RESEARCH ARTICLE

TO ASSESS ABILITY OF PET CT TO DIFFERENTITIATE BENIGN AND MALIGNANT F-18 FDG PET-CT POSITIVE PERIPHERAL LYMPH NODES IN POST TREATMENT CANCER PATIENTS BY HISTOPATHOLOGICAL CORRELATION

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ARTICLE INFO

ABSTRACT

Objective: Our study was focused on patients with various types of malignancies undergoing follow up 18F FDG PET-CT imaging after definitive cancer treatment to assess the ability of F-18 FDG PET CT to differentiate benign and malignant metabolically active peripheral lymph nodes (LNs) with histopathological (HP) correlation.

Methods: Follow up of 115 treated cancer patients with 18F FDG PET-CT imaging who had metabolically active peripheral LNs were included in this prospective study which consist 60 males and 55 females (15-75 years). Various indices like retention index (RI), delayed tumor to non tumor ratio (De T: NT), difference in SUV max (D SUV) were calculated. Receiver operating characteristic (ROC) analysis and Spearman's rank correlation was performed. The results of 18 F FDG PET- CT were correlated to the final HP results.

Results: The overall sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 18F FDG PET-CT to detect metastases in peripheral LNs in post therapy cancer patients were 96%, 75%, 89% and 90% respectively. 18F FDG PET-CT in post treatment setting had the maximum sensitivity (100%), NPV (100%) and PPV (89.65%) for supraclavicular nodes and maximum specificity (80%) for axillary nodes. The D-SUVmax, De T: NT ratio and RI of malignant LNs were significantly higher than benign LNs.

Conclusion: 18F FDG PET-CT has high sensitivity and high NPV which helps to exclude metastasis and guides for metabolic biopsy and paves an important way in the follow up management of treated cancer patients.

INTRODUCTION

Lymphadenopathy is commonly seen in cancer patients in pre and post treatment setting which may be due to malignant, inflammatory or infectious etiologies (Kumar *et al.,* 2011). In post treatment settingwith the advent of novel chemotherapeutics and immune status suppression enlarged nodes need not be necessarily malignant. The coexistence of granulomatous reaction in patients with malignancy may be due to reaction of body to necrotic tumor, changes due to previous procedures and therapies or idiopathic (Uğurluer *et al.,* 2013). Coexistence of two diseases always posesdiagnostic challenge especially in cancer patients, over staging of nodes can occur if not diagnosed accurately. FDG PET-CT being powerful, non-invasive and sensitive modality exploitsthe biochemical differences between benign and malignant cells (Carter *et al.,* 2016).

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However, as many granulomatous diseases like tuberculosis may have SUVmax as high as malignant nodesthe much hyped earlier idea of 'everything that concentrates FDG is malignant', does not hold true always. Dual time point imaging has also been used by the virtue of fact that malignant cells continue to concentrate FDG whereas inflammatory processes do not. Hence, the present study was aimed to assess and explore the role of FDG PET-CT in assessment of peripheral lymphadenopathyin cancer patients post treatment with no local recurrence.

MATERIALS AND METHODS

Patientstreated for various cancers like head and neck, thoracic, abdominopelvic and miscellaneous malignancies and lymphomas were prospectively enrolled at department of Nuclear Medicine, Apollo Hospitals, Chennai between April 2012 and December 2015. Patients with FDG PET-CT negative LN status and with known history of granulomatous

disorders were excluded from the study. All patients underwent histopathological examination (HPE) of the FDG positive accessible LNby department of pathology of same institute and results of FDG PET-CT study were correlated with HPE. The study was approved by the local ethics committee and informed consent was obtained from all participating patients.

Image acquisition

Scans were performed on integrated PET-CT system (Gemini TF; Phillips) consisting of PET scanner and 64 slice CT scanner at department of nuclear medicine, Apollo hospitals. Aftersuring 4 hours of fasting and confirming the peripheral blood sugar to be less than 150mg/dL, 167-222MBq of ^{18}F-FDG was administered and acquisitions were performed 60 minutes after the injection.CT images were obtained from the head to the mid-thigh, according to a standardized protocol with the following settings: 140 kV; 80 mA; tube rotation time 0.8 seconds per revolution; section thickness 5mm acquisition time 22 seconds. Around 1.5 ml/kg of non-ionic iodinated contrast was pushed at the rate of 2.5 ml/ second with a time delay of 10-20 seconds. Immediately after CT scans PET was performed with acquisition time 1 minute 30 seconds per table position; ten incremental table positions; and duration of 14 to 16 minutes in all. Attenuation correction was performed by using CT images. Delayed scan was acquired for the required regions after 120 minutes.

Image Analysis

Images were viewed on extended brilliance workstation (EBW; Philips Medical Systems) by review team which consisted of two nuclear medicine physicians and radiologists. Presence of focal abnormal increased FDG uptake in LNs comparable to normal structures or surrounding tissues, excluding the areas of physiologically increased uptake was considered as positive LNs. A region of interest (ROI) was drawn on positive LNs and similar ROI were drawn in the delayed images and the maximum standardized uptake value (SUV max) was calculated. Image interpretation was based on visual and semi quantitative analysis of abnormally increased focal FDG uptake but strict SUV cutoffs were not used.The FDG PET-CT results were then reported in terms of benign or malignant based on visual appearance, early SUV max and delayed imaging indices. Retention index (RI) = (Delayed SUV max - Early SUV max) / Early SUV max, Difference in SUV max (D-SUV max- Delayed SUV max - Early SUV max) and Delayed tumour-to-nontumour ratio (De T: NT)were calculated. CT based analysis was also done on morphological characteristics of nodes such as size, shape, central necrosis, calcifications, fatty hilum etc.Final decision was arrived as a consensus between PET and CT findings.

Statistical Analysis

Continuous variables were assessed for the normality using Shapiro Wilk's test. If the continuous variables were normally distributed they were expressed as mean ±SD, otherwise median (interquartile range). All the categorical variables were expressed either as percentages or proportions. Comparison of non-normally distributed continuous variables was done by Mann Whitney U test. Comparison of categorical variables was being done by Chi square or Fischer extract test based on the number of observations. Receiver operating characteristic

(ROC) analysis was done to determine an optimum SUVmax cut off to differentiate benign from malignant lesion. It was also done to know the area under curve for various indices calculated from DTPI. Spearman's rank correlation was performed to analyze the correlation between variables such as SUV max and node diameter .Sensitivity, specificity, accuracy, PPV and NPV analysis for tumour detection with FDG PET-CT was also done, with histopathology as gold standard.Data entry was done in MS-excel spread sheet. Data validation and analysis was carried out by SPSS software (version 11.0). All the P values less than 0.05 were considered as statistically significant.

OBSERVATIONS AND RESULTS

Amongst 115 patients 60 were male and 55 were female (range: 15-75 years). The primary types of cancers dealt in this study were: head and neck (n=30), thoracic (n=27), abdominopelvic (n=38), lymphomas (n=15) and miscellaneous (n= 5).The patients were treated with various treatment regimens included Surgery (n=26), Chemotherapy (n=15), Radiotherapy (n=2), Surgery + chemotherapy (n= 37), Surgery + Radiotherapy (n= 7),Chemotherapy + Radiotherapy (n= 15), Surgery +Chemotherapy + Radiotherapy (n=11), Stem cell transplant + chemotherapy (n=2). Amongst 115 patients, 42 (36.5%) patientshad cervical nodes, 24 (20.9%) patients had axillary nodes, 33 (28.7%) patients had supraclavicular nodes and 16 (13.9%) patients had inguinal nodes.The sensitivity, specificity, PPV and NPV of FDG PET-CT to detect metastases in peripheral LNs in post therapy cancer patients were 96%, 75%, 89% and 90% respectively.The mean ± SD SUV max of the malignant nodes was 5.11 ± 2.67 (range2.2-13.7), whereas that of benign nodes was 4.75 ± 2.87 (range 2.3- 17.5).It was observed that there was no significant difference between the SUV max of malignant and benign nodes(p >0.005). From the Fig 1 it can be seen that the ROC curve lies close to the central line and area under curve is 54.

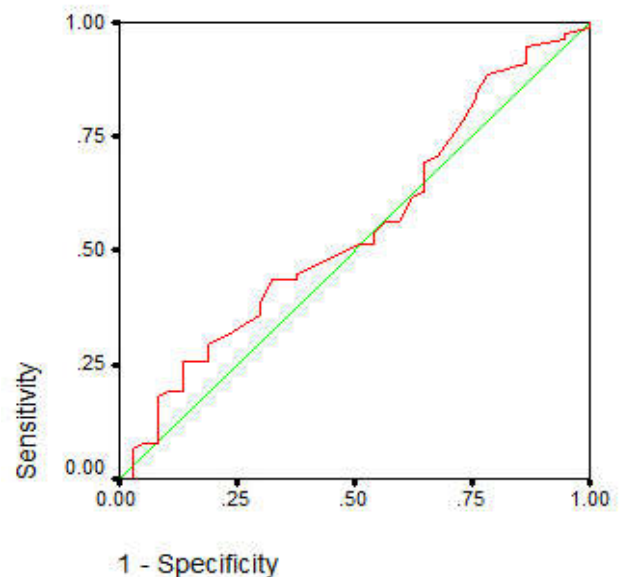

Figure 1. ROC curve analysis to derive an optimum SUVmax cutoff to differentiate benign vs. malignant nodes

The sensitivity, specificity, PPV and NPV were calculated for various cut off of SUVmax, results of which are depicted in Table 1.

Table 1. Sensitivity & Specificity of various SUV max cut offs

Early SUV max	3.0	3.5	4	4.5	5.0
Sensitivity	83%	61.5%	51%	43.6%	35.9%
Specificity	24.3%	32.8%	48.6%	64%	70.3%

From the table it is evident that as cut off increases, specificity increases and sensitivity drops. The size of malignant nodes was not significantly different from benign nodes (p>0.05) but there was a significant correlation between the size of nodes and SUV max (p<0.05), which is depicted in Fig 2.
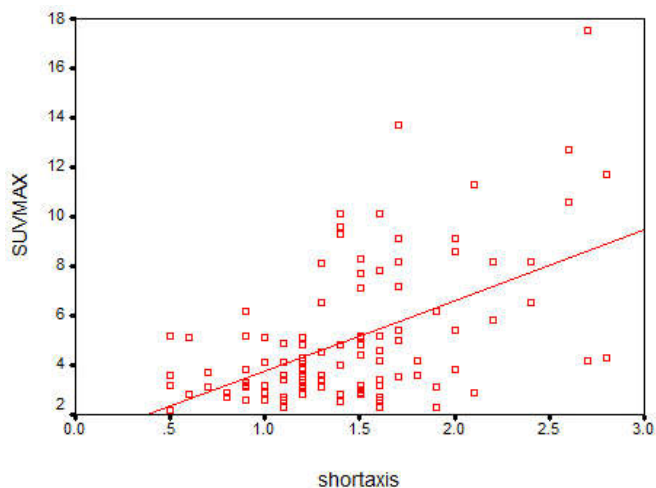

Figure 2. Correlation of Short Axis with SUV max

Table 2 depicts the sensitivity, specificity, PPV and NPV of FDG PET-CT for nodes located at different sites. As the no of cases involving inguinal LNs were small (n=16) region wise assessment not done. It is seen that FDG PET-CT in post treatment setting has the maximum sensitivity (100%) for supraclavicular nodes, maximum specificity (80%) for axillary nodes and maximum PPV (89.65%) and NPV (100%) was for supraclavicular nodes.

Table 2. Comparison of statistics of FDG PET-CT in nodes located in different regions

Region	Sensitivity	Specificity	PPV	NPV
Cervical (n=42)	96%	76.47%	85.71%	92.85%
Axillary (n=24)	85.7%	80%	85.71%	80%
Supraclavicular (n=33)	100%	57.14%	89.65%	100%

Delayed imaging

Various indices like RI, and De T:NT were calculated using the SUVmax of single time point study and that of delayed study, results of which are depicted in Table 3. The D-SUVmax, De T:NT ratio and RI of malignant nodes were significantly higher than benign nodes.

**Table 3. Comparison of various delayed FDG PET-CT imaging indices**

	Malignant	Benign	Significance (p value)
Mean RI	28.7	9.7	<0.05
Mean D-SUVmax	1	0.65	<0.05
Mean De T:NT	4.4	3.4	<0.05

ROC curve analysis was done to find out which of the indices helps in differentiating malignant from benign nodes with reasonable accuracy, results of which are depicted in Table

4and Fig 3. AUC was obtained which was maximum for RI followed by D-SUVmax (RI>D-SUVmax>De T:NT>delayed SUVmax> early SUVmax) Results are depicted in figure and table.

Table 4. Sensitivity specificity and area under curve for FDG PET-CT with delayed imaging and its indices

	Cut off value	Sensitivity	Specificity	AUC
EARLY SUVmax	3.5	61%	32.8%	54
DELAYED	3.8	70%	57%	56
SUVmax	4	62%	60%	
D-SUVmax	1	62%	76%	66
	2	77%	73%	
RI	10	75%	52%	78
	20	71%	65%	
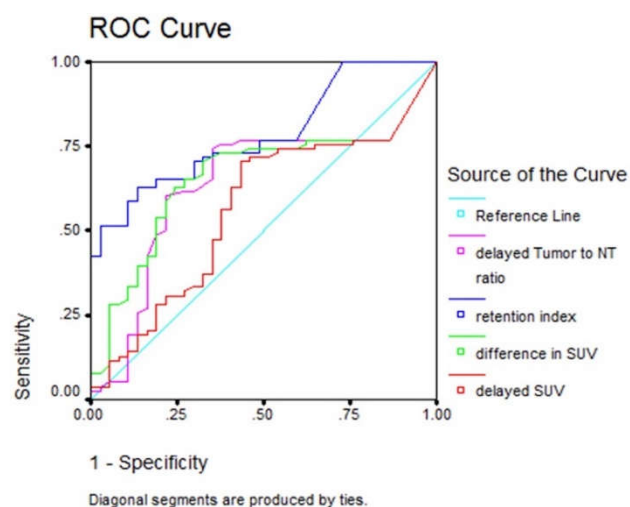
Figure 3. ROC curve analysis to know AUC for early and delayed SUVmax and delayed imaging indices

IMAGES: Figures 4,5,6 and 7 depicts the FDG PET CT images of the patients.
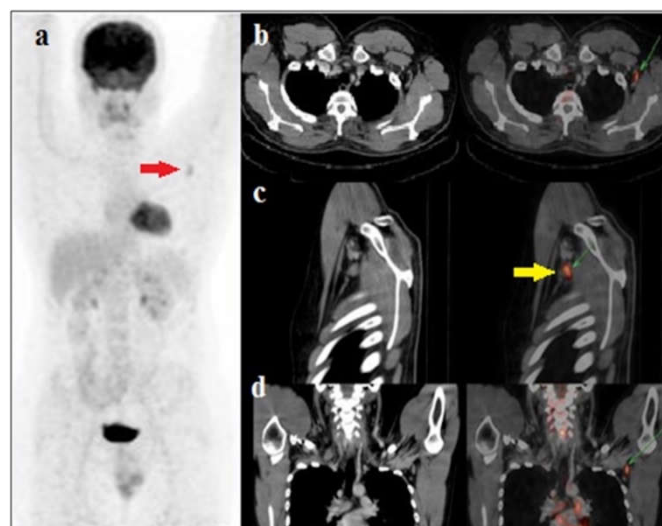
Figure 4. Follow up FDG PET-CT imaging of Hodgkin lymphoma (stage II) patient treated with ABVD regimen after 6 months showed a). Maximum intensity projection image with an abnormal focal FDG uptake in left axillary region (red arrow). b), c) & d) transaxial, sagittal and coronal views showing increased FDG uptake (SUVmax – 4.5) in an isolated left axillary node of size 1.1cm (yellow arrow). The axillary node was negative for malignancy on HPE
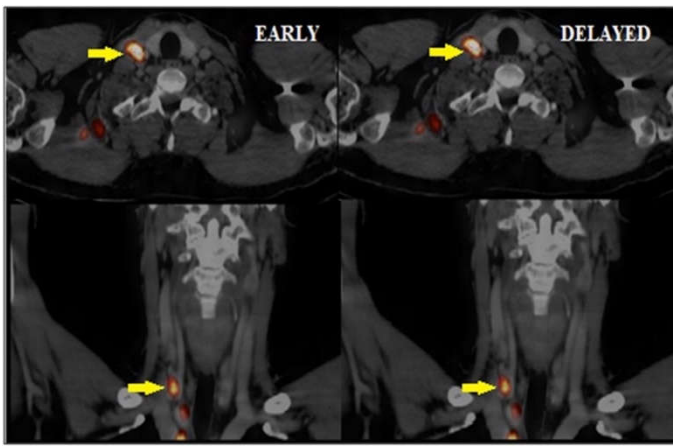
Figure 5. Follow up FDG PET-CT after 1 year of 52 yrs male case of carcinoma oropharynx (stage II) post radiotherapy showed FDG avid right cervical nodes (prominent level IV) (SUV 5.05, size 0.9cm DSUVmax of 5.5and RI was 10.9). The right level IV node was positive for metastases on HPE
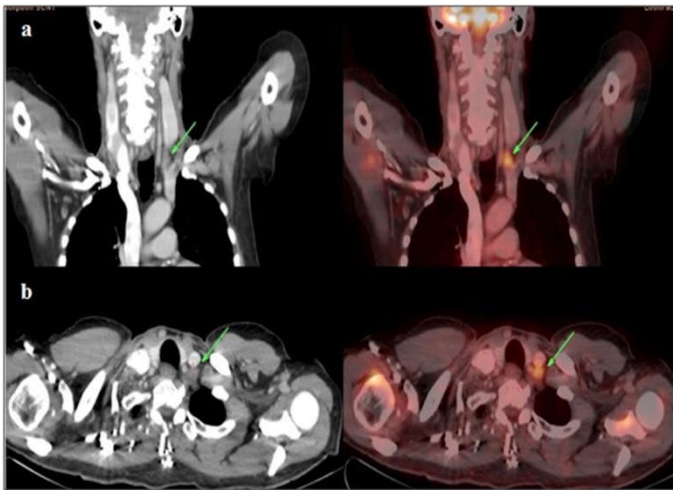
Figure 6. Follow up PET-CT of 40 yr/M k/c/o carcinoma esophagus showed a) Coronal CT and fused- PET-CT images with an abnormal focal FDG uptake in left supraclavicular node sized 1.2cm (SUVmax – 4.1). b) Transaxial CT and fused PET-CT image showing FDG avid left supraclavicular node. The node was found to be reactive on HPE

DISCUSSION

Peripheral lymphadenopathy can be due to variety of causes hence detection of metastatic LNsin follow up of cancer patients has important therapeutic and prognostic implications. FDG PET-CT beingnoninvasive functional imaging modality has high sensitivity and NPV. As FDG is not a tumor specific tracer it accumulates in inflammatory cells also, thus making image interpretation difficult (Kumar *et al.,* 2008). In our study, the (mean ± SD) SUVmax of the proven malignant nodes was 5.11 ± 2.67 (range 2.2-13.7), whereas that of benign nodes was 4.75 ± 2.87 (range 2.3-17.5). The highest SUV max in benign nodes was 17.5 whereas that in malignant nodes was 13.7. Similar higher SUV max values in benign lesions have also been reported in the literature (Teirstein). Reactive nodes associated with granulomatous diseases may show calcification which can cause high FDG uptake. Studies have reported that SUV max as an independent criterion can predict malignant lesions and metastatic nodes (Sathekge *et al.,* 2010). In general, SUVmax of 2.5 is used as a cutoff to differentiate malignant from benign lesion (Knight *et al.,* 1996).
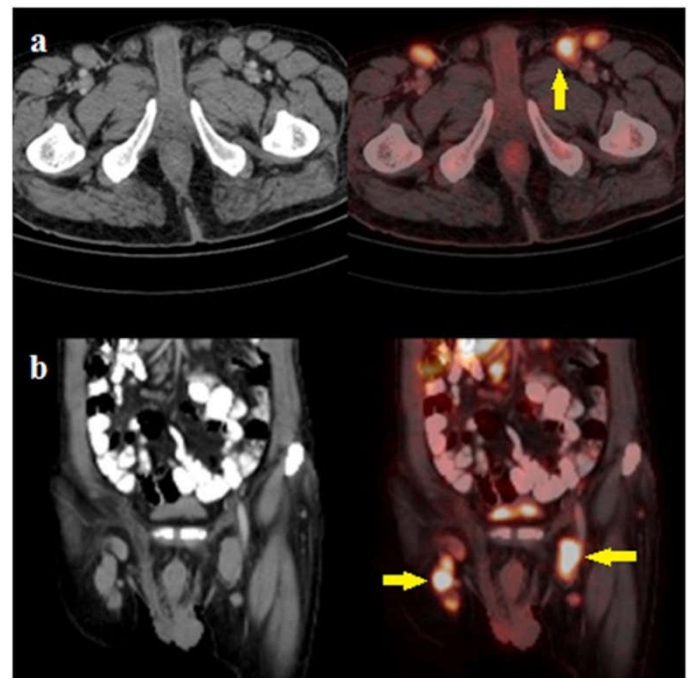
Figure 7. A 62 yr/M k/c/o carcinoma rectum (stage II) treatment follow up FDG PET-CT imaging after 8 months showed a) Transaxial CT and fused PET-CT images with an abnormal focal FDG uptake in bilateral inguinal nodes, highest uptake was in prominent left inguinal node of vertical group (SUVmax 4.2, size – 2.8cm) and b) Coronal CT and fused PET-CT image showing FDG avid bilateral inguinal nodes. The node was positive for malignancy on HPE

Arvind *et al.,* (2011) in his evaluation of mediastinal nodes in 35 patientsfound that conventional SUV max cutoff of 2.5 cannot differentiate benign and malignant lesions. The sensitivity and specificity in their study was 93% and 40%, respectively. Due to widespread prevalence of tuberculosis and sarcoidosis in developing countries like India, theysuggested that specificity can be improved by increasing the cut off value of SUV max, which is in concordance with our study.In our study, with SUVmax cut off of 2.5, sensitivity was 97.4% and specificity was5.4%, whereas on increasing the cutoff of SUVmax the specificity increases at the cost of sensitivity. Ryota Matsubara, *et al.,* (2012) found that malignant nodes had significantly higher SUV max compared to benign nodes which is contrary to the finding in our study. They also found positive correlation between SUV max and size of the nodeswhich is in concordance with our study.

Carkaci *et al.,* (2012) attempted to determine a threshold SUV max value to identify regional metastatic nodes in inflammatory breast cancer patients. A total of about 888 regional LN swhich included axillary, infraclavicular, and internal mammary and supraclavicular nodes were examined in this study in 111 patients.Of the 888 nodal basins, 625 (70%) were negative and 263 (30%) were positive for metastasis. Malignant LNs had significantly higher SUV max than benign l LNs (P < .0001). An SUV max of 2.0 showed the highest overall sensitivity (89%) and specificity (99%) for the diagnosis of malignant disease and they concluded that SUV max cut of 2.0 accurately identifies regional nodal metastases on ^{18}F-FDG PET/CT. In our study, there was no significant difference between SUVmax of malignant and benign nodes. Kwee *et al.,* (2013) had stated that standardization of SUV can reduce the variations in SUV and might improve the utility of SUV for better tumor characterization. However setting SUV

threshold dichotomizes the results. They concluded that SUV max of 2.5 should not be embraced as a magic threshold for separating benign from malignant lesions. Our study findings also support this statement. Studies have shown that the metastatic nodes are usually larger than 1cm (Monig *et al.,* 1999; Herrera-Omelas *et al.,* 1987). A low size threshold provides higher sensitivity with low specificity and a higher size threshold lowers the sensitivity but improves specificity (Kau *et al.,* 1999; Dwamena *et al.,* 1999; Pieterman *et al.,* 2000; Bipat *et al.,* 2003; Anzai *et al.,* 2003; Antoch *et al.,* 2003). The specificity-of-size criterion also deteriorates because of benign inflammatory or infectious LN enlargement, leading to incorrect characterization. Based on the size criterion alone, MRI is no different (Sohn *et al.,* 2000; Curtin *et al.,* 1998). Than CT in the assessment of regional LN metastasis. In our study, the mean short axis diameter of benign nodes was 1.39cm (range 0.5-2.7) and of malignant nodes was 1.45cm (range 0.5-2.8), with no significant difference between the two (p>0.05).Ryota Matsubara, *et al.,* (2012) assessed the metastatic LNs in oral SCC and found a positive correlation between the SUV max and the short-axis diameter of the TP nodes in their study. In our study also, we have found correlation between the SUV max and the size of node (p<0.05).

In our study the sensitivity, specificity, PPV and NPV of FDG PET-CT in assessing peripheral lymphadenopathy was 96%, 75%, 89% and 90% respectively. The highest sensitivity was for supraclavicular nodes (100%) followed by cervical nodes (96%). The NPV has highest for supraclavicular (100%) followed by cervical (92.85%) and axillary (80%). Wong et al has also reported that NPV of FDG PET/CT after treatment of head and neck cancers is generally high (Wong, 2008). The overall specificity was low which can be attributed to higher prevalence of granulomatous diseases in our country and also to the co-existence of both diseases together. In many malignant tumors, scan after 45–60 min have been reported to cause significant underestimation of the SUVs, because SUVs do not reach maximum levels until several hours after F-18 FDG injection (Shinya *et al.,* 2012; Hamberg *et al.,* 1994; Kubota *et al.,* 2001). The present study evaluated the usefulness of delayed imaging and its indices performed at 120 minutes after tracer injection. The AUCs of D-SUVmax and RI were statistically greater than that of early SUVmax, with largest AUC for RI. Our results are consistent with those of few authors who also have reported that RI is a good predictor for diagnosis and prognosis, and is superior to only early imaging (Lyshchik *et al.,* 2005; Uesaka *et al.,* 2008). The exact threshold value of RI used to define malignancy significantly varies among studies. RI >10 % is probably the most commonly used criterion as an indication of malignancy (Choi *et al.,* 2011; Xiu *et al.,* 2007; Schillaci *et al.,* 2009; Matthies *et al.,* 2002; Lan *et al.,* 2008; Cloran *et al.,* 2010; Macdonald *et al.,* 2011). The combination of a delayed time-point SUVmax >2.5 and RI >0 % has been reported by some investigators as the optimal means to define malignancy (Alkhawaldeh *et al.,* 2011; Nishiyama *et al.,* 2008; Suga *et al.,* 2009).

In our study with RI 10% the sensitivity was 75% and specificity was 52% and by increasing the RI criteria for 20% the specificity of the study increases to 65% without affecting the sensitivity much (71%). Nakayama, *et al.,* (2013) also demonstrated that SUV max of both malignant and benign lesions increased from early to late scans; however, like our study, they found a significant difference in RI between the two groups.Sofie Bæk Christlieb *et al.,* (2016) indicate that the RI for DTP FDG PET/CT cannot be used to discriminate between malignant and benign lymphadenopathy. This is contrary to the finding in our study but patients with suspected lymphoma or recently diagnosed treatment-naive lymphoma were prospectively enrolled for DTP FDG PET/CT in the above said study and not post treated patients. And moreover delayed imaging was at done 180 minutes in their study and after 120 minutes in our study. In our study, the De T: NT of metastatic nodes were significantly higher than that of benign nodes (p<0.05). In view of the variation of ^{18}F-FDG plasma clearance during chemotherapy, some authors have proposed the use of tumour-to-background ratio as an adjunct to monitor the reliability of SUV (Huang, 2000). The findings from human studies indicate that the high target-to-background ratio of FDG makes the detection sensitivity and specificity of FDG-PET very good in relatively large (>10 mm diameter) tumours and LN. And however for smaller tumours, biological target-to-background contrast with normal tissues is reduced by resolution effects. This phenomenon affects the ability of FDG-PET to detect tumour-infiltrated LNs, which may be small (<10 mm in diameter) (Raylman *et al.,* 1999). Few authors have reported that DTPI-PET-CT imaging, relative to single scan imaging, does not improve the performance of FDG PET/CT in detecting axillary LN metastasis in known breast cancer patients (Choi *et al.,* 2011). In this study, we emphasize, that caution should be exercised in interpreting follow up FDG PET-CT results, especially when symptomatically patient is improving and tumor markers are within normal limits. FDG PET-CT may have substantially reduced accuracy due to falsely increased FDG uptake causing high false positive rates and thus low specificity. Conversely nodes with high FDG uptake in endemic areas of granulomatous disease may be falsely labeled as benign. One should be aware of protean manifestations of malignancy and granulomatous diseases and have a high index of suspicion for simultaneous and/or misleading presentations.

Conclusion

^{18}F-FDG PETCT has high sensitivity and NPV which helps to exclude disease. SUV max when used as a sole diagnostic criteria, is unable to differentiate between benign and malignant peripheral nodes in treated cancer patients. DTPI and its indices can be used as an aid to differentiate between benign and malignant LNs, in close correlation with history and tumor markers.As the incidence of infection and inflammation is not uncommon in post treatment setup of cancer patientsthe issue of false-positive findings remains with FDG PET CT.So the findings of ^{18}F-FDG PET-CT scan need histopathological correlation and also close correlation of clinical history, treatment history, baseline investigations and tumor markers to improve the diagnostic accuracy of follow up PET CT in treated cancer patients.

Limitations of study

Our study has some limitations. This study included only FDG positive peripheral LNs and non FDG avid nodes with were not assessed. Hence the NPV value may be overestimated. However, the study also had severalstrengths. We not only assessed SUVmax, but also other supportive parameters to ensure validity of our data. Our study is the first to evaluate the role of FDG PET-CT in assessment of peripheral lymphadenopathy in cancer patients post treatment setup.With the limitations in mind, there is a need for larger studies.

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