Original Article

18F-FDG PET/CT Outperforms Contrast Enhanced CT in the Diagnosis of Peritoneal Metastases from Ovarian Tumors

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ABSTRACT

Objectives: To evaluate the diagnostic performance of ^{18}F-Flurodeoxyglucose positron emission tomography/ computed tomography in comparison to contrast enhanced computed tomography alone in the detection of peritoneal metastases after initial treatment of malignant ovarian tumors. **Patients and Methods:** The study prospectively recruited 111 patients with clinical suspicion of ovarian tumor recurrence. Each patient underwent ^{18}F-FDG PET/CT and Ce-CT scans in the same day. Study-based analyses for a total of 136 scans were evaluated. Studies were read independently by one experienced nuclear medicine physician and one experienced radiologist. A four-point score (score 0= definitely benign, score 1 = probably benign, score 2= probably malignant and score 3= definitely malignant) used to assess the presence or absence of peritoneal metastases. The final diagnosis of peritoneal disease status was made on the basis of subsequent follow-up by ^{18}F-FDG PET/CT, conventional imaging (CT/MRI) or histopathology whenever possible. **Results:** Of the 136 studies evaluated, 75 (55%) studies had peritoneal disease and 61 (45%) studies were free based on final diagnosis.^{18}F-FDG PET/CT & Ce-CT had sensitivity, specificity and accuracy of 96% vs 69%, 100% vs 85%, and 98% vs 76%; respectively. ^{18}F-FDG PET/CT was significantly more sensitive, specific and accurate compared to Ce-CT with *P*-values of <0.0001, 0.004 and <0.0001; respectively. **Conclusions:** ^{18}F-FDG PET/CT is superior to Ce-CT in the diagnosis of peritoneal metastases in patients with malignant ovarian tumors.

Key words: ovarian tumors, peritoneal metastases, 18F-FDG PET/CT, Contrast enhanced CT

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INTRODUCTION:

Recurrent ovarian cancer is defined as tumor recurrence following complete initial response to first-line chemotherapy, a negative second-look laparotomy, if performed with disease-free interval greater than 6 months. [1]

Peritoneal tumor spread, the most common pathway of dissemination in ovarian cancer, is found in approximately 70% at initial diagnosis.[2] Peritoneal seeding is caused by distribution of tumor cells within the normal peritoneal fluid circulation.[3] Although all peritoneal parietal and visceral surfaces may be involved, common sites of peritoneal implants in ovarian cancer include the pouch of Douglas, the greater omentum, paracolic gutters, liver, diaphragmatic and bowel surfaces. Less frequent implants in ovarian cancer are found in the mesentery, along the porta-hepatis, lesser sac and the gastro-splenic ligament.[4, 5]

Diagnostic second-look laparotomy (SLL) is, conventionally, considered to be the gold standard of the detection of recurrent ovarian carcinoma;[6] however, SLL is still an invasive modality with potential surgical complications and high anesthesia risk.[7]

Laparoscopy (LPS) is a diagnostic tool already used for the assessment of ovarian cancer intra-peritoneal infiltration.[8,9] The direct visualization of the abdominal organs allows for obtaining a correct topographic mapping of the tumor with a low incidence of false negatives (3%). Nevertheless, LPS is a surgical intervention procedure less invasive than laparotomy, and requires general anesthesia. Moreover, it may be unable to identify 10–20% of the abdominal quadrants in case of adhesions.[9]

The level of CA-125 has been shown to be a sensitive marker for tumor recurrence and levels may rise 3 to 6 months before there is clinically apparent disease, it does not provide information concerning the size and distribution of the lesions**.**Levels may also increase in a number of benign conditions, being a non-specific marker for ovarian cancer. Also a number of patients with relapse of disease present with normal CA-125 levels.[10, 11]

Ce-CT is used to detect suspected recurrent ovarian cancer in the context of an increasing CA-125 or clinical symptoms.[12]Sensitivity of CT in detection of peritoneal carcinomatosis strongly depends on tumor size, site, and morphology; presence of ascites; paucity of intra-abdominal fat; and adequacy of bowel opacification. In small lesions with weak contrast media enhancement, peritoneal carcinomatosis is not detected in its initial stage and CT is often false negative. In addition, after surgery, anatomic structures may appear distorted, resulting in equivocal or inaccurate imaging findings.[13]

FDG-PET/CT imaging for ovarian cancer surveillance has proven useful for detecting early recurrences with a diagnostic accuracy of approximately 80%.[14-19] Recognized limitations 18F

FDG-PET include failure to detect small lesions and misinterpretation of normal physiological abdominal activity on PET[20]. The use of combined anatomical and morphological PET/CT imaging provide improves overall diagnostic accuracy its performance is superior to abdominal Ce-CT.[21] Subtle abnormalities on PET can be confirmed as disease on careful review of the CT images. This is specially observed when small implants or small volume disease show mild FDG uptake, either because of partial volume effect on small sized lesions or due to biologic properties of the tumor itself.[22, 23] In this work, we compared PET/CT using ^{18}F-FDG versus Ce-CT in detection of peritoneal metastases from ovarian cancer.

PATIENTS AND METHODS:

This prospective study was conducted in Alfa Scan Radiology Center, during the period from January 2010 to November 2012

The inclusion criteria: patients with pathologically proven ovarian cancer who were treated with initial standard treatments, referred for post-treatment surveillance for detection of residual disease or recurrence. Patients referred for initial staging or with synchronous or past history of other cancers were excluded together with those who lost their follow-up.

The study was approved by the Institutional Review Board, and each patient signed a written informed consent form.

PET/CT Imaging Protocol: The ^{18}F-FDG PET/CT scans were acquired using a Philips Gemini Time-of-Flight PET/CT machine. The patients were instructed to fast for at least 6 hours before imaging and their blood glucose level was measured at the time of the tracer injection and was less than 160 mg/dl. A dose of 0.1-0.14 mCi/Kg was injected intravenously and adjusted according to patient's weight. For the optimal delineation of bowel structures, 400–600 ml of diluted mannitol solution was administered 1 hour before CT imaging. Approximately 60 minutes after tracer administration, a low-dose CT scan *(5-mm contiguous axial cuts)* was obtained in a 64 integrated multi-slice CT machine, from the skull base to the mid-thigh.

The acquisition was obtained in a helical mode, using 120 kV, 60mAs, and a 512 x 512 matrix size, acquiring a field of view (FOV) of 700 mm in 22.5 seconds. The first CT scan was used for attenuation correction. Immediately after the low-dose CT, an emission PET scan was acquired in a three-dimensional mode over the same anatomical regions starting from the skull vertex to the level of the mid-thigh. The acquisition time was 2 minutes per bed position in 9 bed positions, with a one-slice overlap at the borders of the FOV. Finally, a diagnostic CT was acquired using 120 kV, 300 mAs, and a 512 x 512 matrix size. The acquired FOV was 500 mm using dose automatic modulation in the Z direction.The radiation exposure dose from low-dose CT was in average 3.37

milli Gray (mGy) while that for diagnostic CT was 11.48 mGy.

After completion of acquisition, the images were reconstructed with a standard iterative algorithm, and then the reconstructed CT attenuation-corrected PET images, low dose CT images and Ce-CT images were transferred to the viewing stations for reviewing in axial, coronal, and sagittal planes and in a maximum-intensity-projection (MIP) three-dimensional cine mode using the manufacturer's review station *(Brilliance, Philips, Holland)*. Semi-quantitative analysis of the 18F-FDG uptake in the suspected lesions was carried out by calculating the maximum standardized uptake values of each lesion using a rounded region of interest tool and a systematic slice by slice search for the most intense voxel within a given lesion.

Data Interpretation:

The fused PET/CT and Ce-CT images were separately interpreted by a team of one nuclear medicine physician and one radiologist with knowledge of aim of the study.

For each study, 11 sub-sites were evaluated for the presence or absence of abnormality and recorded in a special database. A four-point score was used to describe the possibility of malignancy for each sub-site: *score 0 = definitely benign, score 1 = probably benign, score 2 = probably malignant and score 3 = definitely malignant*. The sub-sites were: local tumor site, peritoneum, pelvic LNs, abdominal LNs, mediastinal LNs, cervical LNs, liver, lung, bone, brain and other sites *(pleura, muscles, adrenal glands)*.

Follow up:

The final diagnosis of the presence or absence of recurrent/residual disease was made on the basis of subsequent follow-up by conventional imaging (CT/MRI), tumor markers, PET/CT and/or clinical follow-up of at least 6 months or histopathological findings obtained during surgery or biopsy whenever possible. Clinical recurrence was defined as the detection of recurrent disease by subsequent PET/CT, Ce-CT or a continuously rising CA-125 level to a value greater than twice the nadir within 6 months of the FDG PET/CT scan. Recurrent disease detected more than 6 months after the FDG PET/CT scan was interpreted as a new recurrence.

Statistical analysis:

Study-based and site based analyses were employed. True positive, true negative (TN), false positive (FP) and false negative (FN) readings were identified based on subsequent clinical/imaging / histopathological validation. Diagnostic performance parameters were calculated in the form of sensitivity, specificity, PPV, NPV and accuracy. The non-parametric McNemar test was used to evaluate the statistical significance of the differences in sensitivity and specificity *(A two-sided p value <0.05 was considered significant)* while Receiver's Operating Characteristics (ROC) analysis was used to compare the accuracy. Quantitative data were summarized and expressed as mean ± SD, median (range), whereas qualitative data were expressed as frequencies and percentages. The

analyses were carried out using the SPSS 21.0 (SPSS Inc., Chicago, Illinois, USA), *(MedCalc, Ostend, Belgium)*, and Microsoft Excel *(Microsoft, USA)* soft wares.

RESULTS:

A total of 136 studies were performed for 111 patients with pathologically proven ovarian cancer for the purpose of tumor surveillance after initial therapy for detection of residual/recurrent tumor on basis of suspicious clinical, radiological or biochemical relapse or recurrence. The general characteristics of the 111 patients enrolled in this study were summarized in ***(Table 1).*** The median age was 54 year (range: 13-76) with the majority of the patients having epithelial tumors (89.1%).

Table 1: Characteristics for the patients with recurrent ovarian cancer

Parameter	**Post primary treatment Tumor Surveillance**
Number of patients	111 (100%)
Pathologic groups :	
Epithelial	89.1%
Non-epithelial	10.9%
Number of studies	136
Timing of PET/CT after Therapy	0.25-40
Treatment modality	
Surgery alone	27
Surgery + Chemotherapy	102
Chemotherapy alone	7
Tumor markers#	
Elevated	64
Normal	54
Not available	18

* The numbers in parentheses indicate the range of the data.
# Tumor markers are mainly CA-125.

Study-based analyses for the diagnostic performance of PET/CT and Ce-CT.75 (55%) studies were positive for peritoneal metastases and 61 (45%) studies were free of peritoneal disease in the final diagnosis ***(Fig.1).***PET/CT detected peritoneal metastases in (72/75) and excluded metastases in all negative cases of peritoneal metastases yielding sensitivity of 96% and specificity of 100% respectively compared to sensitivity of 69% and specificity of 85% for Ce-CT respectively ***(Table 2).*** There was statistically significant difference in sensitivity and specificity between PET/CT and Ce-CT ***(Table 3).***

Fig.1: Number of true positive and true negative PET/CT and Ce-CT studies.

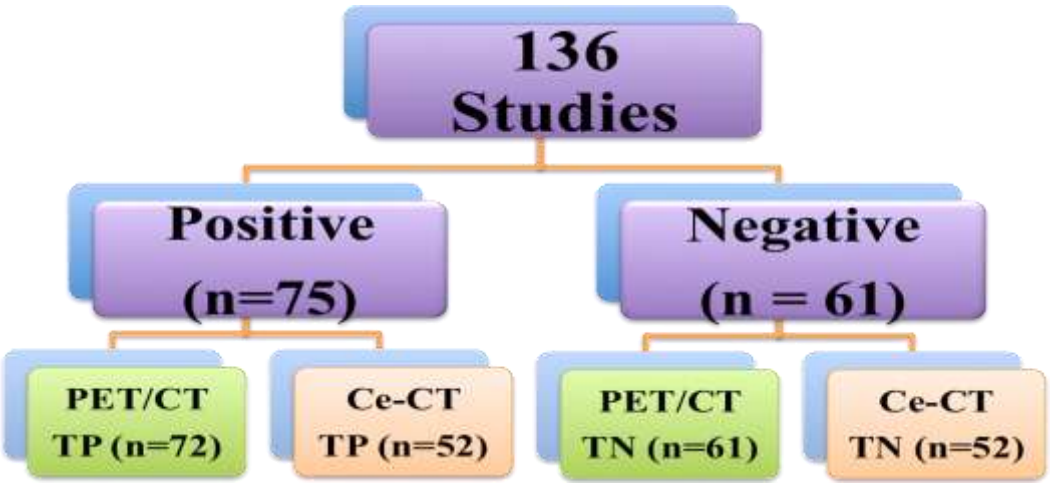

Table 2: Diagnostic performance of PET/CT and Ce-CT in detection of peritoneal metastases

Imaging modality	**Ce-CT**	**PET/CT**
False Negative	23	3
True Positive	52	72
True Negative	52	61
False positive	9	0
Sensitivity (95% CI)	69 (62-77)	96 (93-99)
Specificity (95% CI)	85 (79-91)	100
PPV(95% CI)	85 (79-91)	100
NPV (95% CI)	69 (62-77)	95 (92-99)
Accuracy (95% CI)	76 (69-84)	98 (95-100)

Table 3: Differences in diagnostic performance between PET/CT and Ce-CT on study-basis

Modality		***PET/CT***				***P***
		FN	**TP**	**TN**	**FP**	
Ce-CT	**FN**	**3**	**20**	0	0	< 0.0001[a]
	TP	**0**	**52**	0	0	0.004[b]
	TN	0	0	**52**	**0**	
	FP	0	0	**9**	**0**	

[a] *Difference in sensitivity by McNemar's test.*
[b] *Difference in specificity by McNemar's test.*

The overall accuracy for PET/CT according to ROC analysis was 98% compared to 76% for Ce-CT ***(P< 0.0001) (Fig.2).***Eighteen studies were positive for mediastinal lymph nodes. PET/CT detected 17/18 studies with mediastinal lymph nodes. There was statistically significant association between peritoneal and mediastinal involvement *(P < 0.001)* ***(Table 4).***

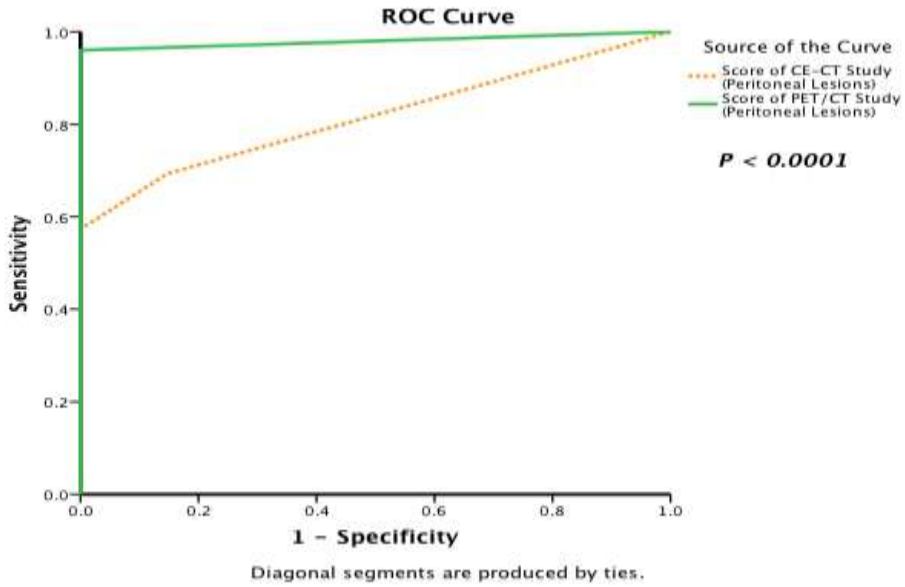

Fig.2: ROC curve analysis for accuracy of Ce-CT and PET/CT in detection of peritoneal metastases.

Table 4: Correlation between presence of peritoneal and mediastinal lymph nodal metastases.

	Mediastinal Lymph nodes			
Peritoneal metastases		Negative	Probably malignant	Malignant
	Negative	62	1	1
	Probably malignant	3	2	0
	Malignant	47	3	17

Four distinct abnormal PET/CT patterns were identified *(single nodular, multiple nodular, diffuse and mixed FDG uptakes).* Most frequent pattern was multiple nodular (35%) followed by single nodule (30%) then mixed pattern (28%) and finally diffuse pattern (7%) ***(Fig, 3).***

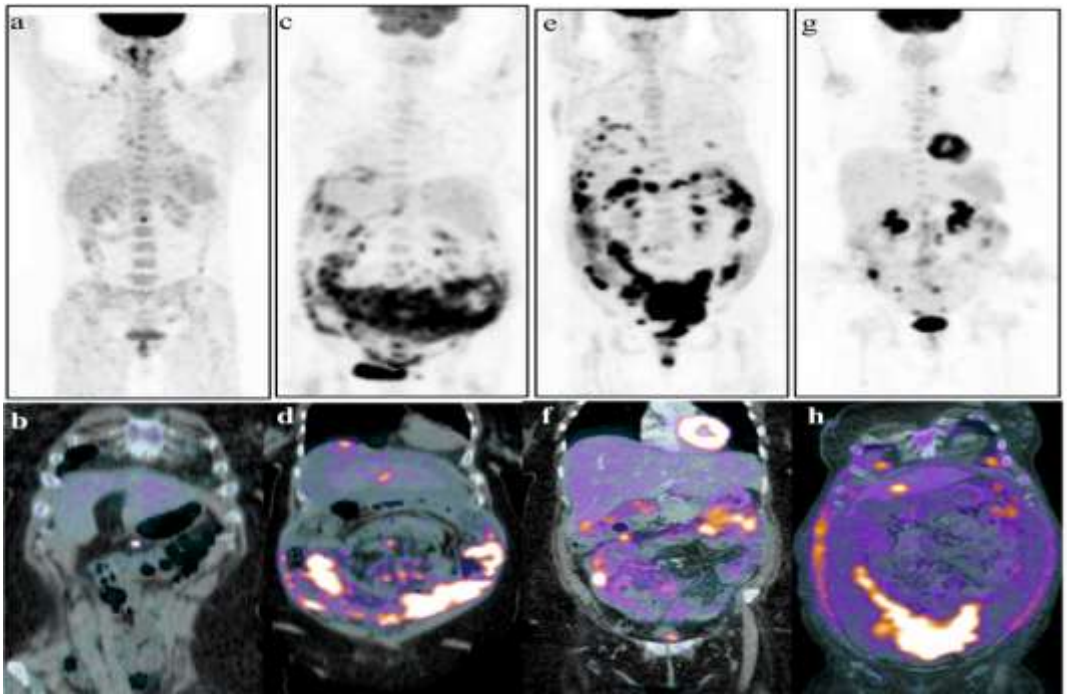

Fig.3: Images for different patterns of peritoneal metastases. PET MIP and Coronal Views for fused PET/CT. Single nodule (a and b), diffuse (c and d), multiple nodules (e and F) and mixed pattern (g and h).

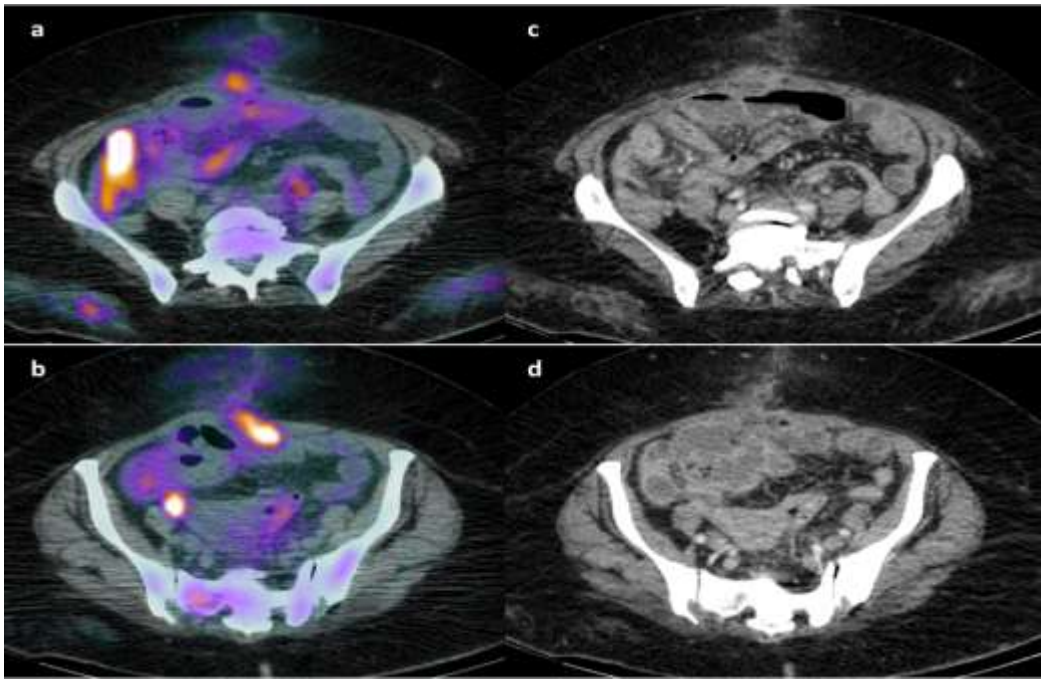

Fig.4: 45-year-old female patient Papillary serous adenocarcinoma underwent surgery and chemotherapy, referred forpost chemotherapy follow-up. CA-125 was normal. Axial fused PET/CT (a and b) and Ce-CT images (c and d). PET/CT revealed metabolically active peritoneal nodules on bowel serosa, mesocolon (a) and in pelvic cavity and small < 1 cm pelvic (b).None of these lesions was appreciable in Ce-CT (c and d)

DISCUSSION:

Ovarian cancer has a propensity for recurrence after treatment, even after surgery and adjuvant chemotherapy in early-stage tumors. Response rates to this standard primary treatment are approximately 80%, but survival rates are low. Approximately 20% to 30% of patients with early-stage disease and 50% to 75% of patients with advanced disease who obtain a complete response after first-line chemotherapy will ultimately develop a recurrent disease. Most patients with treated ovarian cancer relapse or die within 5 years of diagnosis.[10] Therefore, a close follow-up is essential utilizing non-invasive technique such as tumor marker levels and imaging scans.[24]. Metastases from ovarian cancer are unlike most other tumors in that they are primarily peritoneal rather than parenchymal in location. Therefore, they usually occur on the surfaces of the viscera rather than as masses within the viscera. These tumor implants can be miliary and iso-attenuating relative to the viscera at computed tomography, [25] which makes their detection challenging.[26]. The usefulness of concurrent FDG PET/CT for post-treatment surveillance of patients with ovarian cancer has been investigated in several studies.[18]. The reported sensitivity, specificity and accuracy of patient-based analyses were 73-100%, 40-100% and 63-100% respectively[26-34].^{18}F-FDG PET is very sensitive to hyper metabolic activity of peritoneal tumors but it suffers from low specificity because of lack of anatomical localization. Normal physiologic intestinal and urinary tract activity is another potential source of misinterpretation, which may lead to more FP findings.[20, 35] Thus, an ideal imaging modality would combine both high-resolution anatomic details with metabolic and functional imaging information for better characterization of increased FDG uptake. Therefore, the precise localization of hypermetabolic lesions by PET/CT improved the overall diagnostic performance.[36]

In the current work peritoneal metastases were the most frequent site of relapse of disease (55%) followed by local pelvic recurrence and pelvi-abdominal lymph nodes (34%) and other rare sites. PET/CT detected more peritoneal lesions than Ce-CTwith sensitivity, specificity and accuracy of 96% vs. 69%, 100%vs. 85% and 98% vs.76% respectively, for Ce-CT with highly significant statistical difference in overall accuracy ***(Fig.4).*** The FN cases (n=3) were attributed to micrometastases that were beyond the PET/CT resolution and the other two lesions missed due to misregistration (mismatching) due to bowel motility in correlating PET to corresponding CT images.[37] No False positive studies identified in our series. Also two studies with Sister Mary Joseph nodules were identified on PET/CT and missed on Ce-C T.

These results come in line with study of ***Dirisamer et al.*** [38] reported on 62 patients with suspected peritoneal

carcinomatosis using FDG PET/CT and reported a high diagnostic value with sensitivity of 100%, specificity of 97%, and accuracy of 98%. Also ***Kim et al.*** [21] reported sensitivity and specificity of 96.2% and 90%, respectively, for PET/CT and 88.5% and 65%, respectively, for Ce-CT. The accuracy of PET/CT was statistically higher than that of Ce-CT (93.5% vs 78.3%, P = 0.039). They concluded that 18F-FDG PET/CT is superior to Ce- CT in detection of peritoneal metastases.

On the contrary, ***Funicelli et al.*** [39] reported that enhanced abdominal CT had higher detection rate than that of FDG PET/CT. However, this study suffered some major limitations. The study population of PET/CT was different from that with enhanced abdominal CT (two-arms). Additionally, diagnostic CT criteria adopted were more subjective, nonspecific and broad, which could have produced overestimated sensitivity.

One of the advantages of PET/CT is whole body scanning which may aid the detection of additional sites of disease. FDG PET/CT appears very useful in detecting metastases in mediastinal, and supraclavicular lymph nodes that can show normal size even when malignant.[40, 41]

Supra-diaphragmatic disease in this series was 23%, which was slightly more frequent than previously described in literature by ***Iagaru et al*** [34] **and** ***Fulham et al.***[42] Mediastinal lymph nodes were seen in 25/136 cases (18%) and cervical lymph nodes in 7/136 cases (5%).

PET/CT detected 24/25 mediastinal lesions. Six patients were scored 2 *"probably malignant"* and 18 scored 3 *"definitely malignant"*. Among 18 patients with definitely malignant mediastinal lesions, 17 were having peritoneal involvement. There was statistically significant association between peritoneal and mediastinal involvement *(P<0.001).* Trans-diaphragmatic metastatic spread from peritoneal cavity to thoracic is one of the hypothesis.[43]

This work suffers some limitations; firstly, lack of histopathologic correlation of all the sites of abnormal ^{18}FDG uptake. The confirmation of all the sites would not have been ethical solely for the purpose of validation of PET/CT findings. Secondly,impact of PET/CT on change of management and cost-effectiveness of PET/CT versus Ce-CT was not feasible in current study. Data collection about the planned treatment before and after Ce-CT could not be reached.Lastly, semi-quantitative parameters as SUV and metabolic tumor volume that may have prognostic significant were beyond the scope of this study.

Advantages of this study include prospective design with relatively large number of patients that was performed using simultaneous Ce-CT & PET/CT protocol with uniform interpretation criteria.

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