Original article

The Accuracy of Integrated [^{18}F] Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography in Detection of Pelvic and Para-aortic Nodal Metastasis in Patients with High Risk Endometrial Cancer

Nikhil Shirish Gholkar, Subhas Chandra Saha, GRV Prasad, Anish Bhattacharya[1], Radhika Srinivasan[2], Vanita Suri

Departments of Obstetrics and Gynecology, [1]Nuclear Medicine, and [2]Cytology and Gynae Pathology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Abstract

Lymph nodal (LN) metastasis is the most important prognostic factor in high-risk endometrial cancer. However, the benefit of routine lymphadenectomy in endometrial cancer is controversial. This study was conducted to assess the accuracy of [^{18}F] fluorodeoxyglucose-positron emission tomography/computed tomography ([^{18}F] FDG-PET/CT) in detection of pelvic and para-aortic nodal metastases in high-risk endometrial cancer. 20 patients with high-risk endometrial carcinoma underwent [^{18}F] FDG-PET/CT followed by total abdominal hysterectomy, bilateral salpingo-oophorectomy and systematic pelvic lymphadenectomy with or without para-aortic lymphadenectomy. The findings on histopathology were compared with [^{18}F] FDG-PET/CT findings to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of [^{18}F] FDG-PET/CT. The pelvic nodal findings were analyzed on a patient and nodal chain based criteria. The para-aortic nodal findings were reported separately. Histopathology documented nodal involvement in two patients (10%). For detection of pelvic nodes, on a patient based analysis, [^{18}F] FDG-PET/CT had a sensitivity of 100%, specificity of 61.11%, PPV of 22.22%, NPV of 100% and accuracy of 65% and on a nodal chain based analysis, [^{18}F] FDG-PET/CT had a sensitivity of 100%, specificity of 80%, PPV of 20%, NPV of 100%, and accuracy of 80.95%. For detection of para-aortic nodes, [^{18}F] FDG-PET/CT had sensitivity of 100%, specificity of 66.67%, PPV of 20%, NPV of 100%, and accuracy of 69.23%. Although [^{18}F] FDG-PET/CT has high sensitivity for detection of LN metastasis in endometrial carcinoma, it had moderate accuracy and high false positivity. However, the high NPV is important in selecting patients in whom lymphadenectomy may be omitted.

Keywords: [^{18}F] Fluorodeoxyglucose-positron emission tomography/computed tomography, endometrial cancer, high risk, lymphadenectomy, preoperative imaging

Introduction

Endometrial cancer is the second most common gynecological malignancy worldwide and the most common gynecological malignancy in developed countries. Approximately, 49,560 new cases have been diagnosed in the US in 2013.[1] It is the third most common gynecological malignancy in India with recent reports showing a gradual increase in incidence owing to the changing lifestyles.[2,3]

The overall 5 years survival rate for carcinoma endometrium varies between 60% and 90% and patients with spread beyond the uterus have a higher risk for relapse.[4,5]

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Address for correspondence:
Dr. Nikhil Shirish Gholkar, Department of Obstetrics and Gynecology, Post Graduate Institute of Medical Education and Research, Chandigarh - 160 012, India. E-mail: drnikhilgholkar@gmail.com

Lymph node metastasis is the most important prognostic factor in early stage endometrial cancer. Pelvic lymph nodes (PLNs) constitute the most common site of extra uterine disease in patients with clinical early stage disease. The incidence of pelvic nodal metastases in patients with apparent Stage I tumor with Grade 2 or 3 histology and with deep myometrial invasion can be as high as 17-28%.[6-8] The incidence of pelvic and para-aortic nodal metastases increases with the clinical stage of the carcinoma and the incidence of para-aortic nodal metastases further increases with occurrence of pelvic nodal metastases.[9] The incidence of progressive or recurrent cancer is significantly higher and the overall survival is significantly lower in patients with para-aortic nodal involvement.[10,11] Thus, pelvic and para-aortic nodal metastases are of paramount importance in prognostication of endometrial carcinoma.

Considering the importance of lymph nodal (LN) metastases, the International Federation of Gynecology and Obstetrics in 1988 recommended routine systematic pelvic and para-aortic lymphadenectomy as part of surgical staging in endometrial cancer.[12] However, there are no guidelines as to how thoroughly lymphadenectomy should be done. Controversies still exist regarding adequate LN dissection and whether it is truly required in apparent Stage I patients. Randomized trials such as the "MRC ASTEC" and the Italian multicenter trial by Benedetti Panici *et al*., have concluded that lymphadenectomy did not improve the disease free and overall survival in high-risk early stage endometrial cancer and it was associated with more early and delayed complications.[13-15] Thus, the role of lymphadenectomy in early stage endometrial cancer has remained a major controversy in Gynecologic Oncology.

Myometrial invasion and the tumor grade are the two most important factors affecting the LN and distant spread of the disease.[8] Studies have proved that it is difficult to predict with certainty the final histological grade of the tumor based on a preoperative biopsy.[16] Intra-operative palpation of lymph nodes and inspection and frozen section for myometrial invasion are often inaccurate.[17-20] Conventional imaging modalities such as trans-vaginal sonography, computed tomography (CT) and magnetic resonance imaging (MRI) have also proven to be less accurate in the detection of LN status.[21,22]

[18F] Fluorodeoxyglucose-positron emission tomography/CT ([18F] FDG-PET/CT) as an integrated modality combines functional data superimposed on anatomical maps in one acquisition. Although, a few published reports on the role of [18F] FDG-PET/CT in the detection of LN metastasis in endometrial cancer have shown mixed results, the true potential of [18F] FDG-PET/CT as a preoperative imaging tool remains undetermined.[22-26] A recent meta-analysis of seven studies with a total of 253 patients assessing the performance of [18F] FDG-PET and PET/CT in detection of metastatic lymph nodes has concluded that [18F] FDG-PET/CT is moderately sensitive (63%) and cannot actually replace lymphadenectomy at present. However, the high positive likelihood ratio and a low negative likelihood ratio may be useful in the preoperative selection of patients who actually need a lymphadenectomy.[27] This study was planned to further investigate the role of [18F] FDG-PET/CT scan in the preoperative detection of pelvic and para-aortic LN (PALN) metastases in high risk endometrial carcinoma patients.

Materials and Methods

Patients features

The plan of the study was approved by the Medical Ethics Committee of the Institute. Patients with Grade 2 and 3 endometrioid and serous and clear cell carcinomas were included in the study. Patients with claustrophobia, uncontrolled diabetes mellitus (random blood sugar >200 mg/dl) and patients unfit to undergo lymphadenectomy were excluded. All the patients who met the inclusion criteria underwent a set of investigations with CA-125 levels. Routine preoperative imaging for myometrial invasion was not done as it was not found to be cost-effective. A written informed consent was obtained from the patients prior to participation.

Positron emission tomography/computed tomography protocol

Study patients underwent a preoperative [18F] FDG-PET/CT in the Department of Nuclear Medicine. The scan was performed on a PET/CT scanner (DISCOVERY 16 ST-GE Medical systems with BGO crystals, Milwaukee, USA) consisting of a PET scanner and a multi detector CT scanner that permits the acquisition of co-registered PET and CT images in one session. All the patients were kept fasting for 6 h prior to intravenous (IV) injection of 10 mCi of FDG. During the waiting period of 60 min, all the patients were orally hydrated with around 1.5 l of contrast. After 60 min, the combined examination was started after asking the patients to empty the bladder and injecting the IV contrast. The CT scan was acquired first followed by the PET scan.

Image interpretation

The images were interpreted by a nuclear medicine physician who was prior informed about the clinical data of the patient. The images were reconstructed on a Xeleris Workstation which allowed the visualization of the data in coronal, sagittal, and trans-axial planes. The reporting of positive pelvic or para-aortic nodes was based upon

the focal increase in tracer uptake of [18F] FDG on PET images, which was corresponding to lymph node chains on CT images. These findings were independent of the size of the nodes on CT scan. The uptake of FDG on the PET images was graded as shown in Table 1. The lesions with mild, moderate and intense FDG uptake were reported as positive for metastases excluding sites of physiological uptake.

Surgical protocol

The patients were subsequently taken up for surgery, which included peritoneal cytology, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and systematic pelvic node dissection including external iliac, internal iliac, common iliac, and obturator nodes bilaterally. Although, PALN dissection up to the inferior mesenteric artery or sampling was planned in all patients, it was abandoned in seven patients due to technical difficulty in view of obesity or those who were high risk for surgical morbidity. Twelve patients had para-aortic nodal dissection done, while one patient with grossly enlarged para-aortic nodes had fine-needle aspiration (FNA) sampling due to adherence of nodes to underlying vessels.

Histopathology and cytology: Standard of reference

The histopathological evaluation of the lymph nodes and/or cytological analysis of FNA samples were considered the standard of reference. The samples were analyzed by a pathologist who was blinded to the [18F] FDG-PET/CT results. The dissected lymph nodes were subjected to histopathological evaluation with hematoxylin and eosin. In one case where an intra-operative FNA was performed, the smears were stained by May-Grunwald-Giemsa stain. The reporting in all cases was done as positive or negative for metastases.

Statistical analysis

Primary variable of interest was presence or absence of nodes detected on [18F] FDG-PET/CT and subsequently confirmed on histopathology and/or cytology. A true positive (TP) lesion was one detected on [18F] FDG-PET/CT and also found to be positive on histopathology. A false positive (FP) lesion was one detected on [18F] FDG-PET/CT, but not positive on histopathology. True negative lesion was not detected on either and false negative (FN) lesion was one missed on [18F] FDG-PET/CT, but positive on histopathology. Sensitivity, specificity, positive predictive value and negative predictive value (NPV) and accuracy of [18F] FDG-PET/CT imaging in the diagnosis of pelvic and para-aortic metastasis was calculated on a patient based and a nodal site based criteria. The Fisher's exact test was used to compare the size of metastasis positive versus negative nodes. Statistical calculations were done using the SPSS (IBM®)software for Windows, 19.0.0.

Table 1: The definition and grading of FDG avidity on [18F] FDG-PET/CT scan

Grade	Definition of FDG uptake (avidity)	Visual uptake as compared to background	Visual uptake as compared to liver uptake
0	Non	None or less	None or less
1	Mild	More	Less
2	Moderate	More	Equal to
3	Intense	More	More

FDG: Fluorodeoxyglucose; PET: Positron emission tomography; CT: Computed tomography

Results

Patient details

The median age, parity and body mass index of the patients were 57.5 years (range: 40-78), 3 (range: 0-6) and 27.31 (range: 21.64-37.78) respectively. 16 patients had endometrioid sub-type histology, while two patients each had clear cell and papillary serous sub-type histologies. The median time between [18F] FDG-PET/CT and surgery was 10 days (range: 3-20).

Histopathological characteristics

The postoperative histopathological characteristics of the patients have been shown in Table 2. A total of 180 pelvic and 25 PALNs were resected during surgery. A median of 10 lymph nodes (range: 1-21) were resected in each surgery. Pelvic lymphadenectomy was done in all patients, whereas para-aortic lymphadenectomy/sampling was done in 13 patients. One patient underwent a FNA of the PALN. The median number of PALNs resected was two per surgery (range: 0-4). Of the 20 patients, two patients (10%) had LN metastasis on histopathology. In the node positive patients, all the resected pelvic (10) and para-aortic nodal FNA were positive for one patient [Figure 1], while the other patient had only one PLN (obturator) positive out of seven pelvic nodes resected [Figure 2]. The median number of lymph nodes resected in node positive cases was 8.5 as compared with 10.5 for the node negative cases.

[18F] Fluorodeoxyglucose-positron emission tomography/computed tomography findings and correlation

Lymph nodal metastases

Table 3 is shows the performance of [18F] FDG-PET/CT for detection of pelvic and PALN metastasis. [18F] FDG-PET/CT detected PLN metastasis with one showing intense [18F] FDG uptake and the other showing mild uptake. Apart from these TP detections, it detected mild [18F] FDG-uptake at the site of pelvic nodes in seven patients which were negative on histopathology.

One FP detection revealed granulomatous inflammation with caseous necrosis [Figure 3] of lymph nodes. [18F] FDG-PET/CT correctly detected negative nodes in the remaining 11 patients.

For the nodal chain based analysis, the pelvic nodes were divided into right and left iliac and obturator group as exact demarcation of external and internal iliac nodes was not possible. [18F] FDG-PET/CT detected a total of 15 positive pelvic nodal chains in nine patients. Out of these 15, 6 (40%) were right iliac, 8 (53.3%) were left iliac and 1 (6.7%) was left obturator nodal chain. A total of 63 pelvic nodal chains were resected during surgery. Among these 63 chains, there were 20 right iliac, 20 left iliac, 12 right obturator, and 11 left obturator chains. Histopathology detected metastases to be positive in three nodal chains. Among them, one each of right and left iliac nodal chain was detected in one patient and one left obturator nodal chain in another patient. [18F] FDG-PET/CT correctly detected all three PLN chains. There were 12 FP detections. [18F] FDG-PET/CT correctly detected 48 negative pelvic nodal chains.

Table 2: Histopathological characteristics of the patients

Histology findings	No. of patients	Percentage of total patients
Histopathological types		
Endometrioid	15	75
Clear cell	2	10
Papillary serous	2	10
Carcinosarcoma	1	5
Tumor grade		
1	5	25
2	6	30
3	9	45
Myometrial invasion (%)		
<50	9	45
>50	11	55
Peritoneal cytology		
Positive	1	5
Negative	19	95
Stage		
IA	7	35
IB	4	20
II	2	10
IIIA	1	5
IIIB	2	10
IIIC1	1	5
IIIC2	1	5
IVA	0	-
IVB	2	10
Cervical stromal invasion		
Yes	6	30
No	14	70
LN metastases		
Both pelvic and para-aortic nodes	1	5
Pelvic lymph nodes	2	10
Overall	2	10

LN: Lymph nodal

One patient had metastasis to the para-aortic nodes detected on FNA, which was detected by [18F] FDG-PET/CT. [18F] FDG-PET/CT detected a total of five positive patients out of which only one patient had metastasis. One patient with FP node on [18F] FDG-PET/CT showed granulomatous inflammation on histopathology. There were no FNs. [18F] FDG-PET/CT correctly detected eight para-aortic node negative patients.

The median size of positive nodes detected on histopathology was 2 cm (minimum –0.4 cm, maximum –3.5 cm) in one patient and 0.4 cm (minimum –0.3 cm, maximum –0.6 cm) in the other patient. The median size of nodes in the node negative cases was 0.55 cm (minimum –0.36 cm, maximum –1.1 cm). On applying the Fisher's exact test, there was no significant difference in the median size of lymph nodes in the node negative and positive cases (P –0.593).

Distant metastases

[18F] Fluorodeoxyglucose-positron emission tomography/computed tomography scan demonstrated increased FDG uptake at four sites (a mesenteric nodule, left axillary lymph node, left supra-clavicular lymph node, and left kidney) in 3 (15%) patients. Histopathological confirmation was undertaken at these sites by either a biopsy or FNA.

Table 3: The performance of [18F] FDG-PET/CT in detection of pelvic and para-aortic lymph nodes and distant metastases

Statistical variable	Pelvic nodes		Para-aortic nodes (TP-1, FP-4, FN-0, TN-8)	Distant metastases (TP-1, FP-2, FN-1, TN-16)
	Patient based analysis (TP-2, FP-7, FN-0, TN-11)	Nodal chain based analysis (TP-3, FP-12, FN-0, TN-48)		
Sensitivity	100	100	100	50
Specificity	61.11	80	66.67	88.89
PPV	22.22	20	20	33.33
NPV	100	100	100	94.12
Accuracy	65	80.95	69.23	85

TP: True positive; FP: False positive; FN: False negative; TN: True negative; PPV: Positive predictive value; NPV: Negative predictive value; FDG: Fluorodeoxyglucose; PET: Positron emission tomography; CT: Computed tomography

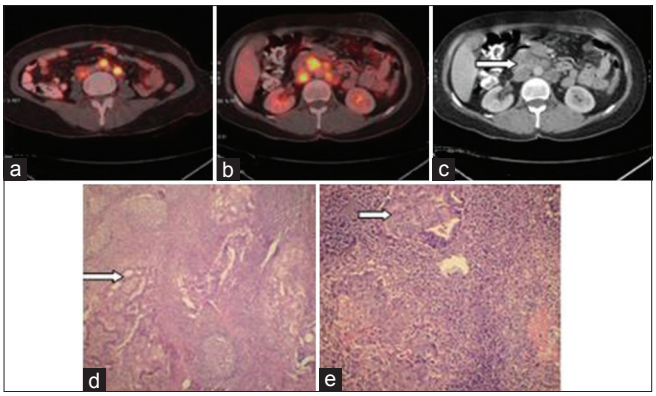

Figure 1: 52 years female with pelvic and para-aortic lymph nodal (PALN) metastases (true positive). (a) Intense fluorodeoxyglucose (FDG) avid B/L iliac LN's. (b) Intense FDG uptake in multiple enlarged B/L PALN's. (c) Contrast-enhanced computed tomography showing necrosis of LN's (white arrow). (d) Right external iliac LN with metastasis (white arrow). (e) Left external iliac LN with metastasis (white arrow)

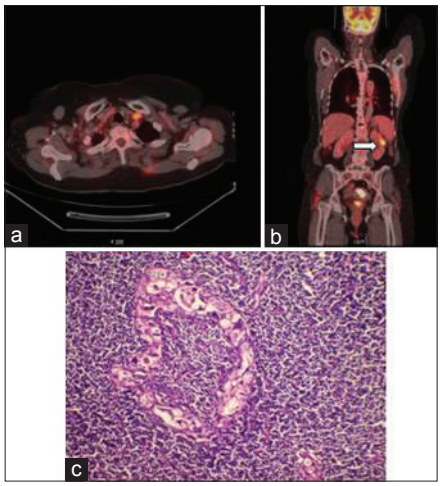

Figure 2: A 78-year-old lady with pelvic lymph nodal (LN) metastases. (a) Mild fluorodeoxyglucose (FDG) uptake in left obturator LN. (b) Positron emission tomography/computed tomography image showing intense uptake of FDG in left kidney (white arrow). Intra-operative assessment confirmed no enlargement or metastatic deposits. No histopathological confirmation was done. (c) Left obturator LN showing metastatic deposit

Two (10%) patients were detected to have distant metastases on histopathology. A 14 cm × 10 cm mesenteric nodule was detected, but a small peritoneal deposit (0.3 cm) was missed on the [18F] FDG-PET/CT scan. The small size of the deposit could be a limiting factor, but this was not observed as a limiting factor in detection of lymph nodes. The performance of [18F] FDG-PET/CT for detection of distant metastases has been shown in Table 3.

Adjuvant therapy and follow-up

The patients were followed-up in the postoperative period for a median of 20 months (range: 16-24). Total of 12 patients (60%) have received postoperative adjuvant therapy. Both patients with LN metastasis were given adjuvant therapy. The patient with both pelvic and para-aortic nodal metastases was given chemotherapy after which her total leukocyte count dropped. Radiotherapy was deferred and she was given hormonal therapy with progestogen. She had recurrence at vault site. She was planned for further chemotherapy, but voluntarily refused and expired 1 year after primary therapy. All the other patients including the one with pelvic nodal metastases are free of recurrence on follow-up.

Discussion

A routine systematic pelvic and para-aortic lymphadenectomy is the standard of care in patients with endometrial cancer patients.[12] It helps in prognostication and decision of postoperative therapy. However, two recent randomized control trials have demonstrated increased morbidity and no survival benefit with lymphadenectomy in high risk early stage endometrial cancer.[13,14] A preoperative imaging modality, which can reliably help us recognize patients who actually need lymphadenectomy is the need of the hour.

Preoperative conventional imaging such as CT and MRI are of limited utility in detection of LN metastases in endometrial cancer.[21,22] Studies assessing techniques for intra-operative visual inspection and frozen section for myometrial invasion have given nonfavorable results.[16-20]

The few reports assessing the role of [18F] FDG-PET scan in detection of LN metastasis in endometrial cancer have concluded that it had low to moderate sensitivity for detection of lymph nodes.[27-30]

[18F] Fluorodeoxyglucose-positron emission tomography/computed tomography which has the advantage of superimposed CT for accurate anatomical localization is a modality of interest in detection of LN metastases in endometrial cancer. Table 4 summarizes the few published studies, which have assessed the efficacy of [18F] FDG-PET/CT for detection of LN metastasis.

Until date, the total number of studies published is few. The recent study by Crivellaro *et al*.,[26] is the single largest study published so far. The earlier studies had suggested a low sensitivity and moderate accuracy, but recent studies by Signorelli and Crivellaro have reported a high NPV and accuracy.[23-26,31] A recent meta-analysis of seven studies with 243 patients has concluded that [18F] FDG-PET or [18F] FDG-PET/CT has moderate sensitivity of 63% in detection of pelvic and/or para-aortic nodes but the overall diagnostic accuracy is high (89.5%). The authors concluded

Table 4: Studies assessing the accuracy of [18F] FDG-PET/CT in detection of nodal metastases

Author and year	Number of patients	Selection criteria	Percentage of lymph node positive patients	PLN's sensitivity %	Specificity %	PPV %	NPV %	Accuracy %	PALN's
Kitajima *et al*.[22]	34/40‡	Clinical stage IA to IIIC	25	50	86.7			77.5	Assessed
Park *et al*.[28]	53	All grades	18	62.5	86.7	45.5	92.9	83	Assessed
Signorelli *et al*.[24]	37	Grade 2 with deep myometrial invasion, Grade 3, serous/clear cell	24.3	77.8	100	100	93.1	96.8	Not assessed
Picchio *et al*.[23]	26/32‡	Grade 3	26.9	57.1	100	100	86.4	88.5	Not assessed
Crivellaro *et al*.[35]	76	Grade 2 with deep myometrial invasion, Grade 3, serous/clear cell	18.4	78.6	98.4	91.7	95.3	94.7	Assessed
Current study	20	Grade 2 and Grade 3 endometrioid, serous/clear cell	10	100	61.11	22.22	100	65	Assessed

PLN's: Pelvic lymph nodes; PALN's: Para-aortic lymph nodes; PPV: Positive predictive value; NPV: Negative predictive value; ‡X/N: X-had lymphadenectomy, *N*-Total patients who had PET/CT; FDG: Fluorodeoxyglucose; PET: Positron emission tomography; CT: Computed tomography

that [18F] FDG-PET/CT had a high positive likelihood ratio (10.465) and a low negative likelihood ratio (0.399) which is of utility in selecting patients who actually need a lymphadenectomy.[27] However, three of the studies included in the meta-analysis were studying [18F] FDG-PET, which is now out-dated and [18F] FDG-PET/CT is certainly better for anatomic localization.[27] The high sensitivity (100%) reported in the current study may be due to the inclusion of mild FDG avidity as positive when compared to other studies, which have defined moderate avidity as positive [Table 1]. The high FP could be due to the lack of differentiation between inflammatory and malignant lesion. Although FP for malignancy in the current scenario, these detections can be of therapeutic significance [Figure 3].

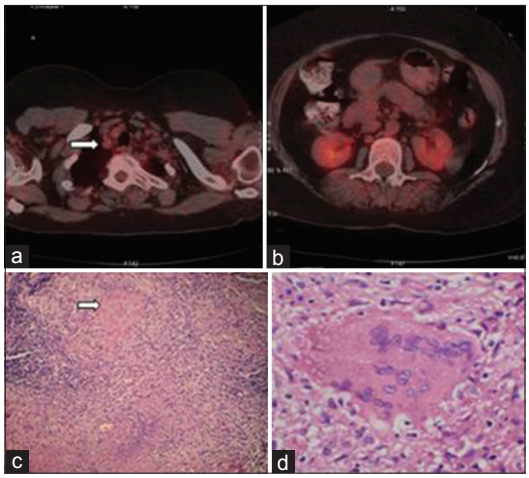

Figure 3: 52-year-old female with caseous necrosis in lymph nodals (LN's) (false positive). (a) Positron emission tomography/computed tomography (PET/CT) was showing mild fluorodeoxyglucose (FDG) uptake in left iliac LN's (white arrow). (b) PET/CT showing mild FDG uptake in para-aortic LN's at L4 level. (c) Right iliac LN with granulomatous inflammation (white arrow). (d) Langhans giant cell in the right iliac LN

In the current study, the proportion of LN involvement (10%) is lesser than in the other similar studies [Table 4] particularly as they had a higher proportion of patients having Grade 3 and advanced stage malignancy.[23-26,31] Although, we had included patients with Grade 2 and 3 adenocarcinoma, five patients had in fact downgrading of tumor on final histopathology and 11 out of 20 patients (55%) had Stage I disease after surgical staging. Thus, a greater proportion of patients having early stage malignancy may have led to the lesser proportion of nodal metastases.

Adequate sampling of lymph nodes is not defined clearly. Studies have suggested about 10–12 total lymph nodes sampled are adequate and predict better survival.[32-33] In the current study, a median of 10 lymph nodes were resected during surgery which suggest an adequate dissection. The median numbers of PALNs resected during surgery were two per surgery. This number is less, but the aim of para-aortic dissection was only to perform sampling to correlate with [18F] FDG-PET/CT and a therapeutic dissection was not intended as it is associated with more delayed complications and morbidity.[12,13] In the current study, the sensitivity of [18F] FDG-PET/CT scan for detection of LN metastases was not limited by the size of the lymph nodes, but this limitation was seen in detection of distant metastases.

The limitations of the study are the small sample size and the nonuniform performance of para-aortic lymphadenectomy. Para-aortic lymphadenectomy was abandoned in seven patients in view of technical difficulty due to obesity or in those who were high risk candidates for surgery. In the MRC ASTEC trial and the studies assessing accuracy of [18F] FDG-PET/CT for detection of LN metastases, para-aortic lymphadenectomy was not done uniformly.[13,23,25,26] In the seven patients who underwent only PLN dissection, [18F] FDG-PET/CT scan did not show LN metastasis in the para-aortic region. In these patients, the PLN were negative for metastases. The likelihood of having positive para-aortic nodes is about 1-2% in the event of negative PLN.[34-36] [18F]

FDG-PET/CT scan detected PALN metastasis in five patients and all had para-aortic nodal sampling.

The high sensitivity and NPV of [18F] FDG-PET/CT is important in detection of truly lymph node negative patients in whom lymphadenectomy and associated morbidity may be omitted. Although, the sample size of our study was small to make strong assertions, but the results are consistent with the previous studies and will therefore add useful data to the available literature on [18F] FDG-PET/CT and pave way for much larger studies in the near future.

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