Review Article

Role of Positron Emission Tomography/Computed Tomography in Epithelial Ovarian Cancer

Abstract

Ovarian cancer (OC) is the most lethal gynecological malignancy with majority of cases diagnosed in advanced stages and associated with high morbidity and mortality. Positron emission tomography/computed tomography (PET/CT) has emerged as an integral part of the management of several nongynecological cancers. We used PubMed search engine using MeSH words "ovarian cancer" and "PET/CT" and reviewed the current status of PET/CT in epithelial OC. Its application related to ovarian tumor including adnexal mass evaluation, baseline staging, as a triaging tool for upfront surgery or neoadjuvant chemotherapy, for response assessment and prognostication, and for relapse detection and treatment planning has been highlighted. we highlight the current guidelines and newer upcoming PET modalities and radiotracers.

Keywords: *Epithelial ovarian cancer, positron emission tomography/computed tomography, recurrent ovarian cancer*

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Introduction

Ovarian cancer (OC) accounted for 313,959 new cases and 207,252 deaths worldwide in 2020 as per GLOBOCAN 2020.[1,2] Epithelial ovarian cancer (EOC) accounts for a majority of malignant ovarian tumors and is diagnosed in advanced stages in two-third of cases. Median age for EOC is 63 years in developed countries but is a decade less in developing/low–middle-income countries.

There have been drastic developments in the past 50 years in the field of imaging, with tools such as ultrasound, Doppler, computed tomography (CT), magnetic resonance imaging (MRI), and F^{18} positron emission tomography (PET) to aid in the evaluation of adnexal masses and to detect malignancies at an early stage to improve patient outcome. However, in spite of these advances, OC has remained an enigmatic disease presenting at an advanced stage with nonspecific symptoms, and trials have also failed to show any benefit of routine screening for OC in average-risk population.[3,4]

Principles of Positron Emission Tomography/Computed Tomography Imaging

PET is a noninvasive nuclear medicine imaging technique, which enables clinicians to view and assess the human body from a functional and metabolic perspective. Its application has evolved from primarily a research tool in the 1990s to an inseparable part of clinical medicine today.

PET imaging involves injecting molecularly targeted radiopharmaceuticals called PET tracers followed by the detection of gamma rays by the PET scanner, which is converted into an image signal. Integrated PET/CT scanners acquire the CT image followed by PET image, which is fused for anatomical localization and attenuation correction. The most commonly and only FDA-approved PET tracer in clinical practice is ^{18}F fluorodeoxyglucose (FDG), which is based on the principle of increased aerobic glycolysis in tumor cells called Warburg effect.[5]

Addition of intravenous (IV) contrast material to PET/CT protocol is beneficial in surgical planning by better local tumor staging and its relation to adjacent vessels. Furthermore, it has shown superior

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delineation of hepatic lesions and pyeloureteral system, which may not be well visualized with PET/CT alone. IV contrast works on the principle of increasing the attenuation difference between normal and abnormal tissues, which also leads to artifacts when these examinations are used for attenuation correction at PET/CT. Oral contrast agents aid in the evaluation of false-positive gastrointestinal tract FDG uptake by increasing the conspicuity of luminal, mural, and extraluminal disease by bowel distension. Low-density and neutral contrast agents can be useful in the evaluation of mucosal and mural disease and complement IV contrast enhancement. However, like with IV contrast, oral contrast leads to attenuation artifacts and possibly risk of increased FDG uptake by bowel due to increased peristalsis.[6]

Parameters for Positron Emission Tomography Evaluation

Standardized uptake value

Standardized uptake value (SUV) is a commonly used parameter for semiquantitative analysis of PET images and is calculated either pixel-wise or over a region of interest (ROI) as the ratio of tissue radioactivity concentration and the injected dose adjusted by body weight.

a. The maximum SUV (SUV max) is obtained for a 1-pixel ROI corresponding to the maximum pixel value in the tumor. This is a frequently used parameter because it provides an observer-independent measurement. However, it does not necessarily represent the total tumor activity for the whole tumor mass because a single pixel may not be representative of nonhomogeneous overall tumor uptake.
b. Mean SUV (SUV mean) is the mean value of metabolic activity in a chosen region
c. Peak SUV (SUV peak) is the average value within a small, fixed-size ROI in the tumor. It may be more suitable for representing whole tumor activity, but it is subjective and prone to observer variability.[7]

Volume-based positron emission tomography parameters

Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) measure metabolic activity in an entire tumor mass. MTV is a volumetric measurement of tumor cells with high glycolytic activity, while TLG is defined as the product of the SUV and the lesion volume. These are not used in routine clinical practice as the measurements are cumbersome and currently are used in the research setting.

Evaluation of Adnexal Masses with Positron Emission Tomography/Computed Tomography

First step for the evaluation of an adnexal mass is a pelvic ultrasonographic examination. In case of indeterminate lesions, MRI is used as a troubleshooter for the characterization of the masses. Ovaries have a physiologically increased FDG uptake in premenopausal women, thereby limiting its value in routine clinical practice. Studies have explored the utility of PET/CT to differentiate:

1. Malignant ovarian tumors from benign ovarian tumors: Castellucci *et al*. compared PET/CT with transvaginal ultrasound (TVUS) using an SUV max cutoff of >3.0. PET/CT had 100% specificity compared to 61% specificity with TVUS for the detection of malignant ovarian tumor.[8] Karantanis *et al*. found the average SUV max for malignant ovarian tumors of 7.6, which was unrelated to the grade or histology.[9] However, Tanizaki *et al*. demonstrated a lower FDG uptake value in clear cell or mucinous histologies compared to serous or endometrioid histologies, suggesting that SUV max may vary depending on the tumor histological subtypes.[10] High SUV max value on PET/CT is highly specific for malignant ovarian tumors barring a few exceptions such as clear cell and mucinous carcinomas
2. Borderline ovarian tumours (BOT) from malignant ovarian tumours: Kim *et al*. used SUV max cutoff of 3.7 to distinguish BOT from stage I OC with a sensitivity of 83.3%, specificity of 85.7%, and area under the curve (AUC) 0.893.[11]

While there is evidence of the utility of PET/CT in adnexal evaluation, the cost-effectiveness is unproven and pelvic ultrasonography remains the most commonly used imaging modality for this indication.

Positron Emission Tomography Scan for Staging of Ovarian Cancer

PET/CT is an effective imaging modality for staging EOC, with 75.5%–83.3% sensitivity, 68.4%–99.4% specificity, 87.5%–95.3% positive predictive value, and 96.5%–98.6% negative predictive value.[12]

Concordance with surgical stage

In a study by Nam *et al*., radiological staging by PET/CT was concordant with surgical staging in 78% of patients.[13] Pireandrea *et al*. used PET/CT as a presurgical staging tool followed by laparoscopic evaluation of abdomen for extent of disease. The authors concluded that PET/CT showed an adequate correlation between SUV max values and laparoscopy findings of lesions >5 mm but a high rate of false-negative results in lesions <5 mm such as in carcinomatosis. PET/CT should be used carefully in early-stage disease, with low risk of peritoneal infiltration, because of high rate of false-positive results, to avoid unnecessary therapy procedures.[14]

Detection of lymph node metastasis and extra-abdominal spread

PET/CT is a more accurate tool (sensitivity 73.2%; specificity 96.7%) than CT/MRI for the detection of lymph

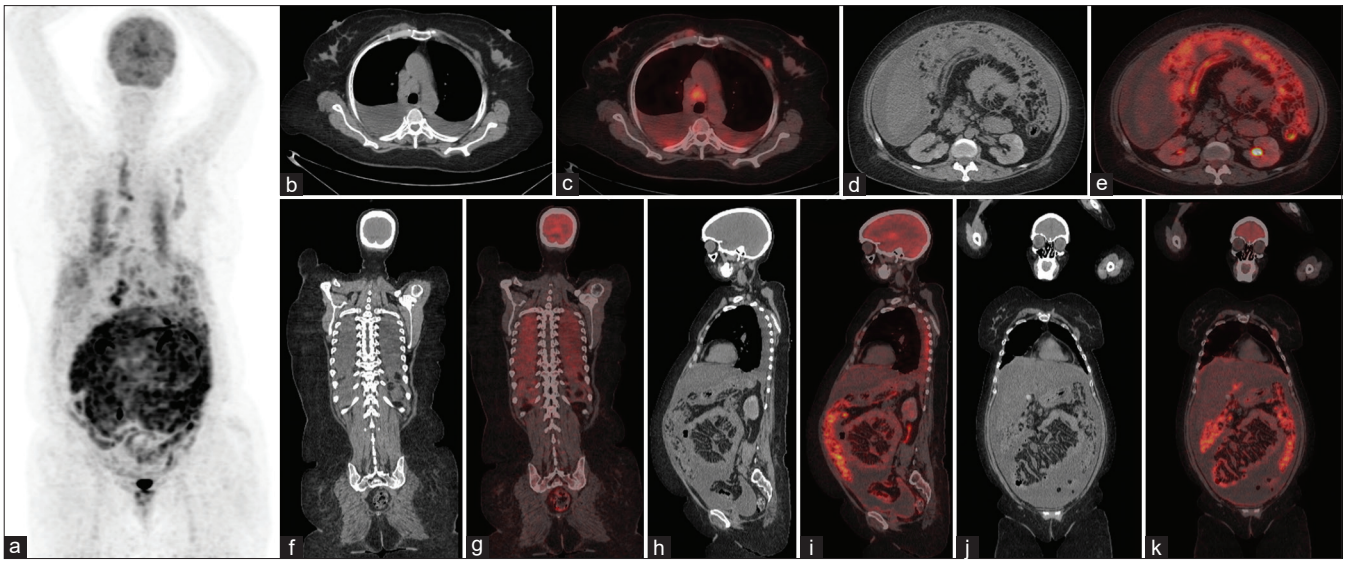

Figure 1: For staging. A 50-year-old female presented with complaints of abdominal distension. Serum CA 125 levels were 4755 U/ml, and omental biopsy showed features of metastatic adenocarcinoma, suspicious of carcinoma ovary. PET-CT for initial baseline staging showed lymph node metastasis and extra-abdominal spread. MIP images (a) shows diffusely increased tracer uptake in the abdominal cavity and also the bilateral hemithorax. Transaxial CT (b and d) and fused PET-CT (c and e) images showed bilateral pleural effusion, enlarged mediastinal lymph nodes, moderate-to-gross, ascites and diffuse omental caking with increased FDG uptake. Sagittal (h and i) and coronal (f, g, j, and k) CT and fused PET-CT images demonstrats bilateral pleural effusion, gross abdominal-pelvic ascites, and FDG avid omental caking. The patient was diagnosed as ovarian carcinoma Stage IVB and started on neoadjuvant chemotherapy. PET/CT: Positron emission tomography/computed tomography, FDG: Fluorodeoxyglucose

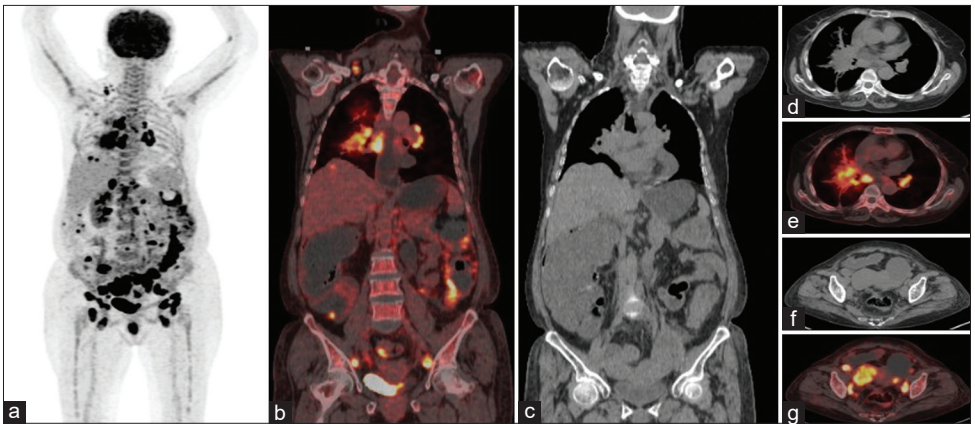

Figure 2: Detection of synchronous malignancies. A 70-year old female patient presented with abdominal swelling for 6 months and enlarged right supraclavicular lymph node; serum CA 125 levels were 1854 U/ml. FNAC from the supraclavicular lymph node was suggestive of a poorly differentiated carcinoma. The patient underwent ^{18}F-FDG PET-CT study; MIP images (a) show multiple foci of increased tracer uptake in the neck, thorax, and the abdomen. Coronal CT and fused PET CT images (b and c) showthe increased tracer uptake in the neck, chest, and abdomen localizing to the right supraclavicular lymph node, right lung mass, and mediastinal lymph nodes and bilateral tubo-ovarian masses. Axial CT (d and f) and fused PET-CT images (e and g) showed metabolically active right perihilar mass images, mediastinal lymph nodes, bilateral solid-cystic lesions in bilateral adnexa along with multiple retroperitoneal lymph nodes and a liver lesion (not shown in the images). The patient was diagnosed as synchronous lung and ovarian carcinoma and planned for neoadjuvant chemotherapy. However, the patient expired prior to starting any treatment. PET/CT: Positron emission tomography/computed tomography, FDG: Fluorodeoxyglucose

node metastasis (LNM).[15] It has been shown to correctly detect unexpected extra-abdominal metastasis compared to CT scan [Figures 1 and 2]. Hynninen *et al*. found PET/CT to be superior to CT for the detection of carcinomatosis in subdiaphragmatic peritoneal surfaces and the bowel mesentery (nonsignificant). However, the sensitivity of PET/CT and CT was poor in certain areas of the peritoneal cavity (64% vs. 27% in the small bowel mesentery and 65% vs. 55% in the right upper abdomen, respectively). They concluded that PET/CT was more effective for the detection of extra-abdominal disease than CT, thereby leading to upstaging of patients in around 31%–41% of patients.[16,17]

Detection of synchronous malignancy

In a prospective study by Dauwen *et al*. in 69 patients suspicious of OC, PET/CT detected another unknown primary tumor in 4.3% of cases.[18]

Preoperative staging by PET/CT shows 70%–80% concordance with surgical staging and should be

interpreted with caution as possibility of false-negative and false-positive findings should be borne in mind [Table 1]. It is highly specific in detecting LNM and extra-abdominal spread of disease, leading to upstaging in 30%–40% of cases, and can detect unsuspected synchronous malignancies.

Role in Ovarian Cancer Treatment Planning: Primary Cytoreductive Surgery or Neoadjuvant Chemotherapy

The gold standard treatment for advanced EOC (AEOC) is primary cytoreductive surgery with no gross residual disease followed by six cycles of platinum-based adjuvant chemotherapy [Figure 3]. In cases where upfront surgery is not feasible due to patient-related or disease-related factors, 3–4 cycles of platinum-based neoadjuvant chemotherapy (NACT) followed by interval cytoreductive surgery and adjuvant chemotherapy has been shown to be noninferior to primary cytoreduction.[19,20]

Several studies have reported on the use of tumor markers and preoperative imaging with CT scan for predicting suboptimal resectability in patients with AEOC.[21] Bristow *et al*. retrospectively reviewed the preoperative CT images of patients with AEOC and correlated them with the surgical findings. They developed a predictive index score based on the site of disease and a score of ≥4 was predictor of suboptimal cytoreduction.[22] However, there is no consensus on accurate prediction for optimal debulking surgery in patients with OC.

Risum *et al*. retrospectively evaluated the role PET/CT in selecting patients with extensive OC for NACT by evaluating predictors of overall survival in patients with stage IIIC/IV disease. They suggested that the PET/CT criteria for NACT should be PET/CT-based stage IV, pleural exudates, and PET-positive large bowel mesentery implants.[23]

The detection of mediastinal nodes on PET/CT has been found to be associated with the higher chance of suboptimal cytoreduction, thereby indicating aggressive tumor biology.[24] Chong *et al*. evaluated the ability of PET/CT to predict suboptimal cytoreduction. The presence of hypermetabolic lesions in the central, right upper, and left upper regions was predictive of suboptimal cytoreduction.[25] Alessi *et al*. evaluated 23 patients with OC with PET/CT, and the sensitivity, specificity, and accuracy of PET/CT to characterize ovarian masses were 91%, 67%, and 86%, respectively. Among the 21 PET/CT-positive EOC, the factors limiting optimal cytoreduction were found in 29% of cases which included hepatic hilum infiltration and root of mesentery involvement.[26]

Gu *et al*. used preoperative PET score to noninvasively reflect tumor burden and predict complete resection at surgery in AEOC patients.[27]

Risum *et al*. prospectively evaluated 179 patients with risk of malignancy index >150 with PET/CT. Using univariate analysis, predictors of incomplete cytoreduction were large bowel mesentery implants (LBMIs) ($P < 0.003$), pleural effusion ($P < 0.009$), ascites ($P < 0.009$), and peritoneal carcinomatosis ($P < 0.01$). Using multivariate analysis, LBMI was the only independent predictor of incomplete cytoreduction ($P = 0.004$). The authors concluded that PET/CT may be used as a supplementary image modality before surgery.[28]

Shim *et al*. prospectively evaluated 343 patients with advanced ovarian cancer (AOC) with PET/CT before primary cytoreduction. Surgical aggressiveness

Table 1: Inherent errors of PET/CT imaging

Potential false positive	Potential false negative
Phsiologically increased FDG uptake	Tumour histology
Ovaries: During ovulation	Mucinous
Endometrium: During menstruation	Clear cell
	Low grade
	Necrotic areas
Benign lesions	Tumour size
Uterine fibroids	Small volume peritoneal disease (<5 mm)
Endometriomas	Small lymph nodes
Urine has increased FDG uptake	Masking of disease by adjacent structures
Focal ureteric activity or focal bladder activity	Physiological bowel activity may mask peritoneal disease, serosal disease and small lymph nodes
Vesicovaginal fistula can limit disease evaluation	Perivesical disease masked by urine with high uptake in bladder

FDG: Fluorodeoxyglucose

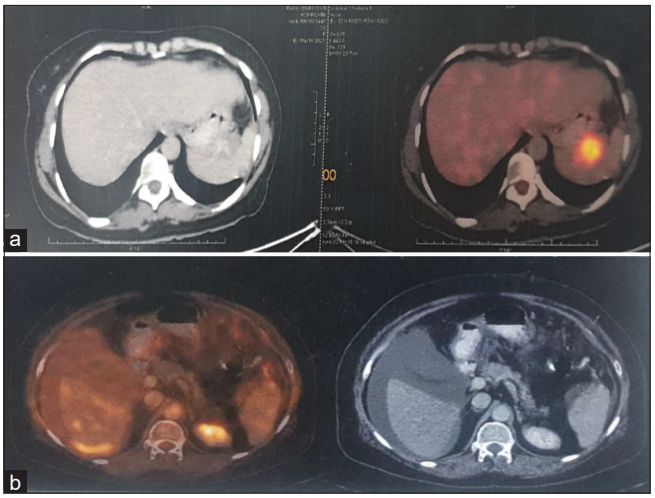

Figure 3: For upper abdomen disease assessment. (a) CT and PET/CT images showing perisplenic tumor deposit. (b) CT and PET/CT images showing right subdiaphragmatic deposit. PET/CT: Positron emission tomography/computed tomography

index (number of high complex surgeries/total number of surgeries) and five PET/CT features (diaphragmatic deposit, ascites, peritoneal carcinomatosis, small bowel mesentery implants, and tumor SUV max uptake ratio) were independent predictors of suboptimal cytoreduction. They developed a nomogram which demonstrated good predictive accuracy (concordance index = 0.881; 95% confidence interval = 0.838–0.923) for suboptimal cytoreduction.[29]

PET/CT features predictive of suboptimal cytoreduction include:

1. Extra abdominal spread (including mediastinal nodes)
2. Diaphragmatic deposits
3. Ascites
4. Pleural exudates
5. Peritoneal carcinomatosis
6. Large bowel mesenteric implants
7. Small bowel mesenteric implants
8. Hepatic hilar infiltration
9. Root of mesentery involvement.

Role in Ovarian Cancer Treatment Prognosis and Response Evaluation

Maximum standard uptake value reduction

Martoni *et al*. prospectively evaluated 42 patients with AOC undergoing NACT with PET/CT at baseline and after 3 cycles and after 6 cycles of chemotherapy and found the median SUV max values of 11, 3, and <2, respectively. Normalization of SUV max after three courses of NACT could predict prognosis after treatment. The authors suggested that patients who achieved good metabolic response (△SUV max = 100%), benefit from completing 6 cycles of NACT before undergoing definitive surgery, whereas those with only a partial metabolic response (△SUV max <100%) should have interval cytoreduction after 3 cycles to remove potentially chemoresistant tumor.[30]

Vallius *et al*. studied 26 patients with AOC treated with NACT. The median omental △SUV max during NACT was −64% (range −16% to −84%), and it was associated with histopathological response. An SUV max decrease of <57% identified histopathological nonresponders, thus concluding that, to obtain a histopathological response in EOC, a substantial metabolic response on PET/CT is necessary.[31]

Chung *et al*. found a significant association with progression free survival (PFS) between metabolic responders and nonresponders and concluded that early assessment of metabolic response with PET/CT after one cycle of NACT can be useful to predict response to chemotherapy before interval cytoreduction in patients with AOC.[32]

Metabolic tumor volume reduction

Vallius *et al*. prospectively evaluated 29 patients with AOC with PET/CT pre-NACT and post-NACT. MTV reduction <85% was associated with progressive disease/stable disease (PD/SD) in patients (sensitivity 70%, specificity 78%, AUC 0.79), which concluded that such patients might be candidates for second-line chemotherapy and clinical trials, instead of interval debulking surgery.[33]

Total lesion glycolysis

Liao *et al*. retrospectively reviewed 47 patients of AOC who underwent PET/CT after cytoreductive surgery and reported that high whole-body TLG was associated with poor prognosis.[34]

Gallicchio *et al*. compared all the three metabolic parameters and reported that quantitative assessment of MTV was most useful for the stratification of patients.[35]

PET/CT can be used as tool to predict the histopathological response among patients with AEOC undergoing NACT by comparing the SUV parameters in the pre-NACT and post-NACT PET/CT imaging [Figure 4]. However, currently, there is no universal cutoff and more research is needed on this subject.

Role in Recurrent Ovarian Cancer

Patients with AEOC recur in two-third of cases after completion of primary treatment. Early identification of relapse is critical for optimal management of patients.

A meta-analysis of 34 studies analyzed the diagnostic accuracy of CA 125, PET alone, PET/CT, CT, and MRI to detect recurrent OC. The authors reported a pooled sensitivity of 69% for CA 125, 79% for CT, 75% for MRI, and 91% for PET/CT, as well as pooled specificity of 93% for CA 125, 84% for CT, 78% for MRI, and 88% for PET/CT. The authors concluded that PET/CT might be a useful supplement to current surveillance techniques, particularly for those patients with an increasing CA 125 level and negative CT or MRI.[36]

For early detection of relapse positron emission tomography/computed tomography versus computed tomography and CA 125

PET/CT has been shown to outperform traditional radiological methods of detection of relapse, i.e., CT scan, in various studies [Figure 5].

Tawakol *et al*. showed that PET/CT has a sensitivity of 96% and a specificity of 100% for detecting peritoneal metastasis.[37] Bhosale *et al*. evaluated 66 patients of AOC on follow-up, and they were able to detect recurrence in 31% of patients with PET/CT in whom the CA 125 values and CT imaging were normal.[38]

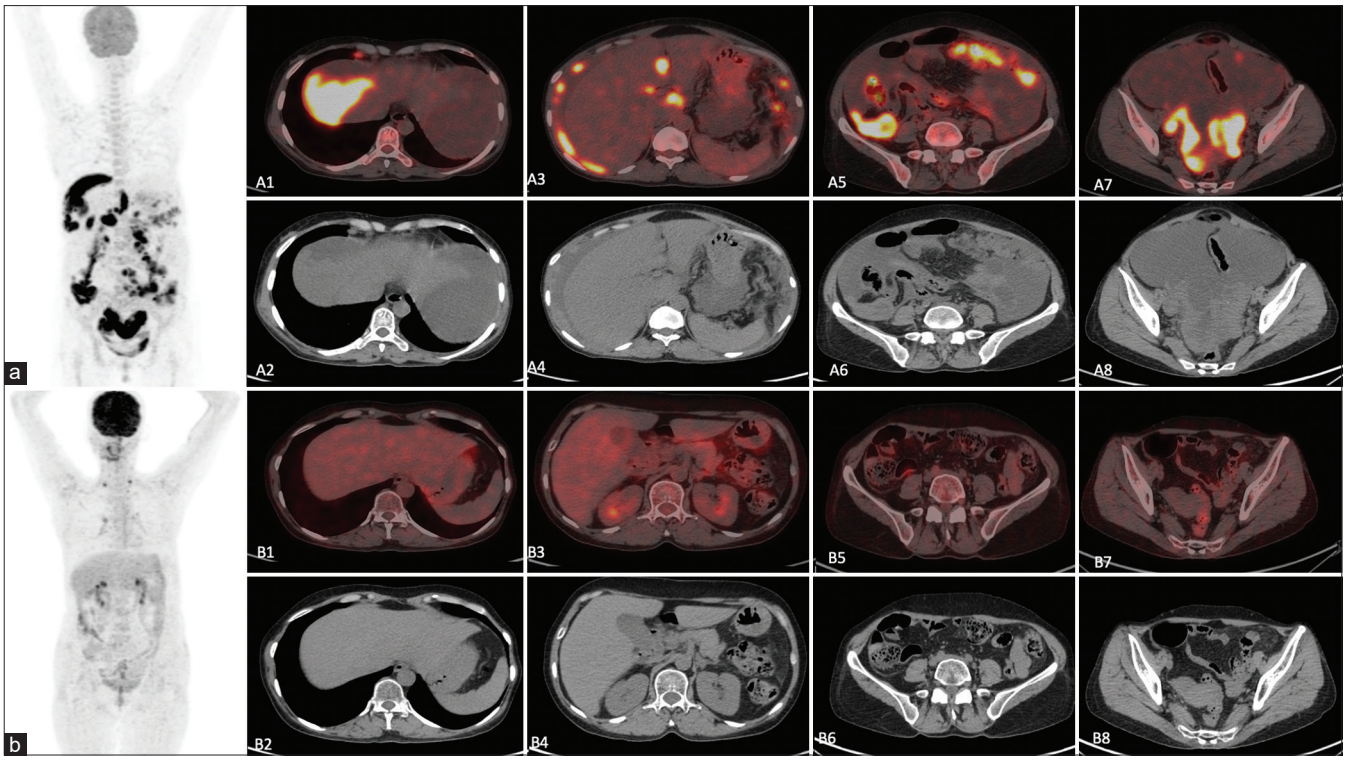

Figure 4: For NACT response evaluation. A 46-year-old female presented with complaints of pain abdomen, abdominal distension, loss of appetite, and nausea and vomiting for 3 months; Serum CA 125 levels were 920 U/ml. A baseline 18F-FDG PET-CT study was ordered; MIP images (a) and transaxial fused PET-CT (a1, a3, a5, and a7) and CT images (a2, a4, a6, and a8) showed hypermetabolic solid-cystic masses involving bilateral adnexa along with multiple peritoneal and serosal deposits, moderate-to-gross ascites, omental caking, and anterior diaphragmatic lymph nodes. Biopsy from the adnexal mass showed a high-grade serous carcinoma. The patient received four cycles of NACT followed by response evaluation with 18F-FDG PET-CT scan. The MIP images (b) and transaxial fused PET-CT (b1, b3, b5 and b7) and CT images (b2, b4, b6, and b8) showed no metabolically active residual disease in the body with resolution of previously noted bilateral adnexal masses, peritoneal, omental and serosal deposits, omental caking, abdominal and pelvic ascites, and right anterior diaphragmatic lymph nodes, suggestive of a complete metabolic response. The patient's serum CA 125 levels at the time of the second PET-CT study was 6.9 U/ml (normal <35 U/ml). PET/CT: Positron emission tomography/computed tomography, FDG: Fluorodeoxyglucose, NACT: Neoadjuvant chemotherapy

Ghosh *et al*. evaluated the role of PET-CT scan in the diagnosis of early relapse in patients with EOC who were asymptomatic but had a rising serum CA 125 level. They studied 16 patients with PET/CT and 15/16 had positive PET/CT findings which was subsequently confirmed with fine needle aspiration cytology (FNAC) (9 patients) and follow-up CT scan at 6 months (5 patients). The sensitivity and specificity of PET-CT scan were 100% for early detection of relapse.[39]

Impact of metabolic parameters

Kim *et al*. retrospectively reviewed patients with recurrent OC who had PET/CT imaging and quantitative metabolic parameters were found to correlate with postrelapse survival.[40]

Change of treatment plan based on positron emission tomography/computed tomography

Fulham *et al*. prospectively assessed the impact of PET/CT on the management of patients with suspected recurrent OC. PET/CT was able to detect 168 additional sites of disease in 61 patients (68%) which were not identified by conventional imaging. In 77% of cases, the additional lesions were located below the diaphragm and most were nodal or peritoneal sites, thereby affecting management in 60% of cases (49% high, 11% medium impact).[41]

Positron emission tomography/computed tomography for guiding intensity modulated radiotherapy

Du *et al*. retrospectively compared the treatment plans, tumor response, and survival following PET/CT-guided IMRT (PET/CT-IMRT group) and CT-guided IMRT (CT-IMRT group) among 58 patients with recurrent OC. PET/CT-IMRT in recurrent OC patients improved the delineation of gross tumor volume, reduce the likelihood of geographic misses, and therefore improve the clinical outcome.[42]

PET/CT is a highly sensitive and specific tool to detect early relapses in the setting of normal tumor markers and imaging. It aids in surgical planning by identifying nodal and extra-abdominal extent of disease which is difficult to assess by conventional imaging.

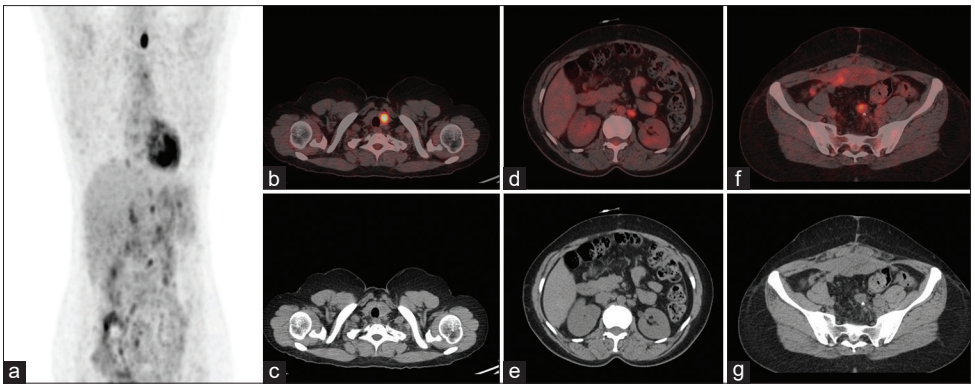

Figure 5: For detection of recurrence. A 36-year-old female with a history of carcinoma ovary Stage IIIC, completed primary treatment 5 years back, presented with rising serum CA 125 levels (patient's serum CA125 levels for 3 months preceding the scan were 46.1 U/ml, 68.1 U/ml, and 250.9 U/ml). 18F-FDG PET-CT study was performed in view of suspected recurrence. MIP image (a) showed few foci of 18F-FDG uptake in the abdomen and another intense focus of tracer uptake in the neck. Transaxial fused PET-CT images (b, d, and f) and CT images (c, e, and g) localized the increased foci of FDG uptake in the abdomen to aortocaval, left renal hilar, and few other retroperitoneal lymph nodes which were diagnostic of recurrent metastatic disease; the focus of increased FDG uptake in the neck was localized to the left lobe of the thyroid gland and an ultrasound-guided FNAC was advised. Upon FNAC and subsequent histopathological examination, the hypermetabolic thyroid nodule was diagnosed as Hürthle cell carcinoma. PET/CT: Positron emission tomography/computed tomography, FDG: Fluorodeoxyglucose

Current Recommendations

NCCN recommendation

a. PET/CT needs to be done for initial workup of patients with EOC for indeterminate lesions only if the results alter management[43]
b. PET/CT can be considered during surveillance of patients with EOC as clinically indicated to detect early recurrences with high specificity.

Good clinical practice recommendations for the use of positron emission tomography/computed tomography in oncology

a. PET/CT is recommended in cases of suspected recurrence of ovarian carcinoma, particularly with elevated serum CA 125[44]
b. FDG-PET/CT can be proposed for the local–regional or whole-body extension assessment of advanced ovarian carcinoma (≥FIGO stage III).

European Association of Nuclear Medicine guidelines

	Level of evidence	Grade of recommendation
Clinical indications for PET/CT in ovarian cancer[45]		
Initial diagnosis and staging in patients presenting with pelvic mass	III	C
Prognostic value	I	B
Treatment planning	IV	C
Therapy assessment	II	B
Relapse detection	I	A

PET/CT: Positron emission tomography/computed tomography

In our opinion, PET/CT is a good modality for early detection of recurrent OC and a select group of patients may benefit from secondary cytoreduction, done early in the timeline of relapse detection.

Positron Emission Tomography Tracers beyond Fluorodeoxyglucose

PET tracers using radioisotopes such as carbon-11, nitrogen-13, oxygen-15, copper-64, gallium-68, and iodine-124 attached to glucose analog, amino acid analog, or thymidine analog are currently under research.

Epithelial ovarian cancer (EOC) expresses estrogen receptors (ERs) in 70% of cases and radiolabeled steroidal estrogen analog (16 αF-18-17 β-estradiol) has been studied as a noninvasive method to quantify ERα expression in multiple metastases throughout the thereby expanding the treatment options.

HER 2 overexpression in OC is associated with poor prognosis and is akin to breast cancer; HER 2-positive tumors are candidates for targeted monoclonal antibody trastuzumab. 89Zr- and 64Cu-labeled antibodies have been developed, with 89Zr-trastuzumab and 64Cu-DOTA-trastuzumab being the two most widely utilized, and have shown promising results in preclinical studies.

Neuroendocrine tumors (NETs) are rare neoplasms characterized by overexpression of somatostatin receptors (SSTRs). SSTRs have been targeted for imaging, most recently with 68Ga for PET imaging (68Ga-DOTA-TOC, 68Ga-DOTATATE, and 68Ga-DOTA-NOC). Most NETs are well differentiated and are not well visualized on FDG-PET requiring 68Ga-DOTA-peptides for accurate assessment.

Fluorothymidine-PET is closely related to cell proliferation and has been found to be more sensitive than CECT in identifying primary tumors and metastasis in OC.

Detection of hypoxia in tumor microenvironment is vital as, under such conditions, tumor cells are resistant to both

chemotherapy and radiotherapy. 18F-fluoromisonidazole is the most widespread tracer used for hypoxia imaging. Others include F^{18} FAZA, F^{18} FETA, Cu-ATSM.

F^{18} Thanatrace is a radiolabeled small molecule poly ADP ribose polymerase inhbitors (PARPi) that has shown to correlate with PARP-1 expression through a receptor-ligand and can be used as potential stratification tool for PARPi therapy.

Positron Emission Tomography/Magnetic Resonance Imaging

PET/MRI is a hybrid imaging modality combining anatomical and metabolic imaging such as PET/CT. A more detailed soft-tissue contrast is provided by MRI along with distant metastasis evaluation by PET. PET/MRI helps in initial characterization, staging, evaluation of advanced disease, and detection of recurrences.

A meta-analysis by Virarkar *et al*. has evaluated PET/MRI for diagnosing gynecological malignancies and shown a pooled sensitivity and specificity of 74.2% and 89.8%, respectively. The authors concluded that PET/MRI is a promising diagnostic method for primary tumors, nodal staging, and recurrence in patients with gynecological malignancies.[46]

At present, routine use of PET/MRI in clinical use is limited by the technically challenging image acquisition with PET/MRI. There is longer duration for image acquisition and difficulty in imaging lungs, abdomen, and upper pelvis due to motion artifacts. Unlike PET/CT, PET/MRI is not based on X-rays and does not provide a direct reference for attenuation correction by the body. To overcome this, Dixon-based technique has been used as a reference for attenuation correction.[47] As of now, lack of widespread availability of PET/MRI and limited evidence on its applications make PET/MRI a research tool.

Positron Emission Tomography Scan in Breast cancer gene-mutated patients

Carriers of BRCA 1/2 mutations are at greater lifetime risk of developing cancer, particularly breast (45%–65%) and OC (11%–40%). They are advised to undergo regular surveillance starting at age of 25 years, with clinical examination, breast imaging, and consider risk-reducing mastectomy and risk-reducing salpingo-oophorectomy at age of 35–40 years. For evaluation of the breast, the recommended imaging modalities are annual breast MRI with contrast or mammogram with consideration for tomosynthesis.

PET/CT has low sensitivity for the detection of primary breast tumor and has high rates of false-positive (e.g., fibroadenoma breast) and false-negative (e.g., lobular breast cancer) results. Thus, it has a limited role in initial detection of primary breast malignancy. Recently, dedicated breast PET systems and single-photon gamma imaging systems of the breast have been shown to have more sensitivity than whole-body FDG-PET/CT.[48] However, breast MRI still remains the gold standard for primary tumor evaluation.

PET/CT can detect unsuspected extra-axillary nodal metastasis and distant metastasis, thereby altering the staging, prognosis, and extent of surgery and radiotherapy in a patient with breast cancer.

Thus, PET/CT may be used in BRCA-mutated patients as a staging tool in equivocal cases but has limited utility for surveillance of such patients to detect breast cancer at early stage.

Conclusion

PET/CT is a useful tool in the clinician's armamentarium for managing patients with EOC. It has role in:

1. Evaluating adnexal masses to differentiate benign from malignant and borderline from malignant tumors
2. Staging the patients, assessing extent of disease, diagnosing unsuspected extra-abdominal metastasis and synchronous malignancy
3. Planning treatment based on disease extent
4. Assessing the response to NACT
5. As a prognostic tool based on metabolic parameters
6. Early detection of relapse
7. Planning further management of relapse based on disease extent: secondary cytoreduction or chemotherapy.

The metabolic parameters are useful prognostic markers which have been shown to correlate with patient survival. Future innovations which may reduce the cost of PET/CT and more prospective studies may establish this modality in routine practice for managing patients with ovarian malignancy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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