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Diagnostic role of 18F-FDG PET/CT in recurrence detection of surgically treated gastric cancer: a cross-sectional study

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Abstract

Background: Radical surgery of gastric cancer is considered as the only curative treatment; however, its poor long-term survival is often occurred due to its recurrence either local and/or distant metastasis. Thus, early detection of recurrence helps in improving the prognosis. Our aim is to assess the diagnostic role of 18F-FDG PET/CT for detecting postoperative recurrence in gastric cancer patients who have a radiological and/or clinical suspicion of recurrence.

Results: The study was carried over 31 males (62%) and 19 females (38%) pathologically proven with gastric carcinoma and underwent surgical intervention. All patients underwent PET/CT scan where the site and number of positive FDG activity analyzed. The sensitivity, specificity, and accuracy for locoregional recurrence were 75%, 81.58%, and 85% with p value 0.001; for regional lymph node recurrence were 100%, 100%, and 100% with p value < 0.001; for liver metastasis were 100%, 100%, and 100% with p value < 0.001; for peritoneum metastasis were 100%, 97.38%, and 98% with p value < 0.001; and for distant metastasis were 100%, 85.7%, and 94% with p value < 0.001.

Conclusion: With agreements to many studies, this study confirms that FDG PET/CT is a highly effective modality for postoperative surveillance detection of recurrent gastric cancer, especially in patients with clinically manifested disease, elevated tumor markers, and an indication of distant metastasis at diagnostic CT.

Keywords: PET/CT, FDG uptake, gastric cancer, recurrence, surgery

Background

Gastric cancer is the second leading cause of death from malignant disease worldwide and the most frequently discovered in advanced stages. Gastric tumors are subdivided into those of epithelial or stromal origin. Malignant tumors are far more common than benign, with adenocarcinomas being the most common type of malignancy. Rarer gastric malignancies include gastrointestinal stromal tumors (GIST), lymphomas, and neuroendocrine tumors [1, 2]. Surgical resection and lymph node dissection remain the definitive therapy for complete cure or long-term survival in case of local disease without distant metastasis [2, 3]. Pathological recurrence has a bad prognosis, and 5-year survival rate remains under 20%. So, early detection of disease recurrence is important and improves the prognosis [4–6]. Diagnosis of definite tumoral recurrence is still based on histopathology. However, getting adequate biopsy cores is often very difficult due to small size of the recurrent tumor or so deeply located or nearby to important vessels or organs. There are many limitations for ordinary methods used for diagnosis of tumoral recurrence, such as tumor markers cannot locate the precise recurrent site and endoscopy is unable to see extra-luminal recurrent lesions [7]. Contrast-enhanced computed tomography (CT) is the frequently used imaging study for detection of gastric cancer recurrence. However, CT has also some limitations, because it is based on the size measurement and gross morphological changes but not tumoral viability; on the other hand, small lesions like peritoneal implants can be easily missed. Also, it is not easy to discriminate the postoperative changes from true recurrence. A limitation of whole body CT and other conventional radiological imaging procedures pertains to their lack of

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Table 1 Patients' demographic data

Patients		n	%
Age	Mean	56.42	
	Range	29–79	
Sex	Male	31	62.0%
	Female	19	38.0%
Tumor site	Upper	32	64.0%
	Middle	19	38.0%
	Lower	4	8.0%
Surgery type	Partial gastrectomy	19	38.0%
	Total gastrectomy	31	62.0%
Histopathology	SRC/mucinous	8	16.0%
	Non-SRC/mucinous	42	84.0%
Neoadjuvant chemo/ radiotherapy		11	22.0%
Adjuvant chemo/radiotherapy		34	68.0%

SRC, signet ring carcinoma; non-SRC, non-signet ring carcinoma

functional data and depending only on morphological assessment. FDG-PET can display accurate functional information; however, based on its limited spatial resolution, it often makes exact anatomical localization and demarcation of the lesion difficult. The hybrid imaging tool (PET-CT) with fusion of functional with morphological data overcoming the limitations of either modality alone thus will be more valuable in postoperative evaluation of gastric cancer improving the ability to detect and characterize malignant lesions [5–10]. Recently, some studies reported the use and importance of integrated PET/CT in evaluation of postoperative gastric cancer patients to exclude or verify recurrence [6].

The main aim of this study is to clarify and emphasize the role of 18F-FDG PET/CT in the diagnosis and follow-up of recurrent gastric cancer patients and check its diagnostic accuracy.

Methods

This is a cross-section study approved by the local ethical committee. It was included patients diagnosed with pathologically proven gastric cancer and treated by surgery. The study was done at Kasr Al Ainy Hospital where the patients were recruited through 2 years starting from 2017 to 2019. Full written consent was delivered by all patients. Fifty patients were included with clinical or radiological suspicious in the post-surgery follow-up period, 31 males and 19 females, with age range from 29 to 79 years with mean 56.42; these patients underwent 18F-FDG PET/CT. Inclusion criteria are the following: (a) patients who did CT or MRI with detection of suspicious lesions, (b) patients who had elevated tumor markers with no conclusive pathological findings at regular diagnostic imaging modalities, (c) patients with alarming clinical manifestations such as recent weight loss, and (d) patients under follow-up by PET/CT according to the clinicians' plan of treatment.

Exclusion criteria were patients with chronic renal impairment and pregnant women.

Patients' demographic data are summarized in Table 1.

Imaging protocol

The study was done by using Siemens Bio-graph true point PET/CT scanner.

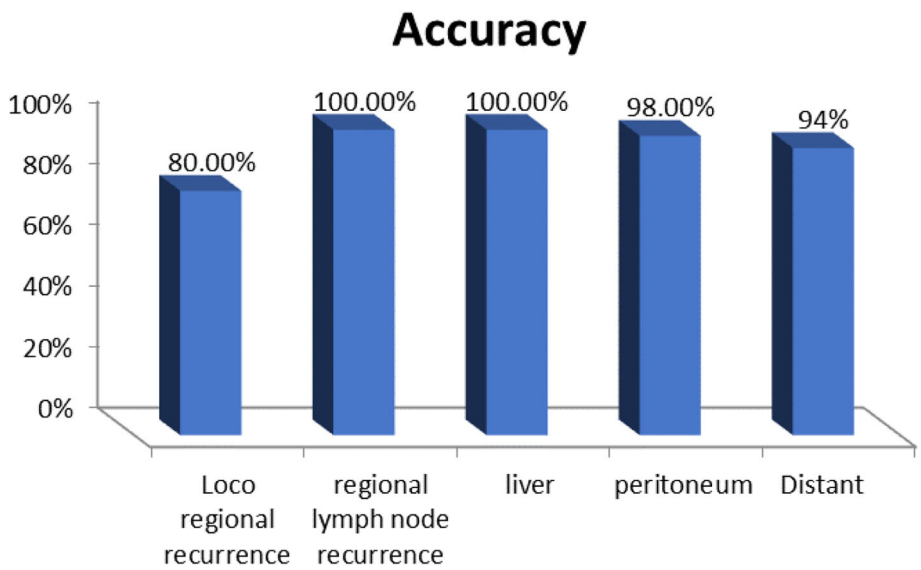

Fig. 1 Graph summarizes the accuracy rates of PET/CT estimated on organ-based analysis

Table 2 Comparison between PET/CT findings and final diagnosis in all five groups

PET/CT findings		Final diagnosis				P value
		Present		Absent		
		n	%	n	%	
Locoregional recurrence	Present	9	75.0%	7	18.4%	0.001
	Absent	3	25.0%	31	81.6%	
Regional lymph node recurrence	Present	13	100.0%	0	0.0%	< 0.001
	Absent	0	0.0%	37	100.0%	
Liver metastasis	Present	10	100.0%	0	0.0%	< 0.001
	Absent	0	0.0%	40	100.0%	
Peritoneum metastasis	Present	13	100.0%	1	2.7%	< 0.001
	Absent	0	0.0%	36	97.3%	
Distant metastasis	Present	29	100.0%	3	14.3%	< 0.001
	Absent	0	0.0%	18	85.7%	

Patient preparation

PET/CT should be done after 3 to 4 weeks of complete stoppage of chemotherapy to avoid reactive bone marrow hyperplasia. Patients were fast for 6 h and asked to void before the examination. The patients were instructed to stay calm and avoid walking or any exercise before and after injection of 18-F FDG to prevent physiologic muscle FDG uptake. Blood glucose level was measured before injection, and fasting levels were 70–170 mg/dl. Warm environment was available before injection to avoid brown fat uptake.

Dosage administration

A dose of 3–7 MBq/Kg (10 mci) of 18F-FDG IV injection 45–90 min was given before the examination. For opacification of bowel loops, 400–600 ml of contrast material was diluted with water and swallowed 1 h before PET/CT imaging.

Timing of exam

Low-dose non-enhanced CT scan is done first, then a whole body PET study followed by enhanced whole body CT scan. The whole study time took about 20–30 min.

Technique

We did contrast-enhanced CT images by intravenous automatic injection of 100–120 mL (at a rate of 4 ml/sec) of nonionic contrast. A CT image is taken before the PET images, as it is used for attenuation correction. Then PET-CT study is performed from the skull through mid-thigh with reconstructions of images at 1 mm interval.

PET/CT fusion

Axial PET and CT images were obtained and then reformatted into sagittal and coronal images to allow easier image interpretation. Manual or automatic attenuation correction was used.

PET/CT interpretation

Analysis of PET/CT images was done considering the number and site of the lesions as well as SUVmax calculated. All data are transferred into the work station and analyzed by nuclear medicine physicians and radiologists. Focal FDG uptake is defined as significant when it appeared higher than the normal FDG background biodistribution. The regional and distant lymph nodes whatever their sizes are considered positive when they show higher SUVmax value more than 2.5. The definitive diagnosis of recurrence is mainly reached by histopatholgical results after surgical interventions, biopsy, clinical, or radiological follow-up of at least 3 months. A negative follow-up by clinical and radiological data of at least 3 months starting at the time of the PET/CT scan is required in order to define a lesion as negative. Clinical recurrence was defined as the lesions seen by

Table 3 Diagnostic performance of PET/CT on the organ-based analysis

Statistic	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Locoregional recurrence	75.00%	81.58%	56.25%	91.18%
Regional lymph node recurrence	100.00%	100.00%	100.00%	100.00%
Liver metastasis	100.00%	100.00%	100.00%	100.00%
Peritoneum metastasis	100.00%	97.30%	92.86%	100.00%
Distant metastasis	100.0%	85.7%	90.63%	100.00%

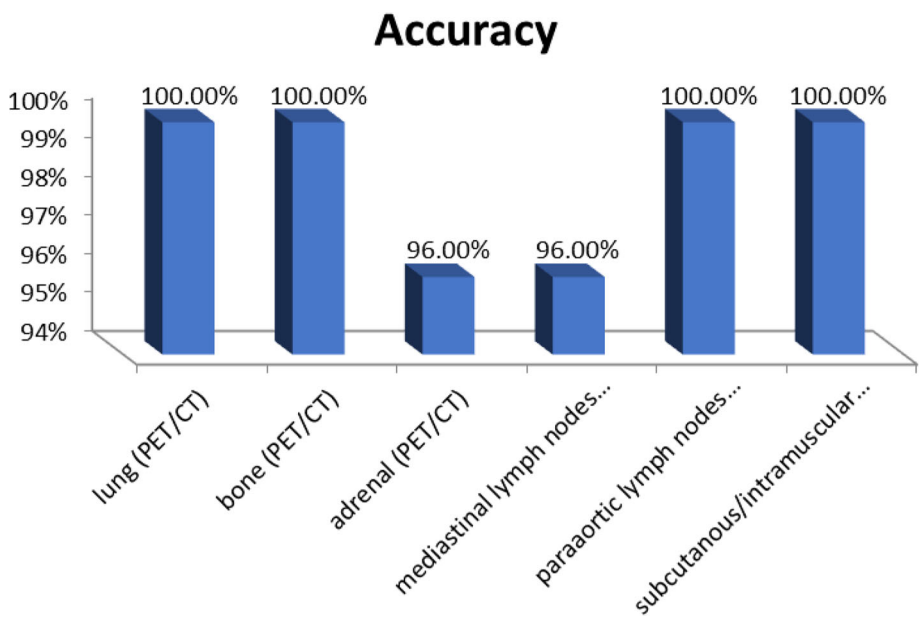

Fig. 2 Graph summarizes the accuracy rates of PET/CT estimated when distant metastatic groups

imaging modalities like diagnostic CT or MRI within 3 months of the PET/CT scan. Radiological recurrence was defined to be present when a suspicious lesion at CT or MRI shows increases in size during follow-up or decrease in size after radio/chemotherapy. Then, the PET/CT data is correlated and interpreted with the final diagnosis, by calculating the diagnostic morphological and quantitative values of PET/CT.

Statistical analysis

For statistical analysis, we considered a *true-positive lesion* which is detected on PET/CT images and confirmed by histopathological results or regular follow-up. We considered a *false-positive lesion* which is detected on PET/CT images and confirmed as a benign lesion at histopathological results or follow-up. A *true-negative lesion* is determined when free FDG PET/CT images are interpreted and no tumoral cells are detected at the histopathology or the patient remains free at regular follow-up. A *false-negative lesion* that overlooked during PET/CT interpretation however is detected at the histopathological examination or during regular follow-up (Fig. 3, 4, 5, and 6).

Table 4 Comparison between PET/CT findings and final diagnosis in the distant metastatic subgroups

PET/CT findings	Final diagnosis					P value
	Present			Absent		
	n		%	n	%	
Lung	Present	4	100.0%	0	0.0%	< 0.001
	Absent	0	0.0%	46	100.0%	
Bone	Present	2	100.0%	0	0.0%	0.001
	Absent	0	0.0%	48	100.0%	
Adrenal	Present	1	100.0%	2	4.1%	0.060
	Absent	0	0.0%	47	95.9%	
Mediastinal lymph nodes	Present	7	100.0%	2	4.7%	< 0.001
	Absent	0	0.0%	41	95.3%	
Para-aortic lymph nodes	Present	5	100.0%	0	0.0%	< 0.001
	Absent	0	0.0%	45	100.0%	
Subcutaneous/intramuscular nodules	Present	2	100.0%	0	0.0%	0.001
	Absent	0	0.0%	48	100.0%	

Table 5 Diagnostic performance of PET/CT at the distant metastatic subgroups

Statistic	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Lung (PET/CT)	100.00%	100.00%	100.00%	100.00%
Bone (PET/CT)	100.00%	100.00%	100.00%	100.00%
Adrenal (PET/CT)	100.00%	95.92%	33.33%	100.00%
Mediastinal lymph nodes (PET/CT)	100.00%	95.35%	77.78%	100.00%
Para-aortic lymph nodes (PET/CT)	100.00%	100.00%	100.00%	100.00%
Subcutaneous/intramuscular nodules (PET/CT)	100.00%	100.00%	100.00%	100.00%

The data was coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data was summarized using frequency (count) and relative frequency (percentage) for categorical data. Standard diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic efficacy were calculated as described by Galen (1980) [11]. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 [12] *(Chan, 2003)*. P value less than 0.05 was considered as statistically significant.

Results

We carried this study over 31 males (62%) and 19 females (38%). According to organ-based analysis, five categories obtained (I) regional recurrence (anastomotic site or residual part of the stomach), (II) regional lymph node recurrence, (III) liver metastasis, (IV) peritoneal metastasis, and (V) distant metastasis. We considered many lesions within the same group as a single lesion.

Among the 50 patients evaluated in this study, a recurrent disease was detected in 34 patients, and 16 patients were negative for recurrence. We reached the final diagnoses by histopathology in 13 (26%) of 50 patients and by clinical and radiological follow-up in the remaining 37 (74%) patients.

In all of five groups, the diagnostic accuracy rates were higher than 80%, which was up to 100% in detecting regional lymph nodes and liver metastasis (Fig. 1). We compared between the PET/CT findings and final diagnosis and found that 11 cases had a true recurrence for locoregional recurrence where the p value was significant at 0.001, 13 were found having true recurrence for regional lymph node recurrence where the p value was significant at < 0.001, 10 were found having true recurrence for liver metastasis where the p value was significant at < 0.001, 13 were found having true recurrence for peritoneal metastasis where the p value was significant at < 0.001, and lastly 29 were found having true recurrence for distant metastasis where the p value was significant at < 0.001 (Table 2). Therefore, the sensitivity, specificity, PPV, and NPV for diagnosing true recurrence were calculated and found to

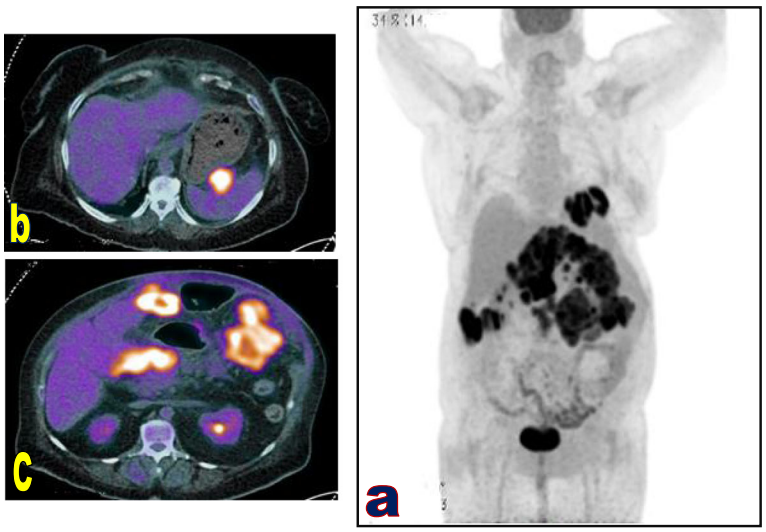

Fig. 3 3D MIP (**a**) and axial fused PET/CT images (**b** and **c**) for a 70-year-old female patient with history of gastric cancer underwent surgical excision. Operative bed is clear. Hypermetabolic peritoneal nodules, masses, and sheet-like infiltrates seen beneath the abdominal wall, in the mesentery, hepatic, and splenic reflections. The largest seen in the left hypochondrium related to hepatic surface at segment III. Final diagnosis obtained by radiological follow-up for peritoneal metastasis

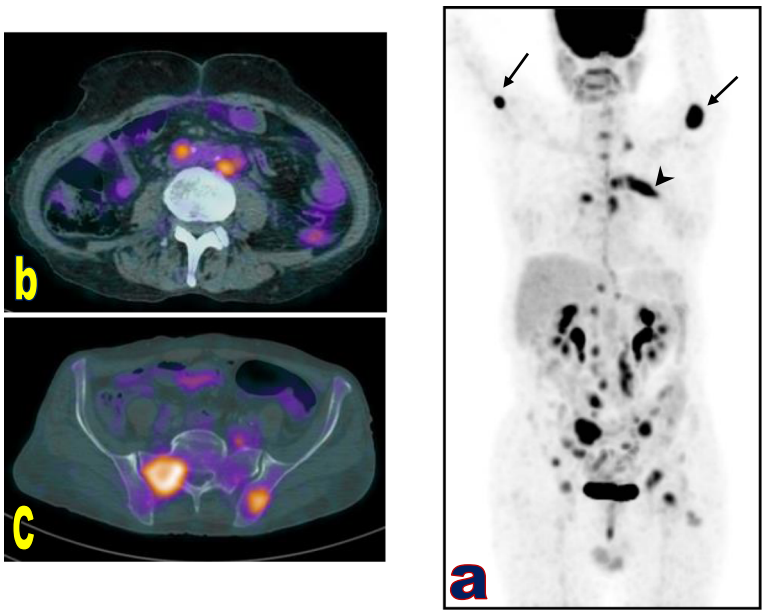

Fig. 4 3D MIP (**a**) and axial fused PET/CT images (**b** and **c**) for a 60-year-old male patient underwent surgical excision of gastric adenocarcinoma followed by radiation and chemotherapy. No FDG avid lesions at the operative bed. Increased FDG uptake by multiple lymph nodes involving porto-caval, para-aortic, aorto-caval, retro-caval, bilateral common iliac, left internal and right external iliac groups as well as mediastinal lymph nodes (left infra-clavicular, pre-vascular, hilar, retro-crural, and posterior mediastinal groups). Multiple mainly lytic lesions involving the humeri (black arrows), few thoracic vertebrae, left sixth rib with soft tissue component (arrow head), sacrum, pelvic bones, and upper left femur. Final diagnosis obtained by radiological follow-up for recurrence

be higher than 75%, except for the PPV of detecting locoregional recurrence (Table 3).

Furthermore, when we evaluated the distant metastasis group in a separate way, we found lung, bone, adrenal gland, mediastinal lymph nodes, para-aortic lymph nodes, and subcutaneous/intramuscular nodules as the most common six remote metastasis sites. All the diagnostic accuracy values were more than 95% in all of these mentioned sites (Fig. 2). When comparing between the PET/CT findings and final diagnosis for the six commonest distant metastatic sites, four were found having true recurrence for lung metastasis where the p value was significant at < 0.001, two were found having true recurrence for bone metastasis where the p value was significant at 0.001, one was found having true recurrence for adrenal gland metastasis where the p value was not significant, seven were found having true recurrence for mediastinal lymph nodes where the p value was significant at < 0.001, five were found having true recurrence for para-aortic lymph nodes where the p value was significant at < 0.001, and lastly two were found having true recurrence for subcutaneous/intramuscular nodules where the p value was significant at 0.001 (Table 4). Therefore, the sensitivity, specificity, PPV, and NPV for diagnosing true recurrence were calculated and found higher than 75%, except for the PPV of detecting adrenal gland (Table 5).

Discussion

Fused PET/CT is an important imaging modality for detection of gastric tumoral recurrence as it gives detailed morphologic and metabolic activity compared to single contrast-enhanced CT [6].

Park et al. reported that the sensitivity, specificity, PPV, NPV, and accuracy of FDG PET/CT for the diagnosis of true recurrence on a per-person basis were 75, 77, 89, 55, and 75%, respectively. So, they concluded that PET/CT has a role in detection of tumoral recurrence in gastric cancer [13].

Sun et al. evaluated the value of PET/CT in postoperative follow-up of gastric cancer patients and reported that the overall accuracy, PPV, and NPV of FDG PET/CT were 82.6, 77.7, and 85.7%, respectively [14]. On the other hand, De Potter et al. reported that FDG-PET has a limitation as a primary tool for follow-up due to its moderate accuracy [15].

In recent studies, Sim et al., Bilici et al., and Baiocchi et al. showed importance of using FDG PET/CT for the diagnosis of tumor recurrence in patients with previously treated gastric cancer and equivocal imaging findings. Also, they made comparative studies between PET/CT and contrast-enhanced CT for detection of tumoral recurrence. They reported that the overall sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for FDG PET/CT were significantly higher to those of diagnostic CT [5, 16, 17].

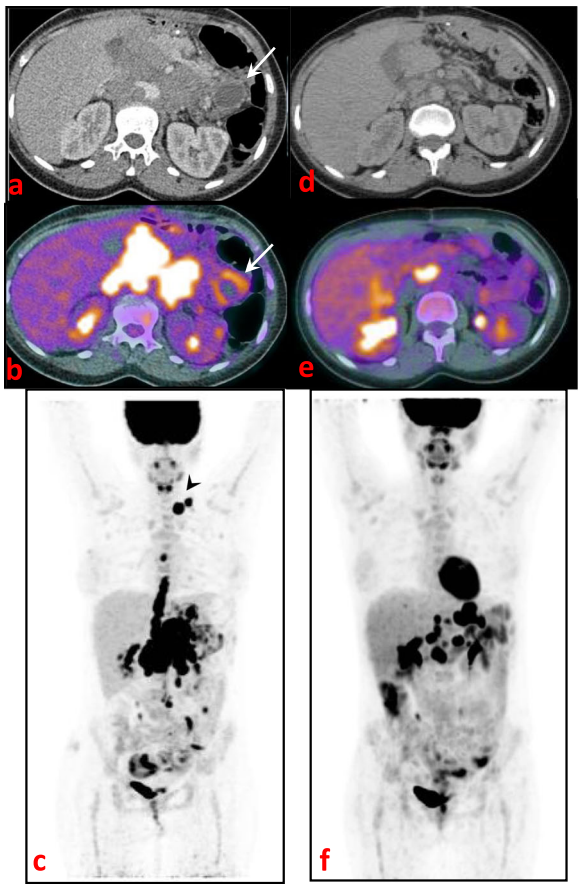

Fig. 5 Axial CT, axial fused, and coronal MIP images for a 60-year-old female presenting with total gastrectomy, splenectomy, and distal pancreatectomy for gastric adenocarcinoma received chemotherapy (**a** and **b**) showed encysted collection seen at the operative bed with marginal FDG uptake (white arrows). (**c**) Showed left supra-clavicular lymph nodes (black arrow-head), mediastinal, abdominal, and pelvic lymph nodes. (**d**, **e**, and **f**) during 3-month interval follow-up after chemotherapy showing resolution of operative bed encysted collection, marked response of the metastatic lymphadenopathy. Thus, final diagnosis approved by clinical and radiological follow-up after chemotherapy

In our study, according to organ-based analysis in the five organ-based groups (locoregional recurrence, regional lymph node recurrence, liver metastasis, peritoneal metastasis, and distant metastasis), we found that all values of diagnostic performance were greater than 80%. The diagnostic accuracy rates were very high reaching up to 100% at regional lymph nodes recurrence and liver metastasis detection. Our results seemed better than those of the fore-mentioned studies as well as the results of Cayvarli et al.; their diagnostic accuracy rates reached up to 80% with low specificity in locoregional recurrence 47.8% and distant metastasis 71%. They explained that the decease of diagnostic specificity in their study is especially due to low specificity value of locoregional recurrence, causing of false-positive FDG uptake in anastomotic site as result of postoperative inflammatory changes. Another reason for that was the low specificity value of distant metastasis. However, in our study, we found seven false-positive patients with locoregional FDG activity. We reached the final diagnosis by biopsy and follow-up as postoperative inflammatory changes. In addition, our study conducted comparison between PET/CT diagnosis and final diagnosis in each organ-based group; the results were statistically significant where p values were 0.001, < 0.001, < 0.001, < 0.001, and < 0.001 for locoregional recurrence, regional lymph node recurrence, liver metastasis, peritoneal metastasis, and distant metastasis, respectively.

Similar to Cayvarli et al., we evaluated the most common distant metastatic groups separately; we showed high diagnostic accuracy values reached up to 100%. These results were better than those of the above-mentioned report. Although, we found low-positive predictive value of adrenal gland metastasis < 50%; this result is almost explained that we found one true-positive and two false-positive patients. Additionally, we found statistically significant difference in diagnostic performance of PET/CT compared to final diagnosis on per-lesion basis in most of the distant metastatic groups. P

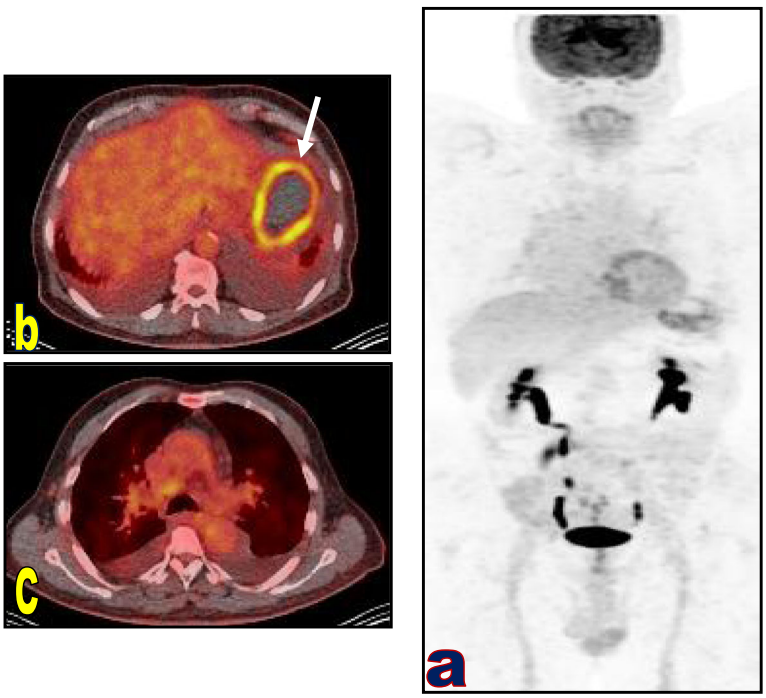

Fig. 6 3D MIP (**a**) and axial fused PET/CT images (**b** and **c**) for a 67-year-old male patient with history of surgically resected gastric adenocarcinoma and splenectomy. No FDG-avid lesions at gastroesophageal anastomotic site, while splenectomy operative bed shows a localized collection with marginal increase of FDG activity and air loculi within (arrow), low-grade mediastinal lymph nodes as well as bilateral moderate pleural effusion and mild pelvic ascites demonstrating low-grade FDG activity. Final diagnosis confirmed by histopathology and radiological follow-up for splenectomy bed collection complicated with infection (an example of false-positive case)

value was statistically significant in lung, bone, mediastinal lymph nodes, para-aortic lymph nodes, and subcutaneous/intramuscular nodules groups (p values were < 0.001, 0.001, < 0.001, < 0.001, and 0.001). No statistical significance was found in the adrenal gland metastasis.

PET/CT has some limitations affecting the sensitivity and specificity of this modality for detection of recurrence such as low-grade metabolic activity of a malignant lesion or small-sized peritoneal deposit can give false-negative results [15, 18, 19]. Some types of gastric cancer such as SRC and mucinous adenocarcinoma also show low-grade FDG activity, and thus they can give false-negative results [20, 21]. We disagreed with these findings in our results, although the number of patients in the SRC/mucinous adenocarcinoma subgroup was small (n = 8). Also, John M. Findlay at el. emphasized the role of PET/CT in finding metastases at which its risk differentiate between false positives and false negatives which justifies its potential benefit [22].

Our study had several limitations; the major limitation of this study was the small sample size. In addition, a short-term follow-up period may not sufficient to confirm the absence or presence of recurrence. Not all the recurred cases were confirmed by histopathological diagnosis. Therefore, there was the possibility of including cases in which false-positive lesions were treated as true-positive lesions by anticancer drugs, or true-positive lesions were not identified in the clinical setting. Further studies with larger number of patients to examine other correlations and to set standard methods of measurement and ranges of normality are recommended.

Conclusion

Despite these limitations, in agreements to many studies, this study supports the fact that our results confirm that FDG PET/CT is a highly effective modality for postoperative detection of recurrent gastric cancer, especially in patients with indication of distant metastasis at diagnostic CT and an increase in tumor markers or clinical manifestations.

Abbreviations

F 18: Fluorine 18; FDG: Fluoro-deoxy-glucose; Met: Metastasis; Non-SRC: Non-signet ring carcinoma; NPV: Negative predictive value; PET/CT: Positron emission tomography/computed tomography; PPV: Positive predictive value; SRC: Signet ring carcinoma; SUV: Standard uptake value

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Authors' contributions

A.A.H and M.F.O Put the idea of the study. Editor of the manuscript. Participated in the study design. N.E and N.D.E: participation in the study design and performed the statistical analysis. M.D.S: patients collection and clinical assessment. All authors read and approved the final manuscript.

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Availability of data and materials
All the datasets used and analyzed in this study are available with the corresponding author on reasonable request.

Ethics approval and consent to participate
Written informed consent was signed by all patients before the examination. The study was approved by the research committee of Faculty of Medicine, Kasr Al Ainy hospital, Cairo University (2017). No reference number provided as the committee just say yes or no according to the system in our Faculty of Medicine at 2017 (date of starting of this research).

Consent for publication
All patients included in this research were fully conscious and gave written informed consent to publish the data contained within this study.

Competing interests
The authors declare that they have no competing interests.

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