	

neck sides underwent dissections. Out of these, 21 sides (41.11%) were finally detected to have occult metastases. Out of the 3, 7 and 17 neck sides reported positive by USG, CECT and PET-CT respectively, 1, 5 and 15 sides actually reported metastases to the neck nodes. Hence, the sensitivity of these three modalities was 4.76%, 23.80% and 71.43% respectively (Table 2). There was statistically significant difference between sensitivities reported at USG and CECT when compared with that of PET-CT, in favor of PET-CT ($p < 0.01$, 99% confidence interval). Similarly out of the 48, 44 and 34 neck sides reported negative by USG, CECT and PET-CT respectively, 28, 28 and 29 sides actually were negative for nodal metastases. Hence the specificity calculated for the three modalities was 93.33%, 93.33% and 96.67% respectively (Table 3). There was no statistical significant difference seen when specificity of USG and CECT was compared with that of PET-CT ($p > 0.05$, 95% confidence interval). The positive predictive value (PPV) thus calculated for USG, CECT and PET-CT was 33.33%, 71%, 93.5% respectively (Table 4) while the negative predictive value (NPV) calculated for the three modalities was 58.33%, 63.63% and 82.85% respectively (Table 5). In case of the two cases which were reported as false positive on PET-CT, no specific histology suggestive of tuberculosis or a chronic granulomatous infection was seen.

Discussion

Knowledge of presence or absence of metastases to the cervical nodes in setting of proven squamous cell carcinomas

Table 3 – Comparison of USG, CT and PET in terms of true negative and false positive rates for N0 neck.

Variable	Necks pathologically negative	%	Specificity
USG finding			
Positive (n = 3)	2	66.66	93.33%
Negative (n = 48)	28	58.33	
CT finding			
Positive (n = 7)	2	28.57	93.33%
Negative (n = 44)	28	63.63	
PET finding			
Positive (n = 17)	1	11.76	96.67%
Negative (n = 34)	29	85	

Table 4 – Comparison of USG, CT and PET in terms of true positivity and false positivity rates for N0 neck.

Variable	USG positive	%	CT positive	%	PET positive	%
Neck histology						
Positive (n = 21)	1	4.76	5	23.82	15	71.55
Negative (n = 30)	2	6.67	2	6.67	1	3.33
PPV	33.33%		71%		93.5%	

of the upper aerodigestive tract is imperative, since the extent of the treatment is determined by the size of the tumor and by the presence or absence of metastatic lymph nodes.^{1,2} In our study we have documented an incidence rate of 41% for occult metastases. This number is similar to those reported by other studies which have reported prevalence rates ranging from 24 to 50%.^{12,13} This relatively high figure may be explained by the fact that there were a large proportion of locally advanced tumors (T3/4) in our series.

Imaging techniques such as US, MRI and CT, which monitor tumors or lymph node metastases by size and structural changes, have improved the staging of the neck as compared to palpation. However, the overall error rate of assessing the presence or absence of cervical lymph node metastasis by palpation has been reported as 20%–28%, while for CT figures range from 7.5% to 28% and for MRI 16% is reported.⁵ Metabolic factors such as glycolysis are independent of morphologic changes, and the increase of these factors is measurable in malignant tumors. The transition from slowly growing and well-differentiated to rapidly growing and poorly differentiated neoplasms is accomplished by a progressive increase in anaerobic glycolysis.¹⁴ The increased glycolysis can be monitored with PET, using the glucose analogue, 2-deoxy-2-[18F] fluoro-D-glucose (FDG). Scanning utilizing FDG has become standard of care for many malignant neoplasms¹⁵ for its ability to more accurately stage tumors, and thus alter therapeutic decision making, compared to conventional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). The use of FDG-PET scanning in head and neck cancer is more controversial. Currently available data from published studies demonstrate large variations in sensitivity and specificity for 18F-FDG PET in the detection of cervical lymph node metastases in head and neck cancers. These ranged from 67% to 96% for sensitivity and from 82% to 100% for specificity.^{6–9,16,17} NCCN guidelines do not include

PET scans as part of routine staging, and many institutions use MRI or ultrasound guided biopsies rather than PET scans. Indeed, the Radiation Therapy Oncology Group (RTOG) utilizes the clinical exam, chest x-ray, and pre-treatment CT scan as their standard workup.¹⁸

In patients with head and neck SCC without palpable lymph nodes in the neck, there is always a risk of subclinical metastases. In clinical practice, the decision to adopt elective neck treatment or a wait-and-watch policy depends on the probability of occult neck metastasis. Various studies propose PET-CT as an ideal screening modality quoting high sensitivity and specificity.^{8,10,16,17} However, there are no large prospective studies from Indian subcontinent which would validate or deny this proposal. While it is widely accepted that PET-CT is far more accurate than either CECT or MRI in detecting occult metastases in the neck, it is more prudent to ask oneself if it accurate enough to alter current treatment paradigm. This question is even more relevant when we consider the high incidence of chronic granulomatous infections which are documented in this country.

Previous studies evaluating PET-CT in N0 neck have documented neck levels when comparing PET-CT with CT and/or MRI. However, for a surgeon the decision to operate would take into account the neck side where this occult metastases is likely to be in, rather than the neck level. Thus, analysis of the sensitivity of imaging studies on a neck-side basis, although less accurate than on a neck-level basis, is more appropriate from a surgical point of view. In our study, there were 51 neck sides in 49 patients which were negative on clinical palpation.

Out of these, 21 neck sides (41.11%) were subsequently found to have cervical nodal metastases on histopathological examination. Our results show that [18F]FDG PET is significantly more sensitive than CT or USG for detecting these occult cervical nodal metastasis (71.43% for PET-CT vs 21.74% for CECT and 4.35% for USG). However, a sensitivity of 71.43% would entail that a rather large number of cases (29%) will not be detected by PET-CT when the modality is used to screen the N0 necks. Limited sensitivity related to size of metastatic deposits is a particular problem in oral squamous cell cancer because >50% of metastases occur in lymph nodes of <10 mm in diameter.¹⁹ Further, an NPV of 82.85% would indicate that a proportion of patients (approximately 17%) which have been indicated as disease free by PET-CT would actually still have disease. Therefore, a negative PET does not reliably exclude occult metastases. With a high PPV (93.5%) PET-CT confers distinct advantage over USG and CECT (33.3% and 71%, respectively) in reliably identifying presence of disease and that the neck needs to be addressed.

One finding in our study which may be pointed out is the rather low sensitivity (4.35%) reported for USG. Studies report that USG alone has accuracy of 70%, with a sensitivity of 60% and a specificity of 77%. US-guided FNAC increases the accuracy to 89% with a sensitivity of 76% and a specificity of 100%.²⁰ High resolution USG not only helps in identifying presence of lymphadenopathy in N0 neck, but also has the potential for characterization of such nodes based on the architecture, blood flow pattern and surroundings.²¹ However, it is a well known fact that USG is operator dependent modality and results depend on experience of the radiologist.

Table 5 – Comparison of USG, CT and PET in terms of true negativity and false negativity rates for N0 neck.

Variable	USG negative	%	CT negative	%	PET negative	%
Neck histology						
Positive (n = 21)	20	95.21	16	76.19	6	28.57
Negative (n = 30)	28	93.33	28	93.33	29	96.66
NPV	58.33%		63.63%		82.85%

Fig. 1 – Case of carcinoma left buccal mucosa in a 56-year old male patient which was clinically N0. CT neck shows right level III node enlargement.

The low sensitivity rates reported by our study maybe attributed to the varying experience of the sonologists conducting the same. We did not attempt USG guided FNAC in our cases.

Fig. 1 illustrates a case where the neck is clinically stage N0. CECT scan upstages in to N1 while PET-CT reports it to be N2C (Fig. 2). The patient underwent bilateral neck dissection based on PET-CT finding. Final histopathology confirmed metastases to ipsilateral side (true positive) but not to contralateral side (false positive) (Fig. 3).

It may further be questioned if any attempt was made at objectively measuring the FDG uptake value i.e. Standard Uptake Value (SUV). In this regard, it is pertinent to mention that the prognostic value of SUVs is another unresolved issue with PET scanning. In theory, a greater SUV would correspond with a more aggressive tumor. While some authors^{22,23} have found a relationship between maximum tumor SUV and clinical outcome, others^{24,25} have not found this to be true. Some²⁶ have been inconclusive. Although prognostic

Fig. 2 – Case of carcinoma left buccal mucosa in a 56-year old male patient which was clinically N0. PET images from same patient shows increased FDG uptake in the right level III nodes as well as left level III nodes.

Fig. 3 – PET-CT fusion images of the same patient. Patient subjected to elective MRND of right side and SOHD of left side. Histopathology indicated presence of metastases on right side (true positive) but negative for metastases on the left side (false positive).

information, such as tumor mass SUV, is useful, it is not used for management changes.²⁷ Hence, we did not take into account the SUV in the study protocol.

Conclusion

In N0 neck in head and neck squamous cell carcinoma, FDG-PET-CT is more accurate than either USG or CECT in staging of the neck. A negative PET does not rule out disease, while a positive PET accurately predicts the disease. This leads to the fact that, irrespective of findings on PET-CT, one would still have to address the neck as per conventional guidelines. Hence, addition of PET-CT would not alter the current treatment paradigm.

Intellectual contribution of authors

Study concept: Surg Cdr Ashutosh Chauhan, Brig Sanjay Kapoor.

Drafting and manuscript revision: Surg Cdr Ashutosh Chauhan, Col Harkirat Singh, Brig Sanjay Kapoor.

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Conflicts of interest

All authors have none to declare.

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