Review Article, PET/CT.

Additional Role 18F-FDG PET/CT in Detection of Ovarian Recurrence or Metastatic Lesions.

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INTRODUCTION:

A number of approaches are used to detect recurrent disease after initial surgery and chemotherapy for ovarian cancer. these approaches include clinical examination, determination of serum CA-125 levels, and imaging using CT, MRI, and PET/CT used to evaluate ovarian cancer recurrence. Recurrent ovarian malignancy may manifest as pelvic masses, peritoneal seeding, malignant ascites, and nodal recurrence[(1)].

Tumor marker CA-125 remains the most important surrogate of follow up of ovarian cancer. However, in the absence of clinical or radiologic recurrence the significance of raising CA-125 level has to be determined. In some patients with disease relapse, CA-125 may be of normal level [(2)]. Pelvic recurrence may involve the vaginal stump, parametria, urinary bladder, and/or bowel adjacent to the surgical bed. peritoneal seeding presents as nodules on the peritoneal surface, most commonly around the liver or cul-de-sac, and mesenteric infiltration. Unusual manifestations include metastasis in the extrahepatic abdominal solid organs, bone metastasis, and an abdominal wall lesions involving subcutaneous fat or muscle [(3,4)].

CT in recurrent ovarian cancer: Patients treated for ovarian cancer can be followed up with serial CT of the abdomen and pelvis. CT of the chest is generally not indicated, unless no sites of recurrence are detected on CT in the presence of elevated tumor marker [(5)].

Keywords; PET/CT & CA-125 & MRI & Ovarian Cancer.

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MRI in recurrent ovarian cancer:

An abnormal MRI examination result with a normal CA-125 value is a strong indication of residual or recurrent tumor with high accuracy, positive predictive value [6]. MRI may be superior to CT in the assessment of pelvic wall extension because of its high soft tissue contrast and multiplanar capability. Preoperative imaging is essential in patients considered for potential secondary cytoreductive surgery. So that the presence of tumor elsewhere and any indicators of non-resectability can be identified, although invasion of the bladder and rectum by itself is not a contraindication to definitive surgical therapy [7].

PET/CT in Recurrent Ovarian Cancer: The sensitivity and specificity for FDG-PET/CT were 100 % and 92.5 %, respectively as reported by ***Nam et al.*** [8]. This was higher than all other imaging modalities including US, CT, MRI, and FDG-PET alone in 50 consecutive patients a sensitivity, specificity, and accuracy of 87, 100, and 92 %, respectively, compared with 90, 61, and 89 %, respectively, for TVUS. The authors concluded that FDG-PET/CT provides additional information to TVUS for differentiating benign from malignant pelvic lesions as well as to CT for the staging of ovarian cancer patients.

These findings were further supported by a prospective study of 133 women with suspected ovarian cancer**.** Ovarian cancer shows variable levels of increased FDG uptake depending on the cellular composition. Abdominal or pelvic masses containing large cystic components as well as mucinous tumors will often not be metabolically active. False negative results are also seen in borderline ovarian tumor and cystadenocarcinoma of the ovary [9]**.** Generally false-positive findings in the abdomen and pelvis are rare, early studies showed that in patients with pelvic masses a number of benign conditions can cause increased FDG uptake. These include benign cystadenomas, endometriosis, and inflammatory process [9]**.** Increased FDG uptake in normal ovaries is found in premenopausal women; this is related to the time point of ovulation. Two studies reported increased FDG uptake in the ovary and uterine endometrium in the late follicular and early luteal phases of the menstrual cycle**.** In order to reduce errors in interpretation, specific emphasis needs to be directed towards a good technique when undertaking pelvic PET/CT imaging. Ideally, the bladder should be empty to avoid artifacts on PET images from a high concentration of radioactivity in the bladder [10].

It is suggested that the patient is scanned in a caudal-to-cranial direction, thus imaging the pelvis at the beginning of the study. The CT portion of PET/CT is often helpful to identify bladder diverticula and focal retained activity in ureters. Pelvic imaging can be improved by intravenous injection of furosemide (20 – 40 mg) to reduce tracer retention in the urinary system.

The CT portion of PET/CT is also helpful in identifying normal physiologic activity in bowel, endometrium, and blood vessels. Bowel preparation can be performed with oral hydration as well and some groups recommend the use of oral contrast [(11)]. FDG-PET/CT can result in a stage migration in a significant number of patients. Out of 66 ovarian cancer patients, 64 % were initially stage III and 2 were stage IV. However, after PET/CT, 51 % were restaged as stage III and 41 % as stage IV [(12)].

In 2001, a study in 24 women reported a diagnostic accuracy of 79.2 % using FDG-PET for detecting recurrent ovarian cancer.The accuracy increased to 94.4 % when combined with conventional imaging modalities. The findings were confirmed by several further studies [(13, 14)].

Various studies have demonstrated the impact of combined functional and structural imaging on the clinical management plan in many patients with suspected recurrent ovarian cancer. In 56 women, the addition of FDG-PET to CT altered the known disease distribution in 61 % of scans leading to a change in management in 57 % of patients [(15)].

A study of 51 patients found that combined FDG-PET/CT provided a statistically significant improvement in accuracy from 83 to 92 %, in the diagnosis of ovarian cancer recurrence, compared to CT alone.The co-registered functional and anatomical information from PET/CT is particularly helpful in the abdomen and pelvis. Another study found a sensitivity of 94.5 % and a specificity of 100 % for FDG-PET/CT in the detection of ovarian cancer recurrence. PET/CT may have the greatest utility in the situation in which CA-125 levels are rising and conventional imaging studies show negative or equivocal findings [(16)]. In addition, FDG-PET/CT was also found to be valuable imaging technique in the evaluation of suspected recurrent ovarian cancer in the setting of normal CA-125 levels.

A study from MD Anderson Cancer Center concluded that FDG-PET/CT is capable of detecting ovarian cancer recurrence in symptomatic patients with normal CA-125 levels and in this setting has slightly better sensitivity than contrast-enhanced CT, thirty-one percent of patients with no indication of malignancy on CT had evidence of disease on FDG-PET/CT which was confirmed on histology. In a direct comparison with second-look laparotomy in 31 women, the lesion-based sensitivity was 45.3 % for FDGPET alone and increased to 58.2 % for FDG-PET/CT [(17)]. Egyptian study of 54 patients with suspected ovarian recurrence and normal tumor marker were evaluated with PET/CT with CE-CT scan in the same study. PET/CT Vs. CE-CT showed sensitivity, specificity and accuracy of 92% Vs. 73 %, 90 % Vs. 55 % and 91 % Vs. 63 % respectively with significant results for PET/CT [(18)]. In 43 patients, FDG-PET/CT had a sensitivity and specificity of 88.4 % and 88.2 %, respectively, for detection of recurrent ovarian cancer using histology and clinical follow-up. More specifically a slightly lower sensitivity of 80.9 % for pelvic disease and 93.5 % for extrapelvic disease; specificity was 93.7 % for both [(18)].

A recent meta-analysis compared FDG-PET/CT, MRI, and tumor marker CA-125 for the detection of recurrent disease. PET/CT (sensitivity, 79 %; specificity, 88 %) performed better than CT (sensitivity, 79 %; specificity, 84 %) or MRI (sensitivity, 75 %; specificity, 78%). The authors concluded that FDG-PET alone appeared to be useful for the diagnosis of recurrence when CA-125 levels are rising and conventional imaging (CT or MR) is inconclusive or negative [(19)]. A patient with pre sacral lesions representing regional neoplastic recurrence is seen in ***figure (1).***

PET/CT in detection of metastatic ovarian cancer:

Lymph Node Metastases: The presence of metastatic lymph nodes is important prognostic factor for patients with ovarian cancer. Recognizing the precise location of metastatic nodes is therefore crucial for selecting appropriate treatment. A recent metaanalysis compared the diagnostic performances of CT, MRI, and PET or PET/CT for detection of metastatic lymph nodes in patients with ovarian cancer. Eighteen eligible studies were included, with a total of 882 patients.

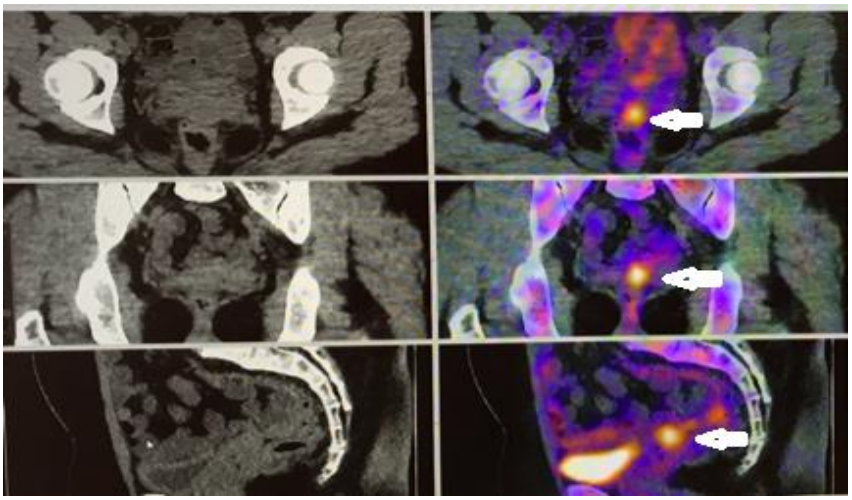

Figure (1): 63-Yrs lady referred to Maadi Armed Hospital with ovarian cancer underwent panhysterectomy and received 6 cycles of C/TH.CT abdomen and pelvis reported well-defined cystic areas in pre-sacral region measuring18 mm and 13 mm in diameter, CA-125 level was 3 folds reference range. PET/CT revealed metabolically active pre sacral lesions, representing regional neoplastic recurrence

FDG-PET or PET/CT was more accurate with a sensitivity of 73.2 % and a specificity of 96.7 % than CT (sensitivity, 42.6 %; specificity, 95.0 %) or MRI (sensitivity, 54.7 %; specificity, 88.3 %) [19]. Lymphatic dissemination to the pelvic and para-aortic lymph nodes is common, particularly in patients with advanced disease.Spread of disease through the lymphatic channels of the retroperitoneal lymph nodes and diaphragm may lead to dissemination into the supraclavicular or superior mediastinal lymph nodes and pleural space, or rarely, the internal mammary lymph nodes [20]**.** Lymph node metastasis is present in 10–20 % of patients with presumed early-stage ovarian cancer, and it is present in 40–70 % of patients with advanced-stage disease. Because PET/CT has a low negative predictive value in the pelvis and skip metastases may occur in as many as 60 % of patients, the lack of hypermetabolism in pelvic nodes does not preclude the presence of pathologic para-aortic nodes [21]**.** In a study of 30 women with advanced-stage (IIC–IV) epithelial ovarian cancer, pretreatment FDG-PET/CT was performed and detected supradiaphragmatic lymph node metastases (LNM) in one or more locations in 67 % (20/30) of patients, whereas conventional CT found LNM only in 33 % (10/30) of patients.

Fourteen patients had parasternal, 14 cardiophrenic, 8 other mediastinal, 6 axillary, and 1 subclavian LNM. The patients with supradiaphragmatic LNM, higher CA-125 levels, and more frequent peritoneal carcinomatosis ($p < 0.03$) compared to patients without supradiaphragmatic LNM in preoperative FDG-PET/CT. These findings suggest that the route of epithelial ovarian cancer cells from the peritoneal cavity to the lymphatic system permeates the diaphragm mainly to the cardiophrenic and continues to the parasternal lymph nodes [22].

Peritoneal Metastases:

Tumor cells tend to follow the circulatory path of peritoneal fluid, implanting in the pouch of Douglas, paracolic gutters, small bowel mesentery, ileocecal junction, diaphragmatic surface – particularly the right subphrenic space along the convexity of the liver – and the hepatorenal fossa. The hepatorenal fossa harbors malignant implants by communicating with the right subphrenic space and the right paracolic gutter. In almost 50 % of patients, gravitational accumulation of tumor cells in the mesenteric recesses leads to seeding of malignant cells on small bowel serosal surfaces and in the ileocecal junction [23]. Other sites of involvement include the sigmoid mesocolon, a result of pooling along its superior border, and the right paracolic gutter, a result of cephalic flow. The right hemithorax also may be involved through its communication with the right subphrenic space. Omental thickening and nodularity with diffuse FDG uptake are indicative of omental involvement. However, PET/CT is limited in detecting small-volume disease (lesions < 5–7 mm) and miliary or diffuse peritoneal involvement, even if the disease process is evident on CT, umbilical metastases (Sister Mary Joseph nodules) are rare and associated with widespread intra-abdominal disease, particularly in patients with serous papillary cystadenocarcinoma [24,25]. Laparoscopy is the standard diagnostic tool for the assessment of intraperitoneal infiltration but it is invasive and requires general anesthesia. The right subphrenic region, the greater omentum, and the pouch of Douglas are the most common locations for peritoneal disease from ovarian carcinoma. In 40 patients with a high suspicion of ovarian cancer, the findings in 9 quadrants of the abdominal-pelvic area (total 346 evaluable quadrants) for FDG-PET/CT and laparoscopy were compared, tumor deposits were found in 308 quadrants and 38 quadrants were free of disease.

PET/CT demonstrated true negative results in 26/346 quadrants (7.5 %) and positive results in 243/346 quadrants (70.2%) [(26)]. False-positive and negative PET/CT results were found in 12/346 and 65/346 quadrants, respectively. False-positive PET/CT findings were present evenly in all quadrants. False-negative PET/CT findings were noted in 31/109 (28.4 %) upper abdominal quadrants (epigastrium and diaphragmatic areas). A high rate of false-negative results was found in lesions <5 mm. The overall sensitivity and specificity for FDG-PET/CT was 78.9 and 68.4%, respectively. The authors concluded that PET/CT may be a useful tool for pre-staging of ovarian cancer. From these results it appears that PET/CT is particularly useful in advanced-stage disease but might be best used in conjunction with laparoscopy if identification of small-volume disease is required. At PET/CT, peritoneal implants appear as nodular soft tissue masses, often with a variable degree of increased metabolic activity. Impaired lymphatic drainage of the peritoneum, a result of blocked diaphragmatic lymphatics, plays an important role in the development of ascites [(26)]**.** 136 studies of Egyptian ovarian cancer were evaluated with 75 (55 %) had peritoneal metastasis were as 61 (45 %) were free based on final diagnosis 18 F-FDG PET/CT and CE-CT had sensitivity and Specifity and accuracy of 96 % Vs. 69 %, 100 % Vs 85 % and 98 % Vs. 76 % with significance difference for PET/CT [(27)].A case of a patient with hyper metabolic peritoneal nodules from NEMROCK Center, Cairo University is seen in ***figure (2).***

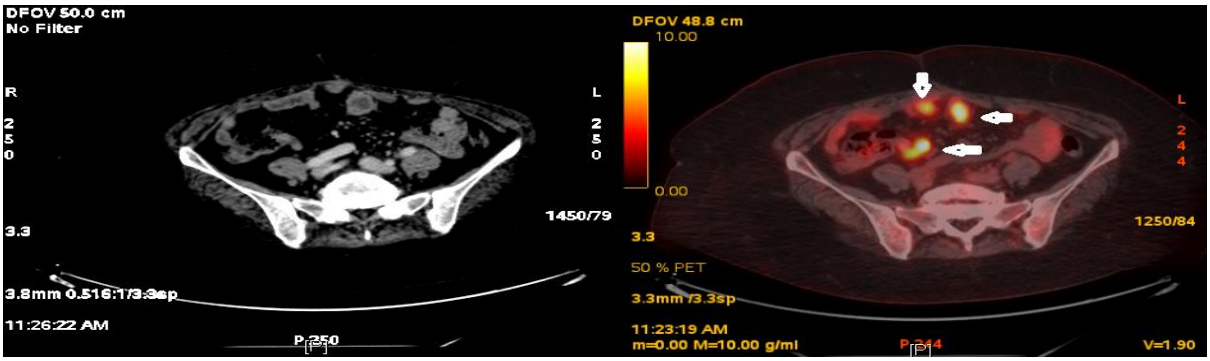

Figure (2): A 55 Yrs lady referred to NEMROCK Center, Cairo University with ovarian cancer underwent panhysterectomy& omentectomy followed by chemotherapy. CA-125 level was elevated 2 folds above normal reference range. CT chest, abdomen & pelvis revealed suspected abdominal peritoneal nodule. PET/CT for status evaluation and revealed multiple hyper metabolic peritoneal nodules (SUV max = 7).

Other metastatic sites: Hematogeneous dissemination of disease at the time of diagnosis is uncommon; only 2–3 % of patients are found to have pulmonary or hepatic involvement. Pleural effusion is the most common finding of stage IV disease, followed by parenchymal liver metastases. Brain metastases are extremely rare. PET/CT has high sensitivity for the depiction of distant metastases, and it may be useful to help determine those patients who are eligible for secondary surgical cytoreduction [28].

CONCLUSION:

18F FDG PET/CT is superior to CT and MRI in diagnosis of viable recurrent and/or metastatic lesions especially peritoneal metastases in patients with rising or normal tumor marker.

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