Diagnostic performance of ^{18}F-FDG PET-CT in patients presenting with secondary neck nodes from an unknown primary

Original Article

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ABSTRACT

Introduction: Clinical examination and even anatomical imaging may fail to identify primary site of malignancy in patients presenting with cervical nodal metastasis. ^{18}F-Fluorodeoxyglucose Positron Emission Computed Tomography (^{18}F-FDG PET-CT) is known to overcome the limitations of anatomic imaging.

Methods: Sixty-three (63) patients (male:female=55:8, age range=32-83 years, mean age=61.14 ±12.6 years) with one or more metastatic neck node (s) from occult primary underwent ^{18}F-FDG PET-CT. Nodal cytological/biopsy findings, IHC of cervical nodal biopsy (whenever available), scan findings, subsequent biopsy findings (PET guided/ directed) of suggested occult primaries were correlated. Subsequent detection of any primary malignancy in whom ^{18}F-FDG PET-CT failed to localize a primary was also documented.

Results: Malignancy was confirmed in eighteen (18) out of those twenty-four (24) patients in whom site of possible occult primary malignancy was suggested out of total sixty-three (63) patients. In five (5) patients out of remaining thirty-nine (39) patients, a site of primary malignancy was detected or a site of primary malignancy was considered based on IHC subsequently. The detection rate of occult primary, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and false positivity rate was calculated to be 28.5%, 78.2%, 85%, 75%, 87.1% and 15% respectively. ^{18}F-FDG PET-CT also detected other lymph nodal and organ metastases in 46% and 23.8% patients respectively.

Conclusion: ^{18}F-FDG PET-CT is a useful modality for detecting unknown primary and other nodal /distant metastases in patients presenting with neck nodal metastases.

Key words: Metastatic neck nodes; Carcinoma of unknown primary; ^{18}F-FDG PET-CT

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INTRODUCTION

Cancer of Unknown Primary (CUP) is a heterogeneous group of patients with metastatic disease in whom the primary site of malignancy remains undetected even after a thorough diagnostic work-up [1] and they comprise around 0.5-10% of all adult malignancies [2]. Many of these patients present with neck lymph nodal metastases and in 2-9% of these patients, thorough physical examination, anatomical imaging studies or endoscopic evaluation would have failed to identify the primary site of malignancy [3]. Reasons such as inhibition of growth of the primary by metastases, involution and slow growth rate of the tumor have been implicated for their occult character [4]. Clinical examination, fibreoptic endoscopy and CT (computed tomography) and/or MRI (magnetic resonance imaging), panendoscopy with blind biopsies and sometimes tonsillectomies are included in workup [5]. CT is known to detect primary in 15–20% of patients [6] but on CT and MRI small or non-enhancing lesions in normal-sized structures may not be detected [7]. Metabolic imaging with positron-emitting tracers like 2-[fluorine-18] fluoro-2-deoxy-D-glucose (FDG) may overcome the limitations of anatomic imaging. FDG a glucose analog is trapped in metabolically active cells [8]. Warburg suggested that many cancer cells derive energy from fermentation and not oxidation [9]. Glucose uptake in tumor cells depends on the expression of glucose transporters, the activity of hexokinases that regulate entry into the glycolytic pathway, and cell proliferation of the tissue. Tissue hypoxia activates the transcription of glucose transporters via hypoxia-inducible factor [10]. Current PET (Positron Emission Tomography) systems have a spatial resolution of 4–7 mm [11] and also high lesion-to-background contrast which effectively means that lesions with a dimension even slightly less than the spatial resolution can possibly be detected. Physiologic FDG distribution in various sites in the head and neck region can pose interpretational difficulties though [12]. However, this can be overcome by the CT component or by dual time point imaging [13]. Detection of a primary tumor can lead to targeted therapy of primary tumour, which translates, into improved chances of survival as well as lowered morbidity [14].

This study was undertaken to evaluate the diagnostic performance of ^{18}F-FDG PET-CT in localizing the occult primary malignancy and distant metastases in patients with proven cervical lymph nodal metastasis from unknown primary presenting to our tertiary care institution.

METHODS

Sixty-three patients (male: female=55:8, age range= 32-83 years, mean age= 61.14±12.6 years) with one or more palpable neck node(s) (either cervical or supraclavicular nodes) and cytologically confirmed to be malignant from occult primary were evaluated with ^{18}F-FDG PET-CT between May 2010 and March 2018. This excluded patients with lymphomas and hematopoietic malignancies, patients with histories of any previous treatments for head and neck or any other malignancy. All patients had been referred for a Whole body ^{18}F-FDG PET-CT following a thorough clinical and investigational workup by our/outside oncology team. A standard protocol for whole -body ^{18}F-FDG PET-CT was followed. Overnight fasting and serum glucose levels below 150 mg/dl at the time of injection of ^{18}F-FDG were ensured. All patients were screened for their renal status prior to using contrast for diagnostic CT part of PET study. 8-10 mCi of ^{18}F-FDG was injected intravenously in euglycemic status and an hour later whole-body PET CT images from head to mid-thigh were acquired using our GE Discovery PET 8 slice CT scanner. A breath held high-resolution contrast CT chest was followed by a head to mid-thigh contrast-enhanced diagnostic CT. Diagnostic CT images were acquired craniocaudally with a linear speed of 27 mm/rotation and a slice thickness of 3.7 mm. The peak voltage was 120 kV, effective variable current strength was between 250-350 mA and the pitch was 1.35:1. Intravenous contrast was administered approximately 1.5 ml/kg in volume, administered at a rate of 1.3 ml/sec with a scan delay of 35-45 seconds. Subsequently, PET images were acquired (approx. 8-bed positions of 15 cm length, each of 3 minutes duration in caudocranial direction). The data sets were reconstructed using iterative reconstruction technique. Subsequently, images were reviewed on ADWPET workstation, which provided multiplanar reformatted images, displayed PET, CT, and combined PET-CT fusion images. Two senior nuclear medicine physicians evaluated both PET and CT data sets and one senior radiologist in consensus, by visual inspection CT data sets as well as by semi-quantitative analysis (standardized uptake values, SUV max in gm/ml). An abnormal increase in ^{18}F-FDG uptake in the head and neck as well as the sites was documented. The CT data was used for anatomical localization and for corroboration of the PET findings. The maximum standardized uptake values (SUV max) were documented. Visual and semi-quantitative estimate of ^{18}F-FDG uptake was used to classify findings as positive (SUV max of more than 2.0) or negative (SUV max of less than 2.0). The CT criteria for positivity was any morphological abnormality (enhancing mass lesion or wall thickening or mucosal irregularity or any such morphological abnormality). Relevant clinical, surgical, IHC findings, subsequent histopathological findings and findings of other modalities, as and when available, were used to correlate the results with ^{18}F-FDG PET-CT. Data collection included information on age, sex, neck lymph nodal level by clinical examination, fine

needle aspiration cytology (FNAC)/histopathology report of the lymph nodes, IHC findings, prior imaging findings if any, FNAC or endoscopic findings, biopsy findings from PET guided biopsies of suggested occult primaries (if suggested) were correlated. Detection rate, sensitivity, specificity, positive and negative predictive values and false positivity rates of ^{18}F-FDG PET-CT for detection of primary malignancy were calculated. A true positive finding was considered when there was histopathological confirmation from the possible primary lesion suggested on ^{18}F-FDG PET or when ^{18}F-FDG PET scan findings were in correlation with immunohistochemistry (IHC) suggested primary malignancy or endoscopic findings. False-positive finding was considered when the ^{18}F-FDG PET-CT suggested possible primary tumor did not correlate with the clinical examination (including endoscopic evaluation) or histological findings. False negative was considered when ^{18}F-FDG PET-CT did not suggest a primary tumor, but subsequent histological diagnosis, clinical examination or tumor markers proved otherwise. A true negative was considered when the ^{18}F-FDG PET-CT did not suggest any site of primary malignancy and subsequently a primary malignancy was never detected. Detection of other lymph nodal or organ metastases was also analyzed.

RESULTS

Suggested sites of possible primary on ^{18}F-FDG PET-CT and detection rate

Overall PET CT findings suggested twenty-four sites of possible occult primary tumor in 24 out of 63 patients. Subsequent biopsies/clinical correlation were confirmatory/indicative of primary malignancy in 18 out of 24 ^{18}F-FDG PET-CT suggested sites (Table 1). Our detection rate of an occult primary by ^{18}F-FDG PET-CT is 28.5% (18 out of 63 patients).

Distribution of occult primary as identified by ^{18}F-FDG PET-CT

In our series primary tumor sites include nasopharynx and oropharynx in four patients each (6.3%), oesophagus, pyriform sinus, ovary, stomach in one patient each (1.5%) and lung in six patients (9.5%) (Table 2). The representative images of one of the patients detected with nasopharyngeal carcinoma are shown in Figure 1. Representative images of patient who was detected to have an esophageal lesion on PET CT and considered primary esophageal malignancy is shown in Figure 2.

Assessment of validity parameters

^{18}F-FDG PET-CT showed a sensitivity and specificity of 78.2% and 85% respectively in detecting a primary site. The positive predictive value (PPV) was 75% and the negative predictive value (NPV) was 87.1%. False positivity rate was 15% (Tables 3 and 4). Figure 3 shows the representative images of a falsely considered malignant primary lesion in thyroid, which was subsequently found to be an adenoma on hemithyroidectomy.

Detection of other lymph nodal or organ metastases on ^{18}F-FDG PET-CT

(i). In patients with cervical nodal metastases (i.e. excluding those with supraclavicular nodal lymph nodal presentation) (total 46 patients): Extracervical lymph nodal or contralateral cervical metastatic disease was detected in 15 patients. Distant skeletal and soft tissue metastases were detected in 9 patients (Table 5).

(ii). In patients with supraclavicular nodal (SCN) presentation (total 17 patients): Extra SCN lymphnodal metastatic lymph nodes were detected in 14 patients and overall skeletal and soft tissue metastases were detected in 6 patients when considered separately (Table 6). Some of the patients had both extra supraclavicular nodal and organ/skeletal metastases.

DISCUSSION

The detection rate of an occult primary on PET CT in our population is 28.5% (18 out of 63 patients) which is similar to other studies done worldwide. Rusthoven et al. in a review of 302 patients in 16 studies had described a detection rate of a primary lesion of 24.5% [15]. The Danish Head and Neck Cancer Group (DAHANCA) DAHANCA 13 study showed a detection rate of 29% (17 out of 59 patients) [16]. Kwee et al. [17] in a meta-analysis of 11 studies showed a primary tumor detection rates ranging from 22-73%, with an overall detection rate of 37%. In another meta-analysis, Hassan et al. found the rate of primary tumor detection to be around 33.5% [18]. Failure to detect the occult primary affects the optimization of therapeutic strategies. This emphasizes the need for an accurate diagnostic work-up. Although prospective biopsy of sites likely to harbor occult primary malignancy and screening tonsillectomies are advocated [19] a non-invasive procedure like PET can possibly precede invasive procedures. Rudmik et al. found that ^{18}F-FDG PET-CT increased the detection of a primary site from 25% to 55% [20]. Also, several studies have found that PET/CT identifies more primary sites (24–44%) compared to anatomic imaging in the form of CT or MRI alone (20–27%) [21, 22]. The sensitivity and specificity of ^{18}F-FDG PET-CT in primary tumor detection in our population was 78.2% and 85%, respectively. Dong et al. in their meta-analysis reported a pooled sensitivity of 81% and a specificity of 82% [23].

Table 1: Possible suggested sites of primary malignancy in 24 out of 63 patients with subsequent clinical correlations and 5 patients where primary was not suggested but subsequently a site of primary was considered.

Sl. no	Suggested possible site of primary	SUV gm/ml *	CT features description (cm)	Correlation	Categor -ization
1.	(L) Lung	19.3	ST mass lesion apicoposterior segment of left lung	considered Lung Ca in clinical context	TP
2.	(R) Lung	7.7	Consolidation upper lobe right lung	considered Lung Ca, HPE and IHC metastatic cervical node, metastatic Adenocarcinoma with CK7+, CK 20-ve,TTF1+ve, CEA+ve, Thyroglobin- ve, Calcitonon-ve	TP
3.	Posterior Naso Pharynx	13.2	Ill-defined ST thickening extending into (R) para pharyngeal space	Nasopharyngeal Biopsy: Suggestive of nasopharyngeal Ca, nonkeratinising type	TP
4.	Primary not suggested	-	-	EBV +ve on lymphnodal IHC, Nasopharyngeal Ca considered	FN
5.	Primary not suggested	-	-	FNAC swelling right lateral border of tongue - squamous cell Ca	FN
6.	(R) tonsil	14.6	Ill-defined heterogeneously enhancing lesion	Clinical correlation	TP
7.	(R) pyriform sinus	7.3	ST thickening (R) pyriform sinus	Bulkiness on endoscopy , considered primary malignancy	TP
8.	(L) vallecula	7.0	Soft tissue lesion obliterating left vallecula	Biopsy- lingual tonsillar tissue showing lymphoid hyperplasia. no dysplasia / malignancy	FP
9.	(L) tonsil	5.2	Asymmetric bulkiness	Tonsillectomy- no malignancy/ dysplasia seen.	FP
10.	(L) nasopharynx	7.5	Soft tissue thickening left nasopharynx	Biopsy - Poorly differentiated Ca,consistent with Nasopharyngeal Ca.	TP
11.	(R) Parotid gland	9.1	Hypodense lesion in superficial lobe of (R) parotid gland	Parotidectomy, HPE-Warthin's tumour	FP
12.	Mid esophagus	3.8	Focal thickening mid esophagus just below carina	CECT abdomen-intramural tumour (considered primary site of malignancy)	TP
13.	Posterior third of tongue	15.6	Heterogeneously enhancing lesion	Considered primary malignancy on clinical correlation	TP
14.	Left Tonsil	6.3	asymmetrical soft tissue bulge at left pharyngeal anterior tonsillar pillar	Biopsy from tonsillolingual sulcus-Moderately differentiated Squamous Cell Ca	TP
15.	Tongue	9.8, anterior aspect	No CT detectable abnormality	Excision Biopsy undersurface tongue tip right side-no dysplasia or malignancy seen.	FP
16.	(L) Tonsil	14.9	Enhancing ST in tonsillar fossa infiltrating posterior aspect of tongue	3x2 cm proliferative lesion in tongue base left side, considered BOT malignancy	TP
17.	Nasopharynx	13.8	ST mass in Nasopharynx (L) side extending into oropharynx	Considered primary on clinical correlation	TP
18.	(R) lung	1.8	Thick walled cavity apical segment of upper lobe of right lung	IHC from nodal metastases (p63 +ve, CK 5/7 +ve, focally CK7 +ve), considered as Lung Ca	TP
19.	Primary not suggested	-	-	In view of IHC (CK 5/6 - strongly positive, EBV +ve, p16 – ve) considered Nasopharyngeal Ca	FN
20.	(L) lung	6.2	Speculated lesion apicoposterior segment (L) lung upper lobe 2.1x2.4 cm	Biopsy lung - Poorly differentiated Ca	TP
21.	Primary not suggested	-	-	Esophageal endoscopic biopsy-Moderately differentiated keratinizing squamous cell Ca	FN
22.	Bilateral ovaries	R-19.5 L-6.3	ST mass in R adnexa Solid enhancing component in (L) solid cystic adnexal mass	TAH and BSO specimen –adeno carcinoma both ovaries	TP
23.	(R) Lung	4.7	ST in posterior segment of (R) lung upper lobe	IHC (CK7,TTF1,focally for CEA and negative for CK20 and p63) and imaging findings correlated and considered Ca Lung	TP
24.	(R) Breast	-	ST lesion 14x 20 mm	Mammogram-Negative	FP
25.	Thyroid	3.1	7x 9 mm hypodense nodule lower pole of right lobe of thyroid	FNAC (thyroid nodule) -follicular neoplasm, (R) Hemi Thyroidectomy - adenomatous nodule (L) MRND specimen- metastatic PD Ca	FP
26.	Nasopharynx	5.7	Illdefined minimally enhancing ST dense lesion 12x 8 mm in right posterior Nasopharynx	HPE, IHC from lymphnodes- PD Ca, CK +ve, considered Nasopharyngeal Ca	TP
27.	Stomach	6.5	No definite CT abnormality	Endoscopic gastric biopsy - Poorly differentiated adenocarcinoma, diffuse type	TP
28.	(R) Lung	5.6	Illdefined lesion 7.6x 4.3 cm superior segment (R) lung lower lobe	Cervical lymphadenopathy-Metastatic poorly differentiated neoplasm. IHC (positive for CK, CK7, negative for S100, CK20, TTF-1, CD30) - considered Ca Lung	TP
29.	Primary not suggested	-	-	USG and FNAC thyroid nodule- suspicious for MTC, Total thyroidectomy, HPE- unifocal MTC	FN

SUV:standardised uptake value, HPE:histopathology examination, Ca:carcinoma, CT:computed tomography, CECT:contrast enhanced computed tomography, (L):left, (R):right, ST:soft tissue, EBV:Epstein Barr Virus, IHC:immunohistochemistry, PD:poorly differentiated, TAH:Total abdominal hysterectomy, BOT:base of tongue, BSO:bilateral salpingoophorectomy, MRND:modified radical neck dissection, CK:cytokeratin, USG:ultrasonography, FNAC:fine needle aspiration cytology, MTC:medullary thyroid carcinoma, TP:true positive, FP:false positive, TN:true negative, FN:false negative, TTF1: Thyroid transcription factor 1, CEA:carcinoembryonic antigen, -ve:negative, +ve:positive

Table 2: Sites of tumour identification on PET CT and detection rate.

Site	Distribution
Nasopharynx	4 (6.3%)
Oropharynx	4 (6.3%)
Pyriform sinus	1 (1.5%)
Esophagus	1 (1.5%)
Stomach	1 (1.5%)
Lung	6 (9.5%)
Ovary	1(1.5%)
Total number of occult primary identified and confirmed	18 in 63 pts
Detection rate	28.5%

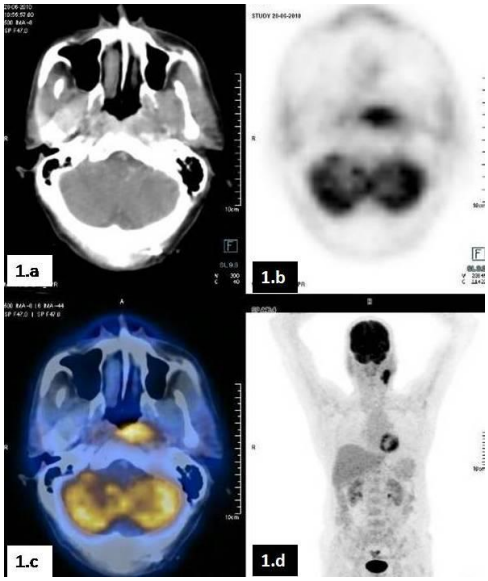

Fig 1. Clinical context: FNAC from cervical lymph node was suggestive of metastasis from moderately differentiated squamous cell carcinoma. (a) CT transaxial image in soft tissue window showing subtle soft tissue thickening in the left side of nasopharynx. (b) Corresponding transaxial Positron Emission Tomography (PET) image which shows an area of intense FDG uptake (SUV max 7.5) on the left side in the nasopharyngeal region. (c) Fused CT and FDG transaxial images showing FDG uptake localized to soft tissue thickening in the nasopharynx. (d) Maximal Intensity Projection (MIP) image of the subject acquired from skull upto mid thigh showing FDG uptake in the left cervical region which were localized to level II, III and V cervical lymphnodes on corresponding CT and also the normal biodistribution of FDG in the subject. Biopsy from nasopharynx - Poorly differentiated carcinoma, consistent with nasopharyngeal carcinoma.

But Kwee et al. in their meta-analysis showed that sensitivity and specificity of ^{18}F-FDG PET-CT in primary tumor detection ranged from 55% to 100% and from 73% to 100% respectively [17]. Hassan et al. in their recent meta analysis found a high sensitivity of 80.6% and specificity of 82.1% in detecting occult primary tumor with cervical metastases in 589 patients indicating the existence of few false-negative and false positive results [18].

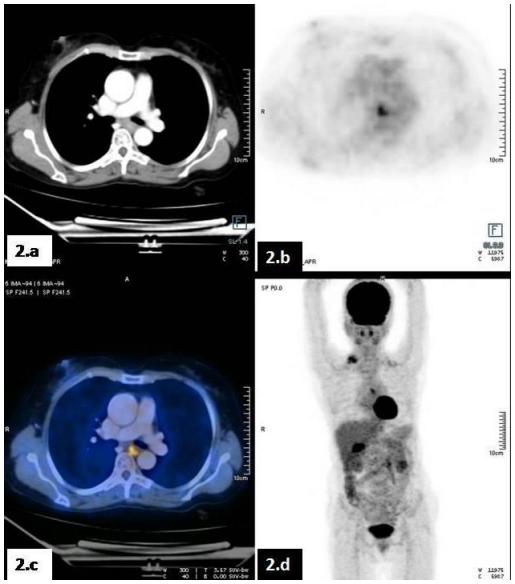

Fig 2. Clinical context: Biopsy from right lower cervical node, supraclavicular node was suggestive of squamous cell carcinoma. (a) CT transaxial image in soft tissue window showing focal thickening of mid esophagus just below the carina. (b) Corresponding transaxial Positron Emission Tomography (PET) image shows an area of intense FDG uptake (SUV max 3.8) in posterior mediastinum. (c) Fused CT and FDG transaxial images showing FDG uptake localized to the focal thickening of mid esophagus just below the level of carina. (d) Maximal Intensity Projection (MIP) image of the subject acquired from skull upto mid-thigh shows FDG uptake in the right lower cervical region which was localized to right supraclavicular lymphnodes (SUV max 6.6) on corresponding CT images, focal FDG uptake in the lower mediastinal region and also the normal biodistribution of FDG. Esophageal lesion was considered primary malignancy of the mid esophagus in the clinical context.

Our false positive rate on ^{18}F-FDG PET-CT was 15%, which is in accordance with some studies like Rusthoven et al. who reported a false-positive PET rate of 16% [15]. In DAHANCA 13 study [16], the false-positive rate was 20%, which was higher than in review by Rusthoven et al. Kwee et al. in their meta-analysis, reported a false-positive rate of 15% [17]. Tonsils, lungs and oropharynx are supposed to be common false-positive ^{18}F-FDG PET-CT findings [15, 17]. We had 6 false-positive sites amongst 29 suggested possible sites of primaries. A vallecula lesion suggested showed no dysplasia/malignancy on biopsy. Similarly, a tonsillar lesion did not show malignancy on tonsillectomy specimen. In another patient, Wartheim's tumor was detected on parotidectomy specimen. Another lesion suggested on ^{18}F-FDG PET in the tongue without CT detected abnormalilty was negative for malignancy on biopsy. An ^{18}F-FDG non-avid soft tissue lesion in breast showed no features of malignancy on mammography. In one patient, a thyroid lesion on hemithyroidectomy turned out to be an adenoma (Figure 3).

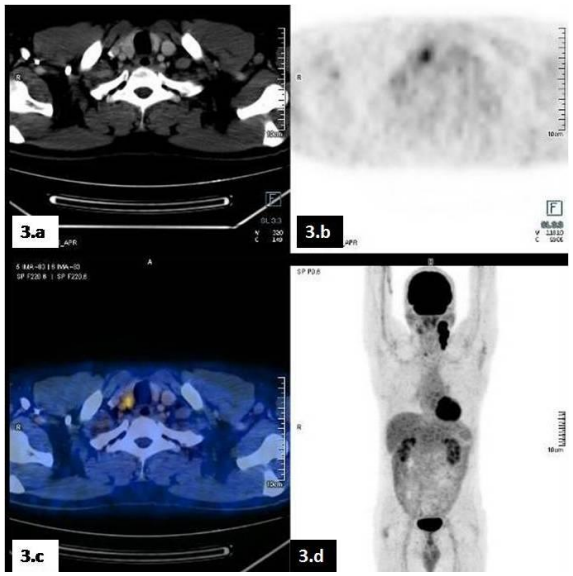

Fig 3. Clinical context: FNAC from left upper neck mass suggestive of metastatic anaplastic carcinoma. (a) CT transaxial image in soft tissue window showing 7x 9 mm hypodense nodule in right lobe of thyroid gland. (b) Corresponding transaxial Positron Emission Tomography (PET) image shows focal FDG uptake (SUV max 3.1) on the right side in the thyroid gland region. (c) Fused CT and FDG transaxial images shows focal FDG uptake localized to the hypodense nodule in the lower pole of right lobe of thyroid gland. (d). Maximal Intensity Projection (MIP) image of the subject acquired from skull upto mid thigh shows abnormal increased FDG uptake in the conglomerate lymphnodal mass involving left level II, III, IV and V cervical nodes (SUV max 12.9), 41mm x 26 mm x 87 mm on corresponding CT and also the normal biodistribution of FDG. Subsequently FNAC from the thyroid nodule showed cellular follicular lesion, suggestive of follicular neoplasm while FNAC from the lymphnodes was suggestive of metastatic poorly differentiated carcinoma, possibly squamous cell carcinoma. Right Hemithyroidectomy histopathology showed the FDG avid nodule to be a adenomatous nodule (a false positive finding on FDG PET CT). Left modified radical neck dissection specimen showed metastatic poorly differentiated carcinoma in lymphnodes at level II, III, IV, V with perinodal spread (10 lymphnodes out of 23 lymphnodes).

False-positive findings can lead to unnecessary investigations and biopsies. False-positive findings include physiologic ^{18}F-FDG uptake in the tonsils, reactive lymph nodes and masticator muscles. Sarcoidosis, granulomatous disease [12] and mucosal biopsy of recent duration, due to tissue repair reaction, are also known to cause false -positive findings [24].

The base of tongue and breast have been considered common sites of false-negative sites ^{18}F-FDG PET-CT [15, 17]. Small (<1 cm), slow growing, low-grade breast cancers with less or no ^{18}F-FDG uptake (e.g., tubular carcinoma and noninvasive cancers such as ductal or lobular carcinoma in situ) may be missed on ^{18}F-FDG PET-CT [25]. Small primary tumors below the resolution of PET machine or with reduced SNR (signal-to-noise ratio) caused by high background and/or well-differentiated tumors with low ^{18}F-FDG uptake may be missed. We had 5 false-negative cases. 2 patients in which Epstein Barr Virus (EBV) had been detected on immunohistochemistry (IHC) and ^{18}F-FDG PET-CT was not suggestive of any primary lesion in the nasopharynx, nasopharyngeal malignancy was considered. In two patients where ^{18}F-FDG PET-CT had failed to suggest a primary lesion, subsequently were confirmed to have primary tongue and esophageal malignancy on biopsy on follow up. In another patient, ultrasound-guided FNAC was suspicious for medullary thyroid carcinoma (MTC) and subsequently total thyroidectomy specimen showed unifocal MTC. However, it needs to be kept in mind that involution, slow growth rate or inhibition of growth of primary by metastases [4], may blur the difference between false-negative study on PET CT and a true negative study.

In our study, positive predictive value (PPV) of ^{18}F-FDG PET-CT was 75% and the negative predictive value (NPV) was 87%. In the review by Kwee et al., they have reported a positive predictive value of 56–83% and a negative predictive value of 75–86% [17]. Our negative predictive value on the higher side the range can be explained by the superior imaging characteristics of newer versions of PET machines. Primary tumor site detection allows for precise therapy. In some cases, this may reduce the morbidity known to occur with wide-field irradiation [14, 26]. Better outcomes have been projected if the primary tumor is detected and targeted therapy is initiated (radiation/surgery) [27].

Table 3: Validity assessment: Categorization.

PET CT	HPR /follow up investigations	Categorisation	No.
Primary suggested	Suggested primary confirmed on histopathology	True positives(a)	18
Primary suggested	Suggested primary not proven on histopathology	False positives(b)	6
No possible primary suggested	Primary detected through other means after PET CT	False negatives(c)	5
No possible primary suggested	Primary not detected through other means also after PET CT	True negatives (d)	34

Table 4: Validity assessment: Calculations.

Parameter	Formula	Calculation	Value (%)
Sensitivity	a/(a+c)x100	18/(18+5)x100	78.2
Specificity	d/(b+d)x100	34/(6+34)x100	85.0
PPV	a/(a+b)x100	18/(18+6)x100	75.0
NPV	d/(c+d)x100	34/(5+34)x100	87.1
Rate of false positivity	b/(b+d)x100	6/(6+34)x100	15.0

Table 5: Distribution of distant metastases for patients presenting with cervical lymphnodal disease (supraclavicular nodal presentation excluded) (Total patients = 46).

Sites of metastases detected on PET-CT	Number of patients*
Extracervical lymphnodal	15
Organ/skeletal metastases	9

*Some of the patients had both extra supraclavicular lymphnodal and organ/skeletal metastases.

Table 6: Distribution of other lymphnodal or organ metastases for patients presenting with supraclavicular nodal (SCN) metastases (Total patients with SCN presentation= 17).

Sites of metastases detected on PET-CT	Number of patients*
Extra SCN lymphnodal	14
Organ/skeletal	6

*Some of the patients had both extra supraclavicular lymphnodal and organ/skeletal metastases.

In those patients with cervical nodal metastases (i.e excluding the patients with supraclavicular nodal metastases) (total 46 patients out of 63 patients) ^{18}F-FDG PET-CT detected extracervical lymphnodal or contralateral cervical metastatic disease in 15 patients and distant skeletal/soft tissue metastases in nine patients. ^{18}F-FDG PET has been seen to have a higher sensitivity ranging from 66 to 87% as compared to CT alone (43%) in detecting distant disease [28]. Presence of distant metastases are known to reduce overall survival, which may range from 4 to 8 months from the time when metastatic disease is first detected [29].

Dietl et al. in a retrospective analysis of 600 patients with head and neck cancer have reported distant metastases in 4.8% of patients at initial cancer diagnosis and in 19% of patients in subsequent course of illness. The increase in metastatic disease during the later part of illness could possibly be explained by a clinically silent process of metastasis at an earlier time point in the disease process [30]. In our patients, with supraclavicular nodal metastases presentation (17 patients out of 63 patients) ^{18}F-FDG PET-CT detected extra supraclavicular lymph nodal metastatic lymph nodes in 14 patients and overall other skeletal and soft tissue metastases in 6 patients. Patients presenting with neck nodal metastases from unknown primary irrespective of the nodal staging have to be given the benefit of a whole-body evaluation in the form of ^{18}F-FDG PET-CT to have an overall assessment of disease spread.

CONCLUSION

^{18}F-FDG PET-CT is a useful imaging modality in the workup of patients with carcinoma of unknown primary presenting with neck nodal metastases. Being a metabolic imaging modality and with newer versions of PET machines with superior imaging characteristics, ^{18}F-FDG PET-CT should be incorporated in the diagnostic imaging algorithm in the workup of patients with neck nodal metastatic disease from unknown primary malignancy with high diagnostic performance.

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