



PET/CT for Evaluation of Ovarian Cancer

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Ovarian cancer is the leading cause of death from gynecologic cancer in the developed countries. It is usually diagnosed in advanced stage since it is often symptomless or symptoms are nonspecific in early course of the disease. It has a high recurrence rate and poor prognosis in advanced disease. Ovarian cancer has distinct type of disease spread in abdomen and above diaphragm. Surgery is irreplaceable in staging but multimodality imaging approach is often needed during the diagnosis, treatment monitoring, and follow-up of patients with ovarian cancer, typically ultrasound, CT, MRI and PET/CT are the main modalities used. The current clinical role of PET/CT in evaluation of ovarian cancer during staging, treatment prognostication and response assessment, and in disease recurrence is discussed in this review compared to conventional imaging.

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Introduction

Ovarian cancer is challenging disease. It is difficult to diagnose at early stage, and it has high relapse rate after initial treatments. During the past decades besides cancer treatments also cancer imaging has developed. Especially molecular imaging with FDG-PET/CT has gained strong role in diagnostic imaging of cancer. FDG-PET/CT is sensitive modality and among its strengths are its ability to localize disease activity before anatomical changes, point out smaller lymph node (LN) metastases than convention imaging, find distant metastases and differentiate post-treatment findings when conventional imaging results are equivocal. However, the unspecific uptake mechanism of FDG may cause false positive findings whereas the size and the histology of the target cancer may be the source of false negative findings. In this review, the current clinical role of PET/CT for evaluation of ovarian cancer is discussed with respect to staging, treatment response evaluation, and disease recurrence.

Ovarian Cancer

Ovarian cancer accounts more than 14,000 deaths per year in United States of America¹ and more than 140,000 estimated deaths worldwide being seventh most common cause of cancer death in women.² Most of the ovarian cancers are epithelial origin (90%).³ Risk factors for ovarian cancer include postmenopausal age, having children late or never, estrogen replacement therapy after menopause, and positive family history for breast and ovarian cancers. Disease is usually detected at advanced stage in majority of women because it is often symptomless or symptoms are nonspecific in early course of the disease.⁴

Abdominal bloating or increased abdominal size caused by ascites, which occur in more advanced stage of the disease, is the most common reason for women seeking medical aid. Other symptoms typically associated to epithelial ovarian cancer (EOC) are fluctuating abdominal pain, dyspnea, changes in bowel function, difficulty in eating, and urinary symptoms. Also venous thrombosis and pulmonary embolism can be the first signs of EOC.⁵ Early stage disease appears often as a fixed unilateral or bilateral palpable pelvic mass.

Spread Patterns

Ovarian cancer metastases occur due to peritoneal, lymphatic, or hematogenous spread. Most commonly the disease spreads via peritoneal fluid circulation and the cancer cells may implant to practically any surface in the abdominal cavity. Common sites for implantation of cancer cells are pelvis with contralateral ovary, bowel, liver surface, omentum, right

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hemidiaphragm, and paracolic recesses, which are the spaces between colon and abdominal wall.⁶ Typical for ovarian cancer is that metastases usually occur on the surfaces of viscera rather as masses within organ parenchyma and implants can be miliary, appearing as a wide spread disseminated disease. Also large palpable omental “cake” is often found. These disseminated implants can also be isoattenuating in CT, which makes them challenging to localize.⁷ Peritoneal carcinomatosis is commonly seen in serous papillary carcinoma and poorly differentiated adenocarcinoma.^{8,9} This may result also to pleural involvement through transdiaphragmatic spread.¹⁰

The lymphatic drainage from the ovaries leads to external and common iliac, para-aortic and supraclavicular LNs.^{10,11} When disease spread is restricted to pelvis, LN metastasis is less common. In stage I and II patients, 13% incidence of LN metastases were reported in 79 patients.¹² However in stage III-IV patients, nodal involvement is very common as expected: 84% had para-aortic and 78% pelvic LN metastasis in study with 116 patients.¹³ LN involvement is more common in serous than other histologic subtypes and mean size of the LN metastases does not differ from the benign ones, which compromise the assessment of metastatic LNs with CT.

Hematogenous spread to liver, lungs, or pleura is possible but less common. This applies also to distant metastases to brain and skin, which usually are late manifestations of relapsed disease.^{14,15} Bone metastases are rare and are associated with poor prognosis.¹⁶

Ovarian Cancer Histology

Ovarian neoplasms are classified histogenetically according to their cell subtypes, which are epithelial, stromal, and germ cells. These are the three main cell types that make up the ovary. Malignant ovarian tumors according to histogenetic classification and their frequency are depicted in Table 1.¹⁷ EOC comprise of 90% of the malignant ovarian tumors. EOC is heterogeneous group of histopathologically different tumors with dissimilar clinical features and outcomes. The main histologic subtypes of EOC are shown in Table 2.

Based on histologic differentiation, EOC has been divided traditionally into three grades. Histologic grade is known to be an independent prognostic factor for patient survival. However, many ovarian cancers are simply categorized as low grade or high grade, where low-grade tumors are slowly

Table 1 Malignant Ovarian Tumors According to Histogenetic Classification Modified From DiSaia and Creasman, 2012

Origin	Tumor Type
Epithelium 90%	Serous
	Mucinous
	Endometrioid
	Clear-cell
	Undifferentiated carcinoma
Germ cells 3%-5%	Carcinosarcomas
	Dysgerminoma
	Immature teratoma
	Secondary neoplasm from mature cystic teratoma
	Choriocarcinoma
Gonadal stroma 5%-10%	Granulosa cell tumor
Nonspecific mesenchyme	Mixed mesodermal sarcoma
	Lymphoma
Metastatic	GI tract
	Breast
	Endometrium
	Lymphoma

growing and well-differentiated tumors not likely to metastasize and high-grade tumors are fast growing undifferentiated carcinomas and usually diagnosed in an advanced stage.¹⁸ Low-grade tumors comprise only one-fourth of the ovarian cancers, and it is reported to account for approximately 10% of the ovarian cancer deaths.¹⁹

Diagnosis

Transvaginal ultrasound or abdominal contrast-enhanced CT (ceCT) is usually the first diagnostic imaging method for malignant ovarian tumors. Ovarian malignancy is suspected when cystic solid process is found in pelvis with septae and papillary structures or ascites, supported by the elevated serum biomarker CA125 levels. However, the diagnosis of the EOC is always based on a histopathologic sample from surgery or image-guided needle aspiration.²⁰

Staging of Ovarian Cancer

EOC staging is surgical. International Federation of Gynecology and Obstetrics (FIGO) staging system is based on the laparotomy or laparoscopy findings.²⁰ Staging defines the extent of the disease and classifies patients into different prognostic groups. The most important prognostic factors for patient survival are FIGO stage, histologic subtypes, and complete tumor debulking in surgery. In addition, independent predictors of prognosis have been found to be stage III patients, age and performance status in retrospective review of 1895 patients.²¹ Preoperative imaging methods for staging of ovarian malignancies include US, ceCT, MRI, or FDG-PET/CT scans, where ceCT is the traditional imaging modality prior surgical staging laparotomy.

Table 2 The Main Histologic Subtypes of EOC According to Their Frequencies (Zeppernick et al, 2014)

The Frequency of Histologic Subtypes of EOC	
High-grade serous (HGSC)	70%
Endometrioid	10%
Clear-cell	10%
Mucinous	3%
Low-grade serous	<5%

FDG-PET/CT

Since the introduction of hybrid PET/CT devices at the end of the 1990s FDG-PET/CT has proven to be a sensitive imaging modality for detection, staging, restaging, and therapy response assessment in many oncological diseases. FDG uptake in tissue is proportional to glucose utilization and enhanced glucose metabolism is characteristic for many cancers.²²

Malignant tumors are usually more active in PET examination than benign or borderline lesions.²³ However, increased FDG uptake is found in many benign pelvic processes and conditions as well, like uterine fibroids, inflammatory conditions, abscess, endometriosis, thecoma, cystadenoma, hydrosalpinx, cholesterol granuloma, and the normal menstrual cycle.²⁴⁻²⁶ Menstrual history is important when evaluating most often unilateral ovarian FDG uptake in premenopausal women.²⁴ Incidental elevated ovarian FDG uptake is found also at the time of ovulation and luteal phase or in situations of ovarian torsion and hemorrhage.²⁷ In postmenopausal women, adnexal mass together with elevated CA125 levels are highly likely to be malignant (97%).²⁸

Moreover, histologic subtypes of EOC may have difference in FDG avidity. Serous and endometrioid subtypes are reported to have higher FDG uptake than clear-cell or mucinous subtypes.²⁹ Mucinous tumors are known to cause false negative PET findings.³⁰ Physiological tracer uptake in bowel loops, especially in type 2 diabetic patients using metformin medication and uptake in urinary system (ureters or bladder diverticles) may lead to false positive image interpretations.²⁵

Characterization of Adnexal Masses

Diagnostic performance of PET/CT in characterization of adnexal masses has been reported to be more accurate than CT or transvaginal ultrasound. Accuracy with PET/CT in these studies has varied from 90% to 97%, sensitivities from 81% to 100% and specificity between 74% and 100%.^{29,31-35} Yamamoto et al showed that although FDG-PET/CT had a high diagnostic value in differentiating between malignant and benign tumors, it had a low diagnostic value in differentiating between borderline malignant and benign tumors.³³

Staging

The EOC staging accuracy of PET/CT compared to FIGO surgical staging is presented in Table 3.

In a study by Castellucci et al PET/CT was particularly useful in stage IV patients where CT was prone to downstage patients by missing distant metastases.³² CT results were concordant with final diagnosis of malignancy only in 53% of cases (17/32 patients) whereas with FDG-PET/CT, the figure was better but not satisfactory, 69% (22/32 patients). In large cohort of 133 patients in Nam et al, PET/CT was found to be concordant with surgical staging in 78% of patients and was significantly more accurate than low-dose CT. In the study of Dauwen et al, FDG-PET/CT performed better in diagnosing retroperitoneal LN metastases.³⁵ However in the assessment of peritoneal or intestinal spread of ovarian cancer PET/CT did not prove to be better than CT and these sites are important when evaluating operability.^{35,36} This was also found in the study of Hynninen et al where the areas requiring extensive surgical procedures patient-based analysis of upper abdomen showed no significant differences between PET/CT and ceCT. However, FDG-PET/CT was superior to conventional CT for the detection of carcinomatosis in subdiaphragmatic peritoneal surfaces and in the bowel mesentery and also for the detection of extra-abdominal disease.³⁷ The overall sensitivity in site-based analysis of nine areas was 51% and specificity 89%. In a study of 40 EOC patients by De Iaco et al, they found that false negative findings were common (28.9%) with tumor lesions <5 mm.³⁸ Kitajima et al concluded overall advantage of PET/CT in tumor staging is generally more due to LN staging and in detecting unexpected distant metastases than in detecting local tumor spread in adjacent organs.³⁹ In a meta-analysis of 882 patients, PET/CT was the most accurate imaging method for the detection of LNM in EOC patients.⁴⁰ Meanwhile the diagnostic performance between MRI and CT was not significantly different in this study where both primary and treated EOC patients were included. Michielsen et al have compared whole-body MRI with diffusion-weighted sequence to CT and FDG-PET/CT for staging and they found that whole-body MRI with diffusion-weighted sequence was superior to CT and provided similar accuracy in characterization in primary lesions and distant metastases as PET/CT but it had significantly better sensitivity and specificity in overall peritoneal staging.⁴¹ In Figure 1, example of EOC patient-staging PET/CT images is shown together with surgeon's view of peritoneal surface carcinomatosis during staging.

Table 3 Studies Where the Staging Accuracy of PET/CT and ceCT is Compared Using Surgical FIGO Stage As a Reference Standard

Author	No. of Patients	PET/CT Accuracy	ceCT Accuracy	Patients With FIGO Stage III-IV
Castellucci, 2007	32	69% (22/32)	53% (17/32)	18
Kitajima, 2008	40	75% (30/40)	55% (22/40)	15
Nam, 2010	91	78% (71/91)	-	64
Dauwen, 2013	56	57% (31/56)	55% (32/56)	36
Hynninen, 2013	41	64%*	57%*	37

*Combined accuracy of nine regions.

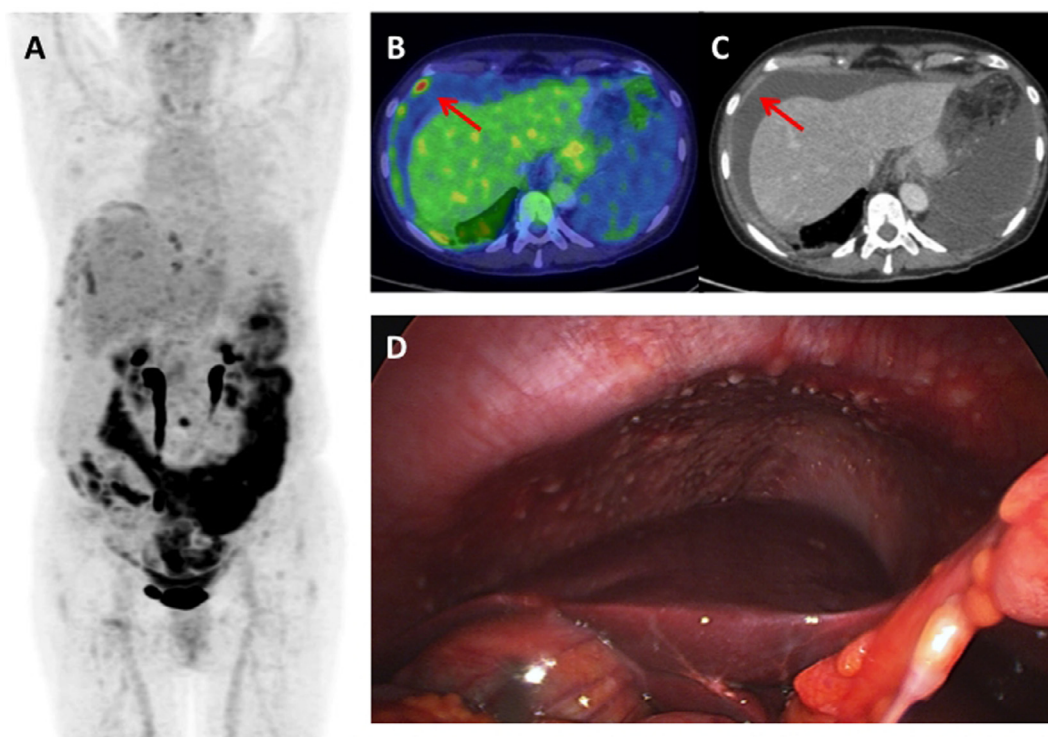


Figure 1 Typical staging PET/CT finding of a patient with EOC. (A) In whole body Maximum Intensity Projection (MIP), primary tumor-related activity is in the left ovarian together with physiological activity in bladder. Big omental “cake” related activity is found in abdomen. Also peritoneal carcinomatosis-related activity is found on the peritoneal surfaces, especially around the liver, and small bowel mesenterium and also in para-aortic lymph nodes. In PET/CT (B) and ceCT (C) images one large peritoneal active and enhancing carcinoma deposit is shown (red arrow). Laparotomy image (D) of the same patient shows multiple small carcinoma nodules on the peritoneal surface in such a rich detail that cannot be achieved with ceCT or PET/CT.

Extra-Abdominal Spread

Greater number of distant metastases is found with PET/CT than with CT alone (Table 3). In a study by Risum et al, 25 of 66 FIGO stage III stage patients were upstaged by PET/CT and 25 of 95 patients in a study by Fruscio et al.^{42,43} Most common site for metastases was supradiaphragmatic lymph nodes (sdLNM). In a retrospective data by Bats et al, mediastinal uptake in EOC patients was common (32%).⁴⁴ Hynninen et al found that significant number of stage III-IV patients, 20 of 30 (67%), have sdLNM. Suggested metastatic spread is via lymphatic system through diaphragm to cardiophrenic space and para-sternal locations and above.⁴⁵ Lee et al investigated the prognostic significance of sdLNMs retrospectively in 295 patients and they found that sdLNMs found in preoperative PET/CT have negative prognostic impact in EOC patients but the resection of these sdLNMs does not bring significant survival benefit.⁴⁶

It is of importance to note that preoperative PET/CT was also reported to found additional malignancies in approximately 2%-4% of patients.^{32,34,35} The typical tumors found were thyroid cancers, breast cancers, and renal cancer.

Although the role of FDG-PET/CT is limited in preoperative staging of ovarian cancer due to sources of false positive and negative findings discussed above and insensitivity with small

lesions (<5 mm) and micrometastases, it allows noninvasive detection of total metabolic tumor burden, with detection of distant metastases and assess equivocal findings of traditional imaging. This is especially important in situations when morphologic information is not helpful to determine the nature of anatomic finding.

Treatment

Surgery and platinum-based chemotherapy are the cornerstones of EOC treatment. Success of tumor debulking in advanced EOC is important prognostic factor and goal for primary surgery should be complete removal of all the visible intra-abdominal disease nodules.^{47,48} This cannot be reached in all patients. Approximately 15%-20% patients need alternative approach with neoadjuvant chemotherapy (NACT) to reduce the tumor volume and extent to optimize the results of debulking surgery.^{49,50} Patients with stage IV disease, high volume tumor load, or poor general condition are usually candidates for NACT treatment. Patients that respond for NACT are considered to benefit from interval debulking strategy. EOC patients typically respond first to platinum-based therapy, but later develop drug resistance. Recently, new, targeted therapies such as bevacizumab and PARP inhibitors have become available for EOC patients.^{51,52}

Treatment Prognostication and Response Evaluation

Important prognostic information can be obtained with PET/CT. It has been shown that disease recurrence is more likely in patients with increased disease distribution above umbilical area.⁵³ Although, high SUVmax of the primary tumor in pretreatment PET/CT is associated to poor prognosis,⁵⁴ it is not a prognostic parameter for predicting complete cytoreduction after primary surgery.⁵⁵

When assessing the response to chemotherapy, it has been shown that metabolic responders had 20% decrease in first cycle and 55% after third cycle resulting 15.2-19.2 months longer overall survival compared to nonresponders.⁵⁶ PET/CT is also able to differentiate histopathologic responders to NACT from nonresponders in primarily inoperable EOC patients when at least 57% decrease in SUVmax was found.⁵⁷ Moreover, metabolic tumor volume change was associated progression-free survival and overall survival.⁵⁸ They concluded also that patients with less than 85% change in metabolic tumor volume might be candidates for second line chemotherapy. Figure 2 is presenting two case examples of PET/CT images from patients with a good and a poor response to NACT treatment. It has been also found that whole body total glycolysis is

independent prognostic factor for disease progression-free survival⁵⁹ and overall survival.⁶⁰ The role of functional imaging in defining response to new, targeted therapies, and immunologic drugs has not been established. However, as EOC treatment has become more individualized and new drugs are typically very expensive, information on early metabolic changes measured with PET/CT could be very valuable.

Hynninen et al evaluated the benefit of PET/CT in treatment response monitoring prospectively in 49 stage III-IV EOC patients where response PET/CT was performed 3-4 weeks after six cycles of platinum/taxane chemotherapy. Image results were opened to clinicians upon disease recurrence. They found that 34% of patients with complete response (n=28) according to RECIST1.1 criteria showed increased activity in end of treatment PET/CT according to PERCIST criteria. In a follow-up scan, the recurrence occurred in majority of cases in the same locations where the end of treatment scan showed suspicious metabolic activity and also additional new lesions were found. Patients with complete response according to RECIST1.1 but with end of treatment residual activity did not progress earlier than patients with negative end treatment scan.⁶¹ Therefore they concluded that routine response evaluation PET/CT might not be needed after EOC primary therapy.

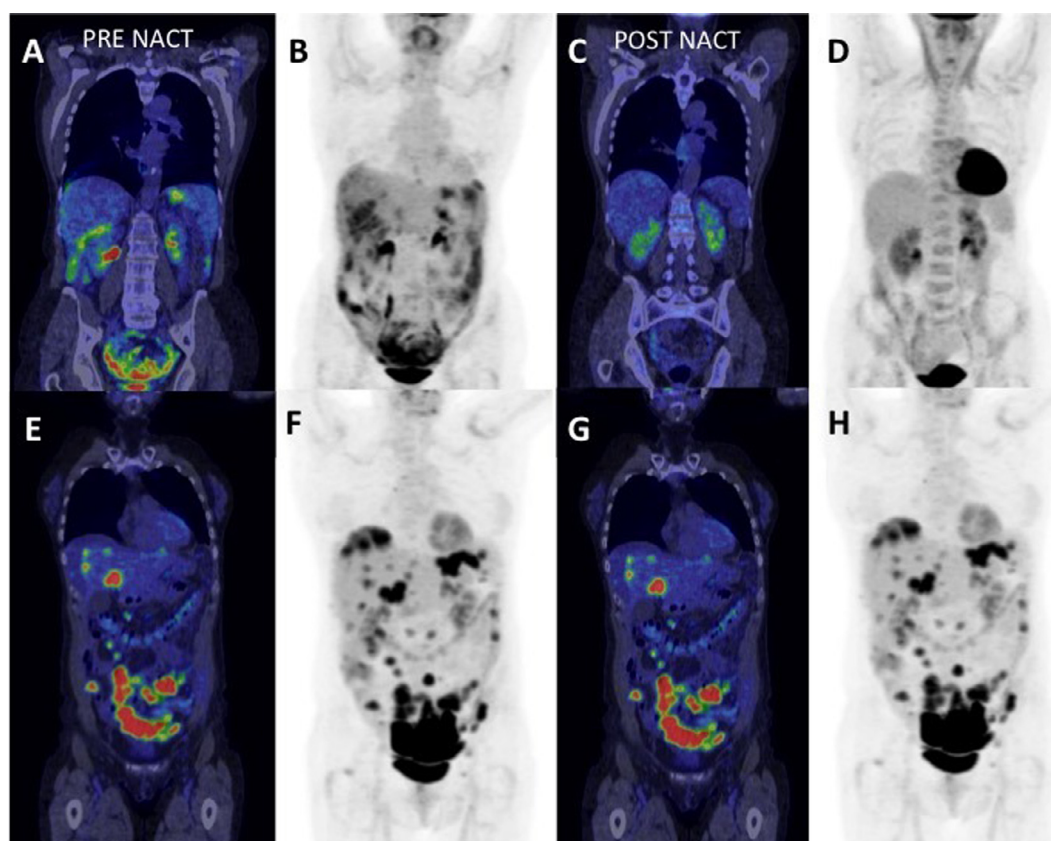


Figure 2 Upper panel (A-D) is presenting a patient with a good response to NACT treatment. Coronal PET/CT image (A) and whole-body MIP image (B) of the EOC patient before NACT and corresponding images (C and D) after the NACT. Lower panel (E-H) shows a patient with poor, no-change response to NACT. Coronal PET/CT image (E) and whole-body MIP image, (F) before NACT treatment and corresponding images, (G and H) after the NACT treatment.

Disease Recurrence

Ovarian malignancies are associated with high relapse rate within 2 years after primary treatment (60%-70%).⁶² First signs of disease recurrence are biochemical relapse observed with serum CA125 levels or patients symptoms or both. Typical symptoms associated with recurrence are decrease in general well-being, abdominal pain, constipation, enlarged LNs, and ascites.⁶³ Positive predictive value of disease recurrence with elevated CA125 is very high and the rate of false positives less than 1%.^{64,65} However, only 80% of all ovarian cancer patients have any increase in CA125 levels. So normal CA125 levels does not exclude the possibility of ovarian cancer recurrence (OCR). Moreover, this tumor marker is neither specific for ovarian cancer nor sensitive for small volume disease.⁶⁶ Also, tumor markers cannot determine the localization of cancer recurrence.

Early localization of recurrent ovarian cancer is highly important since it guides the treatment decisions to identify patients who might benefit from surgery, chemotherapy or local radiation treatment. Together with CA125 measurement, ceCT, MRI, or PET/MRI could be performed for radiological assessment.⁶⁷ CeCT is the most commonly used, widely available, and cost-effective method for this purpose. It has reported to have somewhat limited performance according to meta-analysis where pooled sensitivity was 79% and specificity 84%. Also MRI has similar performance with a pooled sensitivity of 75% and specificity 78%.⁶⁸ Meanwhile FDG-PET/CT scanning outperformed these modalities. Corresponding values for FDG-PET/CT were 91% and 88%.⁶⁸ In a more recent meta-analysis, even more higher figures were presented: 93.9% and 93.8%, respectively.⁶⁹ Performing PET/CT without ceCT imaging decreases the diagnostic performance in detection of OC recurrence. Pooled sensitivity of 89.8% and specificity of 89.6% have been reported in meta-analysis.⁶⁹ FDG-PET/CT has been shown to have significantly higher sensitivity and accuracy in detection of OCR both low- and high-grade tumors compared with serum CA125, 91% vs 63%, respectively.⁷⁰ PET/CT performs efficiently also in very low level change of CA125 levels, with 90.9% detection rate.⁷¹ Studies comparing the detection accuracy of ovarian cancer disease recurrence with PET/CT compared ceCT or MRI are collected in Table 4.⁷²⁻⁷⁶

In a situation with patients having elevated CA125 and negative CT or MRI in surveillance scan, PET/CT has shown

to have high overall sensitivity (97%).^{77,78} In retrospective data by Mangili, ceCT was able to demonstrate disease recurrence in 62.5% and PET/CT in 90.6% of patients. Strikingly 10 of 12 ceCT negative patients had OCR found.⁷⁹ Performance difference is related to higher sensitivity of PET/CT to smaller anatomic lesions, 5-10 mm in diameter, sensitivity in extra peritoneal disease spread, and localization of LN metastases.⁸⁰ As with staging, the sensitivity and specificity to LN metastases are higher in PET/CT than with MRI or CT.⁴⁰

In a retrospective analysis of 44 patients, PET was useful for selecting candidates for cytoreductive surgery in patients with OCR.⁸¹ High risk of disseminated disease was observed in patients with treatment-free interval less than 12 months.⁸¹ PET has reported to lead to change in management in 57%-58% of the patients^{77,81-83} and PET/CT may help to choose patients who will likely benefit from surgery and the ones who will not. Although negative predictive value was relative poor in a prospective study by Simcock et al where seven of nine patients were false negative reflecting failure to diagnose small volume disease, PET/CT was able to define subgroup of patients with localized disease or no definitive evident disease in which improved survival was found compared to those with systemic disease.⁸² Moreover negative PET is associated with longer relapse-free interval compared to positive PET.⁸⁴ These findings are in line with Hynninen et al where low volume post-treatment metabolic activity does not predict earlier disease relapse.⁶¹

Future Perspectives

There have also been attempts to utilize PET-technique with tracers other than FDG as well in OC. Many of these studies are listed in a manuscript by Lin et al where emerging molecular techniques in gynecologic oncology are reviewed.⁸⁵ Among these tracers are proliferation marker ¹⁸F-FLT which has been tested for response monitoring in OC as well as amino acid metabolism with ¹¹C-methionine and lipid metabolism with ¹¹C-choline. There have also been investigations with hypoxia markers, monoclonal antibodies, and affibodies for OC detection. Possible game changers in this field could be related to theranostic strategy from nuclear medicine point of view in patients with advanced disease and resistance to chemotherapy. There are emerging role of beta

Table 4 Detection Accuracy of Ovarian Cancer Disease Recurrence With PET/CT Compared to ceCT or MRI

Author	No of Patients	PET Sensitivity	PET Specificity	PET Accuracy	CI Sensitivity	CI Specificity	CI Accuracy	Reference Standard	Modality
Kitajima, 2008	132	79	91	85	61	85	73	Histology	ceCT
Nasu, 2011	19	82	100	87	96	100	97	Histology/ follow-up	ceCT
Sanli, 2011	47	98	100	98	95	86	94	Histology	MRI
Takeuchi, 2014	48	94	100	97	89	95	93	Histology/ follow-up	ceCT
Tawakol, 2016	111	96	92	95	84	59	76	Histology/ follow-up	ceCT

CI, conventional imaging.

and alpha radionuclid therapy in advanced disease with neuroendocrinological tumors and castration resistant prostate cancer.^{86,87} Interesting new targets for OC imaging and possible new targets for radionuclide therapy could be chemokine receptors and fibroblast activation proteins, which are overexpressed in many cancers, also in OC.^{88,89} Chemokine receptor targeting ⁶⁸Ga-Pentixafor and fibroblast activating protein targeted ⁶⁸Ga-FAPI are the new emerging imaging agents to look for in the near future.^{90,91}

Summary

In general, PET/CT has shown to be more accurate in staging of EOC than traditional CT and MRI imaging. However, the role of surgery in staging is irreplaceable. PET/CT does not perform better than ceCT in the assessment of peritoneal or intestinal spread when evaluating operability and there exists many sources of false negative and positive findings. The clear advantage over conventional imaging is in the ability of PET/CT to detect LN metastases, extra abdominal disease spread and to assess equivocal findings in conventional imaging. PET/CT may be used in situations where it is likely to change the management of EOC in comparison to CT or MRI examinations in preoperative staging. Recist-based treatment response evaluation with conventional imaging might be accurate enough after primary treatment. However, with PET/CT important prognostic information guiding second line treatment options could be obtained from patient receiving chemotherapy or NACT. Disease recurrence is the situation where PET/CT is performing with a high sensitivity and specificity and likely to change patient management, especially in situations with elevating CA125 levels and negative findings in conventional imaging. Negative, low volume, or localized disease recurrence observed in PET/CT is associated with improved survival. Currently, PET/CT is acknowledged in NCCN Guidelines as a staging modality for indeterminate lesions with MRI, modality option to CT or MRI in postprimary treatment assessment, disease monitoring and follow-up and disease recurrence assessment when clinically indicated.

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