Original Article

Efficacy of PET CT scan in detecting occult primary with cervical lymph node metastasis

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Abstract

Introduction: There are several causes of the low rate of detection of the primary. It is hypothesised that in patients who present with CUPS, the primary tumour either remains microscopic and escapes clinical detection or disappears after seeding the metastasis because its angiogenetic incompetence leads to marked apoptosis and cell turnover. Furthermore the sensitivity of conventional diagnostic procedures may not be satisfactory. **Objectives:** To study the efficacy of PET CT scan in detecting occult primary with cervical lymph node metastasis. **Materials and method:** The present study was conducted in the Army Hospital (Research and Referral), Delhi Cantt. The patients attending Head and Neck Oncology clinic with metastatic cervical lymph node (s) without evidence of primary by clinical evaluation were enrolled in the present study. Total 27 patients were selected and were analysed. All the selected patients underwent review of their medical history and thorough medical examination. The patients in whom a primary tumour was not detected were accrued into the study and classified as patients with Carcinoma of Unknown Primary Site (CUPS), and they formed the cohort of our study. All the study patients were subjected to ultrasonography of the abdomen, CT scan of the neck and chest and panendoscopy under general anaesthesia, to look for any evidence of a primary tumour. All the patients were subjected to whole body PET-CT scan. The outcome of tests have been tabulated and analysed to ascertain the sensitivity, specificity, positive and negative predictive values of whole body PET-CT scan in detecting the primary in CUPS with cervical lymph node metastasis. **Results:** It was observed that age profile of the patients varied from 48 to 86 yrs with mean age as 62. Eleven of these patients had squamous cell carcinoma, seven had adenocarcinoma, six had poorly differentiated carcinoma, and remaining three had undifferentiated carcinoma metastases. FDG-PET-CT was negative in 14 (51.85%) patients and was positive in 13 (48.15%) patients. Out of these thirteen patients, nine had primary tumour, while four patients had evidence of distant metastasis. The Sensitivity and specificity of FDG-PET-CT in our study was 87.5 and 89.5% respectively while Positive and Negative predictive values were 77.8 and 94.4% respectively. **Conclusion:** The PET-CT has sensitivity and specificity of 87.5 and 89.5% respectively. Thus it can be used as valuable diagnostic tool in patients with CUPS as it was able to detect the unknown primary tumour, not detected by the other conventional investigative modalities. Additionally it has detected the presence of distant metastases, thereby assisting in both guiding biopsies for histological evaluation (for primary) and selecting the appropriate treatment protocols in these patients.

Key Words: PET CT scan, cervical lymph node metastasis, Carcinoma of unknown primary site.

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INTRODUCTION

Carcinoma of unknown primary site (CUPS) is a syndrome consisting of a biopsy confirmed metastasis with an unidentified primary lesion after careful review of the patient's medical history, thorough medical examination and relevant clinical tests, including fibreoptic endoscopies. CUPS ranks as the seventh most frequent type of cancer in the world and the fourth most common cause of cancer deaths which represent both diagnostic and management challenges[1]. The regression or dormancy of the primary tumour, the development of early, uncommon, systemic metastases, and the resistance

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to therapy are hallmarks of this heterogeneous clinical entity. Although it is widely accepted that CUPS is a heterogeneous cohort of metastatic malignancies, no consensus exists yet on the true nature of this clinical entity[2]. Histopathologic analysis frequently provides hints as to the location of the primary site, not all tumours are identified despite a comprehensive diagnostic work-up. Imaging with CT/MRI and other tumour markers the primary could be detected only in 20-27% and even at autopsy primary site is detected in only 30-62 % of patients[3]. There are several causes of the low rate of detection of the primary. It is hypothesised that in patients who present with CUPS, the primary tumour either remains microscopic and escapes clinical detection or disappears after seeding the metastasis because its angiogenetic incompetence leads to marked apoptosis and cell turnover. Furthermore the sensitivity of conventional diagnostic procedures may not be satisfactory. The inability to detect primary, prevents the optimization of therapeutic strategies, which is dependent on tumour differentiation, tumour location, and tumour stage as determined according to the TNM staging system. Hence, patient prognosis is negatively affected and we need a new investigation tool to detect primary site[4]. All over the world quite a few number of studies have been done which compared diagnostic workups involving various imaging modalities. Positron Emission Tomography (PET) is a nuclear medical imaging technique, and has been in clinical use for the past decade or so. Apart from the study of cerebral and myocardial physiology, PET scan is being widely used in oncologic diagnosis and quite effectively utilised in head and neck cancers[5]. It produces a three dimensional image or map of functional processes in the body. Fluoro Deoxy Glucose (FDG)-PET is a functional imaging modality that characterises different tissues in the body according to glucose metabolism. In contrast to anatomic imaging such as CT and MRI, PET imaging is based on metabolism and tissue perfusion. PET is done using a radioactively labelled glucose analogue (FDG) that can be localised accurately due to its emission of positrons. Because FDG is taken up by the tissue in the same fashion as normal glucose, this radioactive tracer becomes concentrated in cells with high levels of glucose usage. Tumour cells have increased levels of glucose metabolism and rapid cell proliferation. The increased glucose uptake observed in tumour cells has been attributed to either an increase in the transcription and translation of glucose transport proteins in tumour cells or to hexokinase activity. Because of this characteristic, FDG uptake is elevated in malignant cells compared to normal tissue. As a result neoplasia are reliably distinguishable from surrounding tissue on PET imaging[5].

MATERIALS AND METHOD

The present study was conducted in the Army Hospital (Research and Referral), Delhi Cantt. Following inclusion and exclusion criteria was used to select the study subjects.

Inclusion Criteria

1. The patients attending Head and Neck Oncology clinic with metastatic cervical lymph node(s) without evidence of primary by clinical evaluation
2. Those patients referred from oncology clinics from other service hospitals as CUPS.
3. Patients who had no prior history of cancer.
4. Those patients, who had not received treatment if the form of surgery, chemotherapy and/or radiation therapy, for malignancy.
5. The patients who are entitled, for undergoing PET scan at our centre, i.e. Personnel serving in the Armed Forces, their dependants, ex-service personnel and their dependants.

Exclusion Criteria

1. Primary tumour detected during work up prior to undergoing PET-CT scan.
2. Those patients who are not willing for regular follow-up.
3. The patients who has active infection or inflammatory disease at presentation.
4. Patients who were found to be hyperglycaemic.

Total 33 patients were enrolled in the present study. Out of which four patients were detected to have primary and in two patients cervical lymph nodes were not positive for metastases, hence were excluded from the study. Thus the total 27 patients were accrued into the study and were analysed. All the selected patients underwent review of their medical history and thorough medical examination. They underwent relevant clinical tests, including complete blood counts, LFT, RFT, urine analysis, and chest radiography. Further they were subjected to fibreoptic nasopharyngoscopy and laryngoscopy, followed by fibreoptic bronchoscopy and oesophagoscopy to look for any evidence of primary lesion. Those patients, who were found to have suspicious lesions, underwent biopsy of the suspected site. Thus the patients in whom a primary tumour was not detected were accrued into the study and classified as patients with Carcinoma of Unknown Primary Site (CUPS), and they formed the cohort of our study. All the study patients were subjected to ultrasonography of the abdomen, CT scan of the neck and chest and panendoscopy under general anaesthesia, to look for any evidence of a primary tumour. Then all the patients were subjected to whole body PET-CT scan. Written informed consent for PET-CT scan was taken and latest blood sugar level

investigation was done. Patients were kept fasting for 12 hrs before the scan. The outcome of tests have been tabulated and analysed to ascertain the sensitivity, specificity, positive and negative predictive values of whole body PET-CT scan in detecting the primary in CUPS with cervical lymph node metastasis.

RESULTS

Table 1: Age and sex wise distribution of study patients

		No of patients	Percentage
Age	≤50	2	7.41
	51-60	10	37.04
	61-70	11	40.74
	71-80	3	11.11
	>80	1	3.70
Sex	Male	23	85.19
	Female	4	14.81

It was observed that age profile of the patients varied from 48 to 86 yrs with mean age as 62. Majority of the patients were in the age group of 51to 70 years of age (77.78%). Out of the total 27 patients, twenty three (85.19%) were male and four were female patients.

Table 2: Distribution of Cervical Lymphadenopathy

Lymphadenopathy		No of patients	Percentage
Lymphadenopathy	Unilateral	23	85.19
	Bilateral	4	14.81
Level of Lymphadenopathy	Level II and III	3	11.11
	Level IV	5	18.52
	Multiple	19	70.37
FNAC	Sq cell ca	11	40.74
	Adenocarcinoma	7	25.93
	Poorly differentiated	6	22.22
	Undifferentiated	3	11.11

Out of the twenty seven patients, 23 (85.19%) had unilateral and rest of the four bilateral cervical lymphadenopathy. In 19 patients the lymphadenopathy was limited to the level above cricoid while 5 patients had level IV and rest had conglomerate of multiple lymph nodes. Eleven of these patients had squamous cell carcinoma, seven had adenocarcinoma, six had poorly differentiated carcinoma, and remaining three had undifferentiated carcinoma metastases.

Table 3: Distribution of patients according to PET diagnosis

PET diagnosis	No of patients	Percentage
Positive	13	48.15
Negative	14	51.85

FDG-PET-CT was negative in 14 (51.85%) patients and was positive in 13 (48.15%) patients. Out of these thirteen patients, nine had primary tumour, while four patients had evidence of distant metastasis.

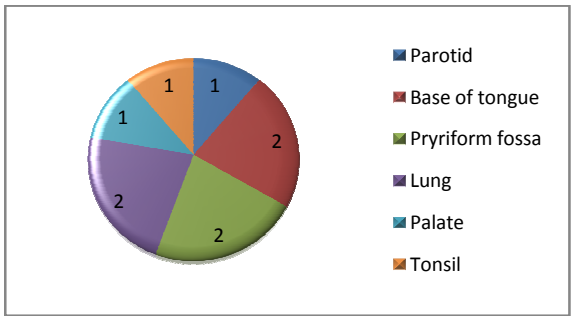

Figure 1: Ditsribution of primary tumour

Among the total 9 primary cases, two patients were PET-CT positive for primary in the base of tongue, two in the pyriform fossa, and one each in the tonsil, parotid gland, and palate and two were outside head and neck region (lungs). Out of the four patients with distant metastasis, one had metastases in the thoracic vertebrae and lungs, while one patient showed skeletal, pulmonary, and adrenal metastases and the remaining two had FDG avid lesions suggestive of skeletal metastases. (Fig.1)

Table 4: Efficacy of FDG-PET-CT as a diagnostic tool

	Histopathological examination	
	Positive	Negative
PET-CT Positive	7 (True +ve)	2 (False +ve)
PET-CT Negative	1 (False –ve)	17 (True –ve)

Table 5:

Sensitivity	87.5 %
Specificity	89.5 %
Positive Predictive value	77.8 %
Negative Predictive value	94.4 %

Among the nine patients PET-CT positive for primary, there were seven cases that showed true positive for PET-CT; five in head and neck and two in lungs. The two patients with primary lesion suspected in the base of tongue underwent direct laryngoscopy and multiple deep biopsies from base of tongue, vallecula, and tonsillo-lingual sulcus. One patient showed well differentiated squamous cell carcinoma on histopathological examination (HPE) at base of tongue and the other moderately differentiated squamous cell carcinoma in the tonsillo-lingual sulcus. Among the two patients with FDG uptake in the pyriform fossa, one showed poorly differentiated carcinoma on biopsy from apex of pyriform fossa whereas the other one revealed squamous cell carcinoma on biopsy from pyriform fossa just below the pharyngoepiglottic fold. The patient with FDG avid lesion in the parotid underwent total parotidectomy and the HPE revealed a tiny focus of moderately differentiated adenocarcinoma involving the deep lobe.

Two patients with primary suspected in the lung underwent transbronchial needle aspiration (TBNA) and CT guided biopsy which revealed adenocarcinoma. The patient with FDG avid lesion in the palate underwent biopsy, which on (HPE) showed no evidence of malignancy, similarly the patient with PET-CT positive for tonsil underwent tonsillectomy but on histopathological examination again there was no evidence of malignancy. These two patients thus turned out to be false positive for PET-CT. Out of 4 cases of PET-CT positive showing metastasis, two of the patients with pulmonary metastasis underwent TBNA which were histopathologically positive for metastases from poorly differentiated carcinoma. One of the two patients with only skeletal metastases, died while undergoing palliative radiotherapy while the other one refused to undergo any further investigative procedures. There was one patient in whom panendoscopy had revealed slight thickening of the left border of epiglottis, without mucosal lesion. PET-CT did not reveal any FDG avid lesion. He was taken up for Radical Neck Dissection (RND) and in the same session CO_2 LASER excision of the thickened part of left border of epiglottis was done. HPE showed well differentiated squamous cell carcinoma. This patient was thus considered false negative for PET-CT. Thus the Sensitivity and specificity of FDG-PET-CT in our study was 87.5 and 89.5% respectively while Positive and Negative predictive values were 77.8 and 94.4% respectively.

DISCUSSION

The present study was conducted at the Army Hospital (Research and Referral) with the objective to study the efficacy of PET CT scan in detecting occult primary with cervical lymph node metastasis. It was seen that majority of the patients were in the age group of 51to 70 years of age (77.78%). The age of patients in the study was in the range from 48 to 86 yrs with mean age as 62. Out of the total 27 patients, twenty three (85.19%) were male and four were female patients. Similar findings were also reported by Myriam Wartski *et al*[1].The male predominance corresponds to the higher prevalence of the common risk factors associated with cancers of head and neck region; tobacco smoking and chewing, one of the major risk factors, is seen more amongst the male population[6]. Out of the twenty seven patients, 23 (85.19%) had unilateral and rest of the four bilateral cervical lymphadenopathy. In 19 patients the lymphadenopathy was limited to the level above cricoid while 5 patients had level IV and rest had conglomerate of multiple lymph nodes. Eleven of these patients had squamous cell carcinoma, seven had adenocarcinoma, six had poorly differentiated carcinoma, and remaining three had undifferentiated carcinoma metastases. According to a study by Stefan AM Paul *et al*[7], the patients with primaries in the head and neck region had metastasis to lymph nodes above the level of cricoid, while those from lungs below the level of cricoids. FDG-PET-CT report was negative in 14 (51.85%) patients and was positive in 13 (48.15%) patients. Out of these thirteen patients, nine had primary tumour, while four patients had evidence of distant metastasis. It was seen that among the total 9 primary cases, two patients were PET-CT positive for primary in the base of tongue, two in the pyriform fossa and one each in the tonsil, parotid gland, and palate and two were outside head and neck region (lungs). Out of the four patients with distant metastasis, one had metastases in the thoracic vertebrae and lungs, while one patient showed skeletal, pulmonary, and adrenal metastases and the remaining two had FDG avid lesions suggestive of skeletal metastases. The rate of primary tumour detection by FDG-PET-CT was 33.33% in the present study and it was in agreement with most studies in the literature, with site detection rates of between 21% and 47%[1,7-11]. Only one study has indicated that PET-CT does not improve the detection of occult primary tumours in head and neck. These authors reported only 8% rate of primary tumour detection (1 out of 13) and also a high false positive rate[12]. Sensitivity of any diagnostic tool depicts the ability to bring out true positive and thereby correctly diagnose the presence of disease factor being studied; thus lesser the false negative, higher the sensitivity. Sensitivity of PET-CT in our study was 87.5%, while review of other studies revealed sensitivity ranging from 67 to 100% [1,7-11]. Specificity of a diagnostic tool represents the ability to bring out the true negative, thus correctly measure the absence of the disease factor being studied; hence lesser the false positive higher is the specificity. Specificity of PET-CT in our study was 89.5% and review of studies by other authors showed specificity of PET-CT ranging from 56 to 79% [1,7-11]. The positive predictive value (PPV) and negative predictive value (NPV) of our study was 78% and 94% respectively, while it ranged between 33 to 88% and 50 to 100% respectively for studies conducted by other authors[1,7-11]. This wide range in various studies have been attributed to the fact that the higher sensitivity, specificity, PPV, and NPV were achieved in studies involving PET-CT coregistration, as compared to P*Et al*one (which showed higher false positive results)[13]. A study was conducted by Stoeckli *et al* towards the impact of PET in lymph node metastasis of squamous cell carcinoma from unknown primary. It was a study in which patients were taken up after all the clinical work up including fibreoptic endoscopy, but prior to panendoscopy. Panendoscopy revealed a primary tumour in eight out of eighteen patients, and out of the eighteen patients, who underwent PET-CT, primary was detected

in five patients and three were false negative, further the PET scan did not reveal any distant metastasis or synchronous second primary in a distant location in these patients with SCC. Thus it was concluded that, apart from being a non-invasive procedure, PET scan did not render any additional advantage, in terms of diagnostic value, as compared to panendoscopy[2]. Nanni *et al* in a study of 21 patients found eight patients with adenocarcinoma, seven had squamous cell carcinoma, one had melanoma, one had spindle cell carcinoma and one had a germ cell tumour, one had transitional cell carcinoma and one flat cell tumour. All these patients underwent FDG PET-CT scan, and in 12 cases (57%) PET-CT correctly detected the primary occult tumour[11]. Miller *et al*, in their study 26 patients with CUPS subjected these patients to PET scan followed by panendoscopy with selected biopsies and tonsillectomy. The PET detected eight occult primary tumours in 26 patients (30.8% detection). Four patients with occult primary were detected during panendoscopy, who had negative PET findings. Thus the sensitivity of PET was found to be 66%, with a specificity of 92.9%. The positive predictive value was 88.8% and the negative predictive value was 76.5%[14]. Myriam Wartski *et al* undertook a study from October 2002 to March 2005, in which there were 38 patients (31 men and seven women, in an age range 36-80 years with a mean age of 57 years) with cervical metastasis from unknown primary tumour and a negative comprehensive diagnostic workup, underwent a hybrid FDG-PET-CT scan in order to localize the primary tumour. PET-CT was found positive for a primary tumour in 26/38 patients (68%)[1].

CONCLUSION

The PET-CT has sensitivity and specificity of 87.5 and 89.5% respectively. Thus it can be used as valuable diagnostic tool in patients with CUPS as it was able to detect the unknown primary tumour, not detected by the other conventional investigative modalities. Additionally it has detected the presence of distant metastases, thereby assisting in both guiding biopsies for histological evaluation (for primary) and selecting the appropriate treatment protocols in these patients.

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