ELSEVIER

Seminars in
NUCLEAR
MEDICINE

PET/CT for Evaluation of Ovarian Cancer

Jukka Kemppainen,[*,†,‡] Johanna Hynninen,[§] Johanna Virtanen,[‖] and Marko Seppänen[*,†]

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.
Semin Nucl Med 49:484-492 © 2019 Published by Elsevier Inc.

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.

*Turku PET Centre, University of Turku, Turku, Finland.
†Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku Finland.
‡Docrates Cancer Center, Helsinki, Finland.
§Department of Obstetrics and Gynecology, Turku University Hospital, University of Turku, Turku, Finland.
‖Department of Radiology, Turku University Hospital, Turku, Finland.
Address reprint requests to Jukka Kemppainen, MD, PhD, Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Hämeentie 11, 1st floor E-part, PO BOX 52, Turku, Finland. E-mail: jukka.kemppainen@utu.fi

Ovarian Cancer

Ovarian cancer accounts more than 14,000 deaths per year in United States of America[1] 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

 https://doi.org/10.1053/j.semnuclmed.2019.06.010
0001-2998/© 2019 Published by Elsevier Inc.

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 visceras 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 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]

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
	Carcinosarcomas
Germ cells 3%-5%	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

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%

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.

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 hemorrage.[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 interpretetations.[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] Yamamote 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.

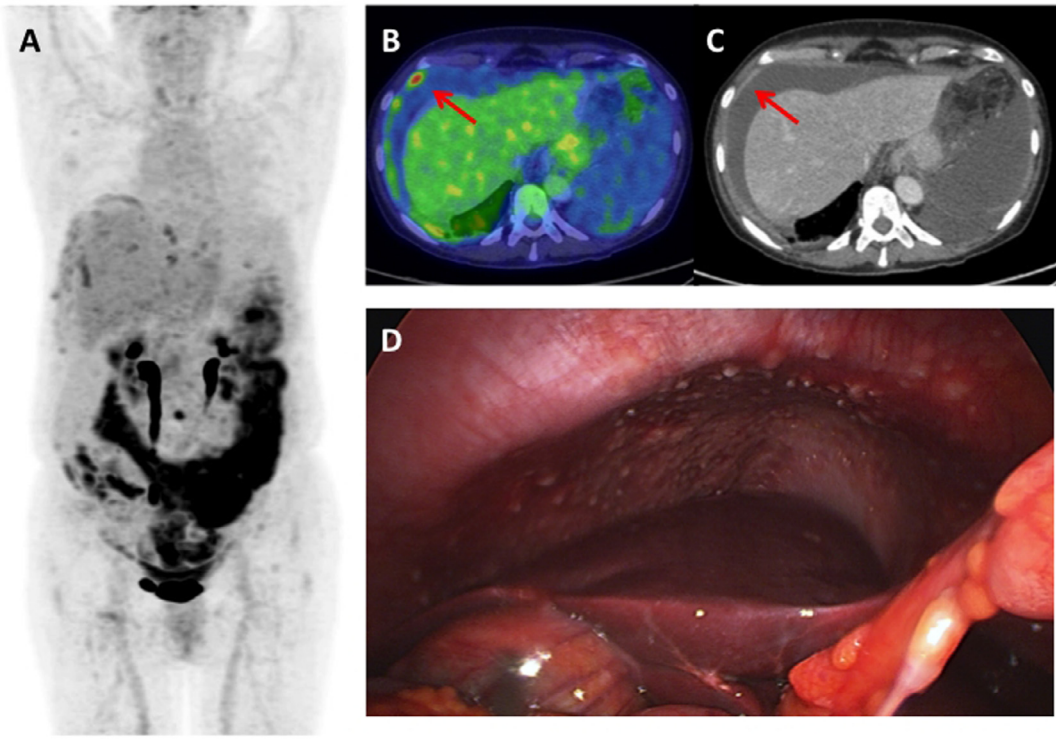

Figure 1 Typical staging PET/CT finding of a patient with EOC. (A) In whole body Maximum Intensity Projection (MIP), primary tumor-related activity is in the left ovarian together with physiological activity in bladder. Big omental "cake" related activity is found in abdomen. Also peritoneal carcinomatosis-related 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 import 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 survival[59] 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 needed after EOC primary therapy.

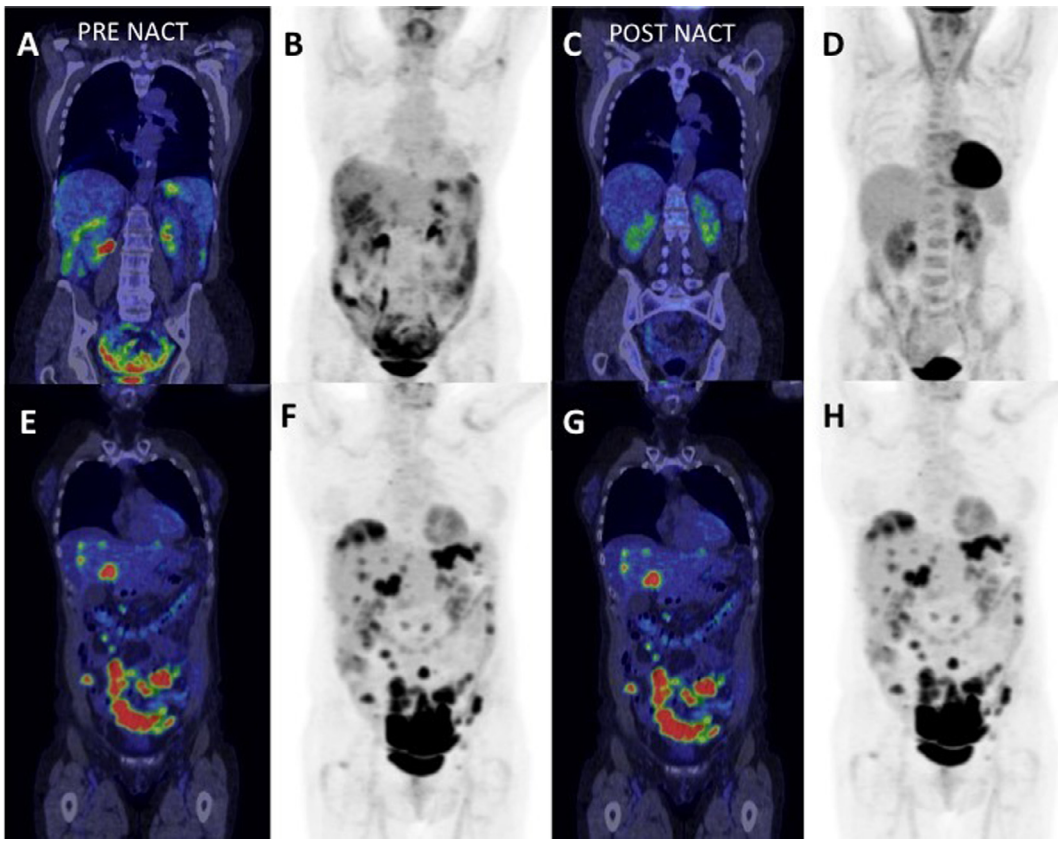

Figure 2 Upper panel (A-D) is presenting a patient with a good response to NACT treatment. Coronal PET/CT image (A) and whole-body MIP image (B) of the EOC patient before NACT and corresponding images (C and D) after the NACT. Lower panel (E-H) shows a patient with poor, no-change response to NACT. Coronal 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 also 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 ^{18}F-FLT which has been tested for response monitoring in OC as well as amino acid metabolism with ^{11}C-methionine and lipid metabolism with ^{11}C-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	Specificity	Accuracy	CI Sensitivity	Specificity	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 alfa 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 ^{68}Ga-Pentixafor and fibroplast activating protein targeted ^{68}Ga-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.

References

1. National Cancer Institute. The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. Cancer Stat Facts: Ovarian Cancer. https://seer.cancer.gov/statfacts/html/ovary.html.
2. Jemal A, Bray F, Center MM, et al: Global cancer statistics. CA Cancer J Clin 61:69-90, 2011
3. Zeppernick F, Meinhold-Heerlein I: The new FIGO staging system for ovarian, fallopian tube, and primary peritoneal cancer. Arch Gynecol Obstet 290:839-842, 2014.
4. Sankaranarayanan R, Ferlay J: Worldwide burden of gynaecological cancer: The size of the problem. Best Pract Res Clin Obstet Gynaecol 20:207-225, 2006
5. Goff BA, Mandel LS, Melancon CH, et al: Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. J Am Med Assoc 291:2705-2712, 2004
6. Forstner R, Hricak H, Occhipinti KA, et al: Ovarian cancer: Staging with CT and MR imaging. Radiology 197:619-626, 1995
7. Chung HH, Kang WJ, Kim JW, et al: Role of [18F]FDG PET/CT in the assessment of suspected recurrent ovarian cancer: Correlation with clinical or histological findings. Eur J Nucl Med Mol Imaging 34: 480-486, 2007
8. Pentheroudakis G, Pavlidis N: Serous papillary peritoneal carcinoma: Unknown primary tumour, ovarian cancer counterpart or a distinct entity? A systematic review. Crit Rev Oncol Hematol 75:27-42, 2010
9. Kim HJ, Kim JK, Cho K-S: CT features of serous surface papillary carcinoma of the ovary. Am J Roentgenol 183:1721-1724, 2004
10. Mourits MJ, de Bock GH: Managing hereditary ovarian cancer. Maturitas 64:172-176, 2009
11. Burghardt E, Girardi F, Lahousen M, et al: Patterns of pelvic and paraaortic lymph node involvement in ovarian cancer. Gynecol Oncol 40:103-106, 1991
12. Nomura H, Tsuda H, Susumu N, et al: Lymph node metastasis in grossly apparent stages I and II epithelial ovarian cancer. Int J Gynecol Cancer 20:341-345, 2010
13. Pereira A, Magrina JF, Rey V, et al: Pelvic and aortic lymph node metastasis in epithelial ovarian cancer. Gynecol Oncol 105:604-608, 2007
14. Kolomainen DF, Larkin JMG, Badran M, et al: Epithelial ovarian cancer metastasizing to the brain: A late manifestation of the disease with an increasing incidence. J Clin Oncol 20:982-986, 2002
15. Kim M-K, Kim S-H, Lee Y-Y, et al: Metastatic skin lesions on lower extremities in a patient with recurrent serous papillary ovarian carcinoma: A case report and literature review. Cancer Res Treat 44: 142-145, 2012
16. Sehouli J, Olschewski J, Schotters V, et al: Prognostic role of early versus late onset of bone metastasis in patients with carcinoma of the ovary, peritoneum and fallopian tube. Ann Oncol 24:3024-3028, 2013
17. DiSaia PJ, Creasman WT: Clinicical Gynecologic Ongology: Epithelial Ovarian Cancer. (ed 8). Philadelphia: Elsevier Saunders, 2012 Classification
18. Shih I-M, Kurman RJ: Ovarian tumorigenesis: A proposed model based on morphological and molecular genetic analysis. Am J Pathol 164:1511-1518, 2004
19. Kurman RJ, Shih I-M: The origin and pathogenesis of epithelial ovarian cancer: A proposed unifying theory. Am J Surg Pathol 34:433-443, 2010
20. Prat J: Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Obstet Gynecol 126:171-174, 2015
21. Winter WE, Maxwell GL, Tian C, et al: Prognostic factors for stage III epithelial ovarian cancer: A gynecologic oncology group study. J Clin Oncol 25:3621-3627, 2007
22. Boellaard R, Delgado-Bolton R, Oyen WJG, et al: FDG PET/CT: EANM procedure guidelines for tumour imaging: Version 2.0. Eur J Nucl Med Mol Imaging 42:328-354, 2015
23. Musto A, Grassetto G, Marzola MC, et al: Management of epithelial ovarian cancer from diagnosis to restaging: An overview of the role of imaging techniques with particular regard to the contribution of 18F-FDG PET/CT. Nucl Med Commun 35:588-597, 2014
24. Lerman H, Metser U, Grisaru D, et al: Normal and abnormal 18F-FDG endometrial and ovarian uptake in pre- and postmenopausal patients: Assessment by PET/CT. J Nucl Med 45:266-271, 2004
25. Subhas N, Patel P V, Pannu HK, et al: Imaging of pelvic malignancies with in-line FDG PET-CT: Case examples and common pitfalls of FDG PET. Radiographics 25:1031-1043, 2005
26. Rieber A, Nüssle K, Stöhr I, et al: Preoperative diagnosis of ovarian tumors with MR imaging: Comparison with transvaginal sonography, positron emission tomography, and histologic findings. AJR Am J Roentgenol 177:123-129, 2001
27. Kim S-K, Kang KW, Roh JW, et al: Incidental ovarian 18F-FDG accumulation on PET: Correlation with the menstrual cycle. Eur J Nucl Med Mol Imaging 32:757-763, 2005
28. Brooks SE: Preoperative evaluation of patients with suspected ovarian cancer. Gynecol Oncol 55:S80-S90, 1994
29. Tanizaki Y, Kobayashi A, Shiro M, et al: ATL. Int J Gynecol Cancer 24:454-460, 2014
30. Kyriazi S, Kaye SB, DeSouza NM: Imaging ovarian cancer and peritoneal metastases—Current and emerging techniques. Nat Rev Clin Oncol 7:381-393, 2010

31. Risum S, Hogdall C, Loft A, et al: The diagnostic value of PET/CT for primary ovarian cancer—A prospective study. Gynecol Oncol 105: 145-149, 2007
32. Castellucci P, Perrone AM, Picchio M, et al: Diagnostic accuracy of 18F-FDG PET/CT in characterizing ovarian lesions and staging ovarian cancer: Correlation with transvaginal ultrasonography, computed tomography, and histology. Nucl Med Commun 28:589-595, 2007
33. Yamamoto Y, Oguri H, Yamada R, et al: Preoperative evaluation of pelvic masses with combined 18 F-fluorodeoxyglucose positron emission tomography and computed tomography. Int J Gynecol Obstet 102: 124-127, 2008
34. Nam EJ, Yun MJ, Oh YT, et al: Diagnosis and staging of primary ovarian cancer: Correlation between PET/CT, Doppler US, and CT or MRI. Gynecol Oncol 116:389-394, 2010
35. Dauwen H, Van Calster B, Deroose CM, et al: PET/CT in the staging of patients with a pelvic mass suspicious for ovarian cancer. Gynecol Oncol 131:694-700, 2013
36. Lopez-Lopez V, Cascales-Campos PA, Gil J, et al: Use of 18 F-FDG PET/CT in the preoperative evaluation of patients diagnosed with peritoneal carcinomatosis of ovarian origin, candidates to cytoreduction and hipec. A pending issue. Eur J Radiol 85:1824-1828, 2016
37. Hynninen J, Kemppainen J, Lavonius M, et al: A prospective comparison of integrated FDG-PET/contrast-enhanced CT and contrast-enhanced CT for pretreatment imaging of advanced epithelial ovarian cancer. Gynecol Oncol 131:389-394, 2013
38. De Iaco P, Musto A, Orazi L, et al: FDG-PET/CT in advanced ovarian cancer staging: Value and pitfalls in detecting lesions in different abdominal and pelvic quadrants compared with laparoscopy. Eur J Radiol 80: e98-e103, 2011
39. Kitajima K, Murakami K, Sakamoto S, et al: Present and future of FDG-PET/CT in ovarian cancer. Ann Nucl Med 25:155-164, 2011
40. Yuan Y, Gu Z-X, Tao X-F, et al: Computer tomography, magnetic resonance imaging, and positron emission tomography or positron emission tomography/computer tomography for detection of metastatic lymph nodes in patients with ovarian cancer: A meta-analysis. Eur J Radiol 81:1002-1006, 2012
41. Michielsen K, Vergote I, Op de beeck K, et al: Whole-body MRI with diffusion-weighted sequence for staging of patients with suspected ovarian cancer: A clinical feasibility study in comparison to CT and FDG-PET/CT. Eur Radiol 24:889-901, 2014
42. Fruscio R, Sina F, Dolci C, et al: Preoperative 18F-FDG PET/CT in the management of advanced epithelial ovarian cancer. Gynecol Oncol 131:689-693, 2013
43. Risum S, Høgdall C, Loft A, et al: Does the use of diagnostic PET/CT cause stage migration in patients with primary advanced ovarian cancer. Gynecol Oncol 116:395-398, 2010
44. Bats A-S, Hugonnet F, Huchon C, et al: Prognostic significance of mediastinal 18F-FDG uptake in PET/CT in advanced ovarian cancer. Eur J Nucl Med Mol Imaging 39:474-480, 2012
45. Hynninen J, Auranen A, Carpén O, et al: FDG PET/CT in staging of advanced epithelial ovarian cancer: Frequency of supradiaphragmatic lymph node metastasis challenges the traditional pattern of disease spread. Gynecol Oncol 126:64-68, 2012
46. Lee IO, Lee J-Y, Kim HJ, et al: Prognostic significance of supradiaphragmatic lymph node metastasis detected by 18F-FDG PET/CT in advanced epithelial ovarian cancer. BMC Cancer 18:1165, 2018
47. du Bois A, Reuss A, Pujade-Lauraine E, et al: Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: A combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials. Cancer 115:1234-1244, 2009
48. Chang S-J, Bristow RE, Ryu H-S: Prognostic significance of systematic lymphadenectomy as part of primary debulking surgery in patients with advanced ovarian cancer. Gynecol Oncol 126:381-386, 2012
49. Kang S, Nam B-H: Does neoadjuvant chemotherapy increase optimal cytoreduction rate in advanced ovarian cancer? Meta-analysis of 21 studies. Ann Surg Oncol 16:2315-2320, 2009
50. Vergote I, Tropé CG, Amant F, et al: Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 363: 943-953, 2010
51. Walsh C: Targeted therapy for ovarian cancer: The rapidly evolving landscape of PARP inhibitor use. Minerva Ginecol 70:150-170, 2018
52. DiSilvestro PA: Shaping the standard of care in ovarian cancer management: A review of Gynecologic Oncology Group (GOG)/NRG oncology clinical trials of the past twenty years. Gynecol Oncol 153:479-486, 2019
53. Chung HH, Kwon HW, Kang KW, et al: Preoperative [18 F]FDG PET/CT predicts recurrence in patients with epithelial ovarian cancer. J Gynecol Oncol 23:28, 2012
54. Nakamura K, Hongo A, Kodama J, et al: The pretreatment of maximum standardized uptake values (SUVmax) of the primary tumor is predictor for poor prognosis for patients with epithelial ovarian cancer. Acta Med Okayama 66:53-60, 2012
55. Risum S, Loft A, Høgdall C, et al: Standardized FDG uptake as a prognostic variable and as a predictor of incomplete cytoreduction in primary advanced ovarian cancer. Acta Oncol (Madr) 50:415-419, 2011
56. Avril N, Sassen S, Schmalfeldt B, et al: Prediction of response to neoadjuvant chemotherapy by sequential F-18-fluorodeoxyglucose positron emission tomography in patients with advanced-stage ovarian cancer. J Clin Oncol 23:7445-7453, 2005
57. Vallius T, Peter A, Auranen A, et al: 18F-FDG-PET/CT can identify histopathological non-responders to platinum-based neoadjuvant chemotherapy in advanced epithelial ovarian cancer. Gynecol Oncol 140: 29-35, 2016
58. Vallius T, Hynninen J, Kemppainen J, et al: 18F-FDG-PET/CT based total metabolic tumor volume change during neoadjuvant chemotherapy predicts outcome in advanced epithelial ovarian cancer. Eur J Nucl Med Mol Imaging 45:1224-1232, 2018
59. Lee JW, Cho A, Lee J-H, et al: The role of metabolic tumor volume and total lesion glycolysis on 18F-FDG PET/CT in the prognosis of epithelial ovarian cancer. Eur J Nucl Med Mol Imaging 41:1898-1906, 2014
60. Liao S, Lan X, Cao G, et al: Prognostic predictive value of total lesion glycolysis from 18F-FDG PET/CT in post-surgical patients with epithelial ovarian cancer. Clin Nucl Med 38:715-720, 2013
61. Hynninen J, Laasik M, Vallius T, et al: Clinical value of 18 F-fluorodeoxyglucose positron emission tomography/computed tomography in response evaluation after primary treatment of advanced epithelial ovarian cancer. Clin Oncol 30:507-514, 2018
62. Ledermann JA, Kristeleit RS: Optimal treatment for relapsing ovarian cancer. Ann Oncol 21:vii218-vii222, 2010
63. Fehm T, Heller F, Krämer S, et al. Evaluation of CA125, physical and radiological findings in follow-up of ovarian cancer patients. Anticancer Res. 25:1551-1554.
64. Högberg T, Kågedal B: Long-term follow-up of ovarian cancer with monthly determinations of serum CA 125. Gynecol Oncol 46:191-198, 1992
65. Niloff JM, Knapp RC, Lavin PT, et al: The CA 125 assay as a predictor of clinical recurrence in epithelial ovarian cancer. Am J Obstet Gynecol 155:56-60, 1986
66. Santillan A, Garg R, Zahurak ML, et al: Risk of epithelial ovarian cancer recurrence in patients with rising serum CA-125 Levels within the normal range. J Clin Oncol 23:9338-9343, 2005
67. NCCN.org. NCCN clinical practice guidelines in oncology (NCCN Guidelines®) ovarian cancer including fallopian tube cancer and primary peritoneal cancer version 4. 2017.; 2017.
68. Gu P, Pan L-L, Wu S-Q, et al: CA 125, PET alone, PET-CT, CT and MRI in diagnosing recurrent ovarian carcinoma: A systematic review and meta-analysis. Eur J Radiol 71:164-174, 2009
69. Suppiah S, Chang WL, Hassan HA, et al: Systematic review on the accuracy of positron emission tomography/computed tomography and positron emission tomography/magnetic resonance imaging in the management of ovarian cancer: Is functional information really needed. World J Nucl Med 16:176-185, 2017
70. Antunovic L, Cimitan M, Borsatti E, et al: Revisiting the clinical value of 18F-FDG PET/CT in detection of recurrent epithelial ovarian carcinomas: Correlation with histology, serum CA-125 assay, and conventional radiological modalities. Clin Nucl Med 37:e184-e188, 2012
71. Peng N-J, Liou W-S, Liu R-S, et al: Early detection of recurrent ovarian cancer in patients with low-level increases in serum CA-125

Levels by 2-[F-18]Fluoro-2-Deoxy- d-Glucose-positron emission tomography/computed tomography. Cancer Biother Radiopharm 26:175-181, 2011
72. Kitajima K, Murakami K, Yamasaki E, et al: Performance of integrated FDG−PET/contrast-enhanced CT in the diagnosis of recurrent ovarian cancer: Comparison with integrated FDG−PET/non-contrast-enhanced CT and enhanced CT. Eur J Nucl Med Mol Imaging 35:1439-1448, 2008
73. Nasu K, Abe W, Takai N, et al: Impact of positron emission tomography/computed tomography in the management of patients with epithelial ovarian carcinoma after treatment. Arch Gynecol Obstet 283: 1121-1126, 2011
74. Sanli Y, Turkmen C, Bakir B, et al: Diagnostic value of PET/CT is similar to that of conventional MRI and even better for detecting small peritoneal implants in patients with recurrent ovarian cancer. Nucl Med Commun 33:509-515, 2012
75. Takeuchi S, Lucchini M, Schmeler KM, et al: Utility of 18F-FDG PET/CT in follow-up of patients with low-grade serous carcinoma of the ovary. Gynecol Oncol 133:100-104, 2014
76. Tawakol A, Abdelhafez YG, Osama A, et al: Diagnostic performance of 18F-FDG PET/contrast-enhanced CT versus contrast-enhanced CT alone for post-treatment detection of ovarian malignancy. Nucl Med Commun 37:453-460, 2016
77. Thrall M, Deloia J, Gallion H, et al: Clinical use of combined positron emission tomography and computed tomography (FDG-PET/CT) in recurrent ovarian cancer. Gynecol Oncol 105:17-22, 2007
78. Menzel C, Döbert N, Hamscho N, et al: The influence of CA 125 and CEA levels on the results of (18)F-deoxyglucose positron emission tomography in suspected recurrence of epithelial ovarian cancer. Strahlenther Onkol 180:497-501, 2004
79. Mangili G, Picchio M, Sironi S, et al: Integrated PET/CT as a first-line re-staging modality in patients with suspected recurrence of ovarian cancer. Eur J Nucl Med Mol Imaging 34:658-666, 2007
80. Rubello D, Marzola MC, Colletti PM: The prognostic value of 18F-FDG PET/CT in monitoring chemotherapy in ovarian cancer both at initial diagnosis and at recurrent disease. Clin Nucl Med 43:1, 2018
81. Ebina Y, Watari H, Kaneuchi M, et al: Impact of FDG PET in optimizing patient selection for cytoreductive surgery in recurrent ovarian cancer. Eur J Nucl Med Mol Imaging 41:446-451, 2014
82. Simcock B, Neesham D, Quinn M, et al: The impact of PET/CT in the management of recurrent ovarian cancer. Gynecol Oncol 103:271-276, 2006
83. Rusu D, Carlier T, Colombié M, et al: Clinical and survival impact of FDG PET in Patients with suspicion of recurrent ovarian cancer: A 6-Year follow-up. Front Med 2:46, 2015
84. Zimny M, Siggelkow W, Schröder W, et al: 2-[Fluorine-18]-fluoro-2-deoxy-d-glucose positron emission tomography in the diagnosis of recurrent ovarian cancer. Gynecol Oncol 83:310-315, 2001
85. Lin G, Lai C-H, Yen T-C: Emerging molecular imaging techniques in gynecologic oncology. PET Clin 13:289-299, 2018
86. Chakravarty R, Siamof CM, Dash A, et al: Targeted α-therapy of prostate cancer using radiolabeled PSMA inhibitors: A game changer in nuclear medicine. Am J Nucl Med Mol Imaging 8:247-267, 2018
87. Strosberg J, El-Haddad G, Wolin E, et al: Phase 3 Trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med 376:125-135, 2017
88. Muralidhar GG, Barbolina M V: Chemokine receptors in epithelial ovarian cancer. Int J Mol Sci 15:361-376, 2013
89. Thuwajit C, Ferraresi A, Titone R, et al: The metabolic cross-talk between epithelial cancer cells and stromal fibroblasts in ovarian cancer progression: Autophagy plays a role. Med Res Rev 38:1235-1254, 2018
90. Vag T, Steiger K, Rossmann A, et al: PET imaging of chemokine receptor CXCR4 in patients with primary and recurrent breast carcinoma. EJNMMI Res 8:90, 2018
91. Kratochwil C, Flechsig P, Lindner T, et al: FAPI-PET/CT: Mean intensity of tracer-uptake (SUV) in 28 different kinds of cancer. J Nucl Med 2019. jnumed.119.227967