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ROLE OF FDG PET/ CT IN EVALUATION OF METASTATIC BREAST CANCER

By

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ABSTRACT

Background: Breast Cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% of the total cancer cases, and 14% of the cancer deaths.

Objective: To evaluate the role of [(18F)2-fluoro-2-deoxyglucose] (FDG) Positron emission tomography combined with computed tomography (PET/CT) in early detection of breast cancer metastasis.

Patients and Methods: The current study was a prospective observational study. The study is performed at Mustafa Kamil Military Hospital during the period between January 2021 till July 2021. The study population consisted of 50 female breast cancer patients which were to be under investigation for suspicion of breast cancer recurrence or metastasis especially patients who had previously been cleared of breast cancer.

Results: FDG PET/CT was very useful for restaging of cancer in patients with documented breast cancer recurrence or in those who were suspected of having breast cancer recurrence and was more efficient than PET alone and conventional imaging methods. Among the 50 patients referred for initial staging by PET/CT, only 8 patients (16%) returned back for restaging after receiving neoadjuvant chemotherapy and /or radiotherapy. PET/CT showed 4 patients (50%) in stationary course and down staged 4 patients (50%).

Conclusion: The use of maximum standard uptake value (SUVmax) proved to be more efficient in restaging studies after neoadjuvant therapy more related to the functional activity of the residual tumor cells rather than to the size of the tumor in which tumor regression can be masked by peritumoral scar tissue formation and edema. PET/CT provided information about biologic aggressiveness of the tumor and prognosis.

Keywords: Positron emission tomography, computed tomography.

INTRODUCTION

Breast cancer is considered the most frequently diagnosed neoplastic disease in women around menopause often leading to a significant reduction of these women's ability to function normally in everyday life. Eighty percent of these cancers are diagnosed in women aged 50 and more *(Kaminska et al., 2015)*.

Metastatic breast cancer is rarely curable, and it remains a matter of controversy whether early detection of recurrence is clinically relevant. However, there are several reasons why early detection of metastases is significant. Firstly, metastases may be more effectively treated if detected early than if found at a more advanced stage. Early treatment of metastases may prolong

survival and improve physical quality of life. Secondly, early detection, or a negative work-up, may be of emotional value to the patient or the treating physician. Finally, some patients with an isolated metastasis may benefit from either palliative or curative surgery *(Kaminska et al., 2015)*.

PET/CT is a new imaging modality in oncology it has re-defined as the gold standard for oncologic imaging compared with other imaging modalities to demonstrate proper extent of the disease and metastatic spread within a single non-invasive investigation *(Zhang et al., 2014)*.

In patients with metastatic breast cancer, sequential 18F-FDG PET/CT allowed prediction of response to treatment after the first cycle of chemotherapy. The use of 18 F-FDG PET/CT as a surrogate endpoint for monitoring therapy response, offers improved patient care by individualizing treatment and avoiding ineffective chemotherapy *(Zhang et al., 2014)*.

FDG PET/CT is useful for evaluating asymptomatic treated breast cancer patients with rising levels of tumor markers without clinical symptoms. In this clinical scenario, FDG PET/CT allows more accurate diagnosis of metastatic disease compared with conventional imaging *(Paydary et al., 2019)*.

The accurate restaging of recurrent breast cancer is important for identifying patients with limited disease who could potentially benefit from curative treatment. Traditionally, routine evaluation of suspected recurrent breast cancer has involved physical examination, testing for biological markers (cancer antigen 15-3 and/or carcinoembryonic antigen) and a multi-modality conventional imaging approach including mammography, breast US and MRI for local recurrence, and chest radiography, whole-body CT and bone scanning for distant recurrence. However, this conventional approach is often time-consuming and potential false-negative findings may delay appropriate therapy. FDG-PET/CT can evaluate the whole body (except the brain) in a single examination and is very useful for detecting recurrent or residual tumors because of its high sensitivity and specificity in comparison with conventional techniques *(Kazuhiro et al., 2016)*.

One of the most commonly used metabolic parameters is the maximum standard value (SUVmax) derived from 18F-FDG PET/CT of the primary tumor, which was demonstrated by several studies to be correlated with ALN metastasis in breast cancer. In clinically negative axillary lymph nodes in case of breast cancer, the higher SUVmax of the primary breast lesion revealed a higher incidence of axillary lymph node metastasis according to a previous study *(Yoo et al., 2018)*.

The purpose of our study was to evaluate the role of (FDG PET/CT) in early detection of breast cancer metastasis.

PATIENTS AND METHODS

The current study was a prospective observational study performed at Mustafa Kamil Military Hospital. Ethical approval from Al-Azhar university Ethics committee was obtained. the study was carried during the period between January 2021 till July 2021.The study population

consisted of 50 female breast cancer patients which were to under investigation for suspicion of breast cancer recurrence or metastasis especially patients who had previously been cleared of breast cancer.

Inclusion Criteria: No age predilection, female gender.

Exclusion Criteria: Patients with strong history of hypersensitivity disorders to the CT contrast agents. Patients with renal function impairment (with serum creatinine > 2 mg/dl) because they were liable to contrast nephropathy. Pregnant patients as the patient have high dose of radiation exposure.

All patients were submitted to the following:

Demographic and clinical data collection: Including patient's name, age, residence, phone number, past history.

The procedure was conducted using a combined PET/CT scanner (Biograph, SIEMENS Medical Solutions, North Barringiton, USA). Full history taking with emphasis on the clinical data of the patient's biopsy and histopathology (either FNAC or excisional biopsy), US breast and mammography, CT scan, PET and CT examination. MRI (for one patient).

All patients were asked to fast for six hours prior to scan. All metallic items were removed from the patients and they were given gown to wear. Patients were asked to empty the bladder before the procedure. An I.V. cannula was inserted in the patient's arm for administration of 18F-FDG. The patients were instructed to avoid any kind of strenuous activity prior to the examination and following injection of the radioisotope to avoid physiologic muscle uptake of FDG and the patient was asked to void prior to scanning.

Serum glucose was routinely measured prior to 18F-FDG injection, and fasting levels ranged from 70–170 mg/dl. The strategies for decreasing brown fat were; providing a controlled-temperature (warm) environment for patients before 18F-FDG injection and high-fat, low-carbohydrate, protein-permitted diet before the examination.

About one liter of negative oral contrast agent (5% mannitol) approximately one hour before the exam. A dose of 0.1 mCi/kg of 18F-FDG IV injection 45–90 minutes before examination was administered. This period referred to as the uptake phase and was the necessary amount of time for the FDG to be adequately bio-distributed and transported into the patient's cells. Patients were asked to rest in a quiet room, devoid of distractions, and they were also asked to keep their movements, including talking, at an absolute minimum. This minimized physiologic uptake of FDG into skeletal muscles, which can confound interpretation of the scan. Patients should be comfortable and relaxed.

The patients were positioned in a comfortable head fixation with arms up.

Scanning Technique:

I. **CT Technique:** Helical CT was performed following injection of about 125 mL of a non-iodinated contrast medium at a rate of 4 mL/sec using a power injector. For a typical whole body PET/CT study (neck, chest, abdomen, and pelvis), scanning began at the level of the skull base and extended caudally to the level of the upper thighs. The total length of CT coverage was an integral number of

bed positions scanned during acquisition of PET data. The study was performed with the patient breathing quietly. Scanning parameters are collimation width of 5.0 mm, pitch of 1.5, and gantry rotation time of 0.8 second and field of view of 50 cm. The helical data are retrospectively reconstructed at one mm intervals

II. **PET Technique:** PET was performed following the CT study without moving the patient. Approximately six to seven bed positions are planned in the three-di-mensional acquisition mode for scanning the entire patient with 3–5-minute acquisition at each bed position.

III. **PET/CT Fusion:** Hundreds of trans-axial PET and CT images were first reconstructed. These are then reformatted into coronal and sagittal images to facilitate image interpretation. For each of these sets of PET and CT images, corresponding fusion images, combining the two types of data, also were generated. The whole acquisition time for an integrated PET/ CT scan was approximately 25-30 minutes. PET image data sets were reconstructed using CT data for attenuation correction and co-registered images were displayed using special software.

Image interpretation:

All PET/CT examinations were analyzed by a consensus of two experienced observers of nuclear medicine physicians and radiologists. The PET images and the volume of CT scans were evaluated for the presence and extent of 18F-FDG-positive primary breast and distant metastatic lesions in the initial staging studies as well as for restaging after therapy.

Abnormal 18F-FDG uptake was defined as radiotracer accumulation outside the normal anatomic structures and of greater intensity than background activity, excluding normal areas of physiological uptake. In all cases estimation of 18-FDG uptake was done using SUVmax values for any lesion or enlarged nodes.

Different methods were used for assessment of radio- tracer uptake by normal and pathologic tissues; analysis of PET images was via visual and semi-quantitative assessment (SUV max measurement). Active lesions were recorded at areas of high FDG uptake. SUV max was measured at each lesion and compared to background activity. The standard background activity was measured at the liver (right lobe). In patients having diseased liver, the background activity was measured at the mediastinal blood pool.

The diagnosis of the breast cancer, recurrence, and distant metastasis was made after histo-pathological analysis and clinical and imaging follow-up.

Statistical Analysis:

Data were collected, revised, coded and entered to the Statistical Package for the Social Sciences (IBM SPSS) version 20. The qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations, ranges and median.

P value > 0.05 was considered significant.

RESULTS

This study was conducted on 50 patients with pathologically proven breast cancer. Their age ranged between 25 to 78 and mean age of 52 ± 12.39 SD years old **(Table 1)**.

Table (1): Distribution of the studied cases according to Age

Variables	Mean ± SD	Range
Age	52.0 ±12.39	25.0 – 78.0

Among 30 patients, there were different sizes of the primary breast masses. PET/CT detected 26 patients showed primary breast mass size ranged from 2.0 – 7.o cm with a mean value of 4.12± 1.67 SD while significantly ($p \leq 0.026$) couldn't detect 4 patients showed primary breast mass size ranged from 1-1.20 cm with a mean value of 1.10 ± 0.14 SD **(Table 2)**.

Table (2): Relation between size of primary breast mass and detection by PET CT (n=30)

Detection by PET CT / Size of primary breast mass (cm)	indeterminate (n = 4)	Detection (n = 26)	P
Min. – Max.	1.0 – 1.20	2.0 – 7.0	0.019*
Mean ± SD.	1.10 ±0.14	4.15 ±1.61	
Median	1.10	4.0	

U, p: U and p values for Mann Whitney test for comparing between the two categories
*: Statistically significant at $p \leq 0.05$

In our present study among 50 patients, there were 10 patients (20%) with local metastasis, 26 patients (52%)with nodal metastasis, 9 patients (18%) with pulmonary nodules, 4 patients (8%) with pleural glucose avid lesions, 4 patients (8%) with glucose avid effusion, 28 patients (56%) with bony metastatic lesions, 11 patients (22%) with hepatic metastatic lesions, one patient (2%)with adrenal metastasis, one patient (2%) with peritoneal glucose avid deposits, 4 patients (8%) with genital metastasis, 2 patients (4%) with brain metastasis , one patient (2%) with omental glucose avid lesions, one patient (2%) with chest wall metastatic lesion and one patient (2%) with anterior abdominal wall metastatic nodules **(Table 3)**.

Table (3): Distribution of the studied cases according to site

Site	No.	%
Local	10	20.0%
Nodal	26	52.0%
Pulmonary	9	18.0%
Pleural	4	8.0%
Effusion	4	8.0%
Osseous	28	56.0%
Hepatic	11	22.0%
Adrenal	1	2.0%
Peritoneal	1	2.0%
Genital	4	8.0%
Brain	2	4.0%
Omental	1	2.0%
Chest wall	1	2.0%
Anterior abdominal wall	1	2.0%
Subcutaneous nodule	1	2.0%

In present study, PET/CT detected 28 patients (65%) showed bone metastasis, 12 patients with distant lytic bone metastases; PET/CT detected all 12 patients (100%). Among 8 patients showed mixed bone metastases; PET/CT detected all 8 patients (100%). Among 8 patients showed sclerotic bone metastases; PET/CT detected all 8 patients **(Table 4)**.

Table (4): Detection of distant bone metastases by PET/CT.

Distant bone mets	PET CT	
	No.	%
Lytic		
Detection (High FDG uptake)	12	24.0
No detection	0	0.0
Mixed		
Detection (High FDG uptake)	8	16.0
No detection	0	0.0
Sclerotic		
Detection (Low FDG uptake)	8	16.0
No detection	0	0.0

In present study, 8 patients (16%) had no surgical treatment, 36 patients (72%) had undergone modified radical mastectomy and the other 6 patients (12%) had undergone conservative breast surgery with higher incidence among modified radical mastectomy **(Table 5)**.

Table (5): Distribution of the studied cases according to Surgery

Variables		No.= 50
Surgery	No surgery	8 (16.0%)
	Surgery	42 (84.0%)
	Modified radical mastectomy	36 (72.0%)
	Conservative breast surgery	6 (12.0%)

In this case (A1) axial CT and (A2) axial hybrid PET/CT at the level of chest to detect glucose avid lesions in the lung and pleura.

(B1) axial CT and (B2) axial hybrid PET/CT at the level of pelvis to detect glucose avid lesions in the pelvis **(Figure 1)**.

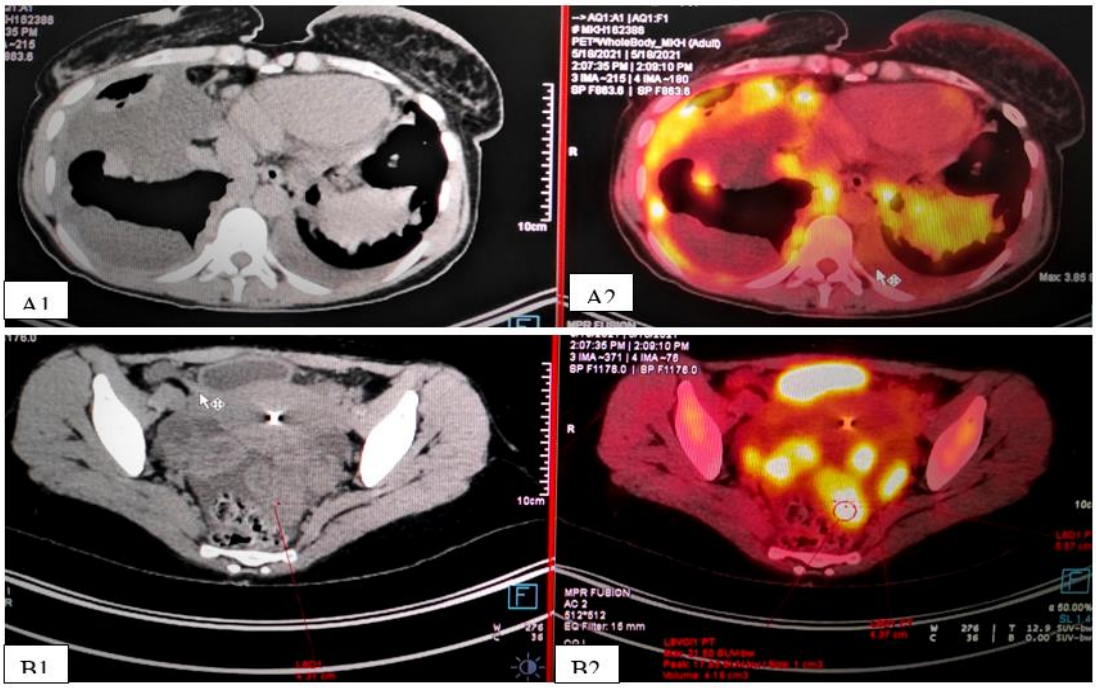

Figure (1): 43-years-old lady with history of left breast cancer.
(A1-A2) FDG-avid Rt. pleural circumferential thickening involving the entire leaflets, reaching ~ 12mm, with SUVmax ~ 19. To a lesser degree FDG-avid Lt. pleural nodular thickening more prominent at mediastinal and diaphragmatic leaflets, reaching ~ 10mm, with SUVmax ~ 7.Tracer-starved mild right pleural/fissural effusion and to a less degree left pleural effusion noted.
(B1-B2) FDG-avid bi-adnexal complex soft tissue masses are seen, measuring 4cm at Rt. side and 7cm at Lt. side; with SUVmax ~ 14.5n associated with mild tracer-starved pelvic fluid collection.

DISCUSSION

Positron Emission Tomography with 18F-fluorodeoxyglucose (FDG-PET) has been used for diagnosis, staging, monitoring response to therapy and restaging patients with breast cancer *(Groheux and Hindie., 2021)*.

This study was conducted on 50 patients with pathologically proven breast cancer. Their age ranged between 25 to 78 and mean age of 52 ± 12.39 SD years old.

Our results were concordant with a study carried out by Salman et al, who reported that the mean age of study performed among 60 breast cancer patients was 51 years old. Also, a study carried out by Kelly A. Hirko et al, showed that the majority of breast cancer cases during the study period were diagnosed among women aged 40–49 years (31.8%) and among women aged 50–59 years (29.8%) *(Hirko et al., 2013)*.

In present study, 8 patients (16%) had no surgical treatment, 36 patients (72%) had undergone modified radical mastectomy and the other 6 patients (12%) had undergone conservative breast surgery with higher incidence among modified radical mastectomy.

This was concordant with a study conducted by Daniela Francescato Vega et al who reported that 58 patients had undergone modified radical mastectomy and 38 had undergone conservative breast surgery *(Veiga et al., 2010)*.

In our present study, among 15 (30%) patients with loco regional metastasis; PET/CT detected 5 patients (10%) with loco regional recurrence in the same side and one patients (2%) with loco regional recurrence in the contralateral side and only one patient (2%) was indeterminate confirming the higher sensitivity and accuracy of PET/CT for diagnosis of tumor recurrence.

Our results are concordant with many other early reports. In a study conducted by Chandra et al. that was performed on 46 patients showed that 30 (65%) patients had tumor recurrence, and 16 (35%) patients showed no further evidence of disease. 31 patients had abnormal PET/ CT studies, and 15 patients had normal studies with an overall sensitivity, specificity, and accuracy of 90%, 71%, and 83%, respectively *(Chandra et al., 2020)*.

In our present study, PET/CT detected 12 patients (24%) showed metastatic axillary LNs,2 patients (4%) showed metastatic internal mammary LNs, 8 patients (16%) showed both metastatic supraclavicular and retro pectoral LNs, 5 and 7 patients (10%) (14%) showed distant metastatic mediastinal and pelvi-abdominal LNs respectively, one patient (2%) showed infraclavicular LN and one patient (2%) showed distant infiltration of pectoralis muscle.

Our results are concordant with many other reports. *Riegger C et al.* showed that the sensitivity, specificity, PPV, NPV, and accuracy of FDG-PET/CT for the detection of axillary lymph node metastases were 54%, 89%, 77%, 74%, and 75%, respectively. For ultrasound it was 38%, 78%, 54%, 65%, and 62%, respectively. FDG-PET/CT was significantly more accurate than ultrasound for the detection of axillary lymph node metastases. There was no statistically significant difference between the sensitivity of both modalities. FDG-

PET/CT detected extra-axillary loco regional lymph node metastases in seven patients (8%) that had not been detected by another imaging modality *(Riegger et al., 2012)*.

In present study, PET/CT detected 28 patients (65%) showed bone metastasis, 12 patients with distant lytic bone metastases; PET/CT detected all 12 patients (100%).Among 8 patients showed mixed bone metastases; PET/CT detected all 8 patients (100%). Among 8patients showed sclerotic bone metastases; PET/CT detected all 3 patients.

Also, in the study performed by *Groheux et al.* among 39 women with stage II or III breast cancer, PET-CT showed occult bone metastases in a further 3 women relative to the standard work-up, however many teams have found that while PET is more efficient than CT or bone scintigraphy in detecting lytic and mixed bone metastases and bone marrow involvement, it sometimes lacks sensitivity to sclerotic bone metastases and a multimodality approach is suggested *(Hyland et al., 2020)*.

In our present study, among the 9 patients (18%) showing distant pulmonary nodule metastases. PET/CT detected only 4 patients (44.4%) showed distant metastatic pulmonary nodules measured more than one centimeter with high FDG uptake and 5 patients (55.6%) couldn't be detected by PET/CT fore sure as distant metastatic pulmonary nodules; these nodules were subcentemetric pulmonary nodules with low FDG uptake.

PET lacks sensitivity for smaller nodules. Careful scrutiny of CT images from PET/CT can reveal small nodules without 18F-FDG uptake, however CT performed during free breathing is less efficient than standard diagnostic thoracic CT *(Groheux et al., 2016)*.

In our study 4 (8%) patients showed thick pleura with or without effusion, according to SUV max and FDG uptake PET/CT could differentiate all 2 patients as malignant pleural effusion, also PET/CT detected one patient with active pleura with high FDG uptake and one Patient showed reactive pleura due to inflammation.

Our results were concordant with a study conducted by *Alkhawaldeh et al. (2011)* that was performed on 61 patients with non-small lung cancer and pleural effusion were included, this study showed 29 patients with malignant pleural disease and 31 patients with benign pleural effusion. The average SUVmax in malignant effusions was 6.5 ± 4 versus 2.2 ± 0.9 in benign effusions. The average %SUV in malignant effusions was +13 ± 10 versus −8 ± 11 in benign effusions.

Among 11 (22%) patients showed distant hepatic deposits; PET/CT detected all 11 patients. In our study, PET/CT could detect 4 patients (8%) showed distant genital mets, one patient (2%) showed peritoneal mets, one patient (2%) showed omental mets and one patient (2%) showed adrenal metastasis.

In a study conducted by Shim et al. (2018) that was performed in detecting hepatic metastases, showed that 18F-FDG-PET/CT yielded 96% sensitivity and 75% specificity, whilst CECT showed 88% sensitivity and 25% specificity. 18F-FDG-PET/CT and CECT were concordant in 102 out of 131 patients (78%).

CONCLUSION

PET/CT proved to be essential component in the diagnosis, staging, monitoring response to therapy and restaging patients with breast cancer besides better loco-regional metastasis detection, FDG-PET-CT was generally more sensitive in the detection of distant metastases than conventional imaging, and more accurate method of determining recurrence of the disease. One exception was the detection of sclerotic bone metastases as these lesions were often not metabolically active enough to be detected by FDG-PET.

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دور FDG PET / CT في تقييم سرطان الثدي النقيلي

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خلفيـــة البحـــث: ســـرطان الثـــدي هـــو الســـرطان الأكثـــر شـــيوعا والســـبب الرئيســـي للوفـــاة بالســـرطان بـــين الإنـــاث، وهـــو مـــا يمثـــل 23٪ مـــن إجمـــالي حـــالات الســـرطان، و 14٪ مـــن وفيـــات السرطان.

الهـدف مـن البحـث: تقيـيم دور (FDG PET / CT) فـي الكشـف المبكر عن ورم خبيث لسرطان الثدي.

المرضـــى وطـــرق البحـــث: الدراســـة الحاليـــة هـــي دراســـة قائمـــة علـــى الملاحظـــة. أجريـــت الدراســـة فـــي مستشـــفى مصـــطفى كامـــل العســـكري فـــى الفتـــرة مـــابين ينـــاير 2021 حتـــى يوليـــو 2021. تـــألف مجتمـــع الدراســـة مـــن 50 مريضـــة بســـرطان الثـــدي كـــان مـــن المقـــرر أن يخضـــعن للتحقيـــق للاشـــتباه فـــي تكـــرار الإصـــابة بســـرطان الثـــدي أو ورم خبيـــث خاصـــةً المرضـــى الـــذين تـــم تطهيـــرهم ســـابقًا مـــن سرطان الثدي.

نتـــائج البحـــث: يعـــد FDG PET / CT مفيـــدًا جـــدًا فـــي اســـتعادة الســـرطان لـــدى المرضـــى الـــذين يعـــانون مـــن تكـــرار ســـرطان الثـــدي الموثـــق أو فـــي أولئـــك الـــذين يشـــتبه فـــي تكـــرار الإصـــابة بســـرطان الثـــدي وهـــو أكثـــر فعاليـــة مـــن التصـــوير المقطعـــي بالإصـــدار

البوزيتروني وحده وطرق التصوير التقليدية. من بين 50 مريضًا تمت إحالتهم إلى المرحلة الأولية باستخدام PET / CT، عاد 8 مرضى فقط (16٪) مرة أخرى للترميم بعد تلقي العلاج الكيميائي المساعد الجديد و / أو العلاج الإشعاعي. أظهر 4 PET / CT مرضى (50٪) في دورة ثابتة و 4 مرضى في المرحلة السفلى (50%).

الاستنتاج: ثبت أن استخدام الحد الأقصى لقيمة الامتصاص القياسية (SUVmax) أكثر فعالية في إعادة إجراء الدراسات بعد أن يكون العلاج المساعد الجديد أكثر ارتباطًا بالنشاط الوظيفي لخلايا الورم المتبقية بدلاً من حجم الورم الذي يمكن أن يكون فيه انحدار الورم ملثمين عن طريق تكوين النسيج الندبي الصفاقي وذمة. يوفر PET / CT معلومات حول العدوانية البيولوجية للورم والتشخيص.

الكلمات الدالة: التصوير المقطعي بالإصدار البوزيتروني، التصوير المقطعي المحوسب.