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A Role of PET Agents Beyond FDG in Gynecology

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Gynecologic cancers comprise a varied group of malignancies with diverse clinical presentations and prognosis. Positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG), the most commonly used functional imaging for staging, treatment planning, and therapy response evaluation in gynecological cancers, is limited in providing information about the unique biological features of these tumors. There is an increasing need to noninvasively determine the patient's distinct tumor biological features in order to select the most appropriate therapy. This article presents an overview of the key PET biomarkers other than FDG that have been used for imaging of the three most common gynecological malignancies; cervical, endometrial, and ovarian cancers. These functional molecular imaging applications by PET have the potential to be translated to clinical practice for more complete evaluations of these cancers.
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Functional imaging plays an important role in the management of gynecological cancers. To improve the management of these cancers, there is a need for noninvasive imaging biomarkers to provide more detailed information about the tumor phenotype in order to personalize treatment approaches and improve outcomes. Positron emission tomography (PET) biomarkers are emerging as promising tools for better evaluation of these cancers. This review focuses on the potential applications of functional molecular imaging by PET in assessing tumor biology and cellular characteristics in the three main gynecological cancers.

Radionuclide Imaging As a Cancer Biomarker

There is considerable molecular and cellular heterogeneity within tumors; thus, it is becoming increasingly recognized that a single biopsy may not be an accurate representative of the tumor's unique features in order to guide patient management. Morphological imaging is typically used to guide clinical decisions; however, patient management can be improved using functional imaging due to its ability to demonstrate biological tumor features not identifiable by anatomical methods. Molecular imaging is also being explored as an early predictive biomarker in clinical trials of novel drugs, and increasingly being considered for noninvasive monitoring of the pharmacokinetic properties and pharmacodynamic changes of novel drugs in clinical trials. Imaging biomarkers have been defined as characteristics that can be objectively measured from imaging data as indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.[1] Imaging biomarkers play a crucial role, allowing noninvasive visualization of various tumor-biological processes, which can be used for diagnosis, predicting prognosis, selection of therapy, and treatment response monitoring.

PET using [^{18}F]fluorodeoxyglucose (FDG), a glucose analogue, is the most commonly used functional imaging radiotracer in oncologic patients, and plays a key role in staging, treatment planning, and monitoring treatment response in numerous cancers, including gynecological malignancies. Tumors have a high degree of dependence on glucose as the metabolic substrate, called the Warburg effect, which provides the basis for metabolic imaging. The Warburg effect is based on the observation that even under aerobic conditions, cancer cells tend to favor metabolism via glycolysis and convert glucose into lactate to generate energy. The preferred

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use of glucose as substrate, by many tumor types, is the cause for avid uptake of FDG, and the reason for the important clinical role of FDG-PET in evaluating tumors. Despite its primary role, false-positive and false-negative results are associated with the use of FDG, including increased metabolic activity in nonmalignant lesions such as inflammation and infection, and no or low metabolic activity in tumors due to their size and/or histological features.

Novel molecular imaging biomarkers, using specific PET radiolabeled ligands, have been used to evaluate tumor phenotypes, known as "hallmarks of cancer".[2] Phenotypic characteristics account for differences in tumor biologic features and clinical behavior, which may vary significantly within an individual patient or from patient to patient. These include the rate of proliferation, angiogenesis, hypoxia, metabolism, inflammation, and apoptosis. In addition, PET provides whole-body imaging, allowing for assessment of the heterogeneity of biological features between and within patients before and after therapy to monitor treatment response more accurately. The focus of this article is to provide an overview of the most common non-FDG radiotracers that are used primarily in research studies to evaluate the unique biological features of gynecological cancers, and their potential clinical applications.

Novel PET Tracers in Gynecological Cancer

PET Imaging of Tumor Receptors

PET Imaging of Steroid Receptors

Steroid hormones have an important role in the development and growth of several cancers via activation of their corresponding receptors. The hormone-receptor complex functions as a transcription factor, and activates pathways that typically control cell growth resulting in increased proliferation in hormone-dependent cancers. Estrogen receptor (ER) is an important predictive biomarker, and its status has been shown to predict prognosis and the probability of response to hormone therapy in breast cancer.[3,4] Due to its importance, ER has been targeted for both therapy and imaging.

PET allows noninvasive evaluation of receptor expression in tumors, providing information that can support therapy selection. Radiolabeled steroidal and nonsteroidal estrogens have been developed for PET imaging of ER. 16α-[^{18}F]fluoro-17β-estradiol (FES) is an estrogen analogue that has been successfully used for ER imaging in patients with breast and some gynecological cancers. There are two isoforms of ER; ERα and ERβ.[5] FES selectively binds to ERα, and can be used to determine the receptor status of all disease sites simultaneously, and is particularly helpful when suspected metastatic lesions cannot be biopsied.

PET Imaging of Steroid Receptors in Ovarian Cancer

While approximately 70% of epithelial ovarian cancer is ERα-positive, several studies[6-9] have reported poor response rate to endocrine therapy with the highest objective response rate of 19% and clinical benefit of 51%. In a study[10] of 15 patients with suspected ovarian cancer, van Kruchte et al found 32 measurable lesions >10 mm. FES uptake was quantified for 28 of these lesions while the remaining four lesions were visible but not quantifiable given the high uptake in adjacent tissues (Fig. 1). Histology was obtained on 23 of 28 lesions with measurable FES uptake, and showed a significant correlation between FES uptake and the semiquantitative immunoscore for tumor ERα ($\rho = 0.65$, $P < 0.01$) in these patients. An optimum threshold to discriminate ERα-positive and ERα-negative lesions was derived. They found that the maximum standardized uptake value (SUV_{max}) >1.8 has a 79% sensitivity, 100% specificity, and area under the curve of 0.86 (95% confidence interval, 0.70-1.00) for distinguishing ERα-positive from ERα-negative lesions. In addition, FES identified discordance in ER status in 2 of 7 patients with available cytology/histology between the primary diagnosis and debulking surgery. Given that the receptor status can change over time and assessment of ER by tissue sampling is not often possible and can be associated with morbidity and sampling error, a noninvasive method such as FES-PET to quantify ERα expression in multiple metastases throughout the body and at different time points is quite valuable. In a pilot study,[11] Yoshida et al reported FES uptake at the primary and metastatic sites in three patients with advanced ovarian cancer. Furthermore, the FES uptake was associated with ER status, mostly ERα status, as assessed by immunohistochemistry analysis of tumor biopsies. These results suggest that FES information may be beneficial in expanding treatment options for these patients. The significant limitation of FES to only quantify ERα expression, has led to the development of new PET tracers such as 2-^{18}F-fluoro-6-(6-hydroxynaphthalen-2-yl)pyridin-3-ol (FHNP) to evaluate ERβ,[12] and 16β-[^{18}F]fluoro-5α-dihydrotestosterone (FDHT), a fluorinated testosterone analogue which binds to the androgen receptor, both of these receptors are expressed in ovarian cancers.[13] FHNP is a promising radiotracer that has not yet been studied in humans, while FDHT has been evaluated successfully in patients with prostate cancer, but not in patients with gynecological cancers. Patients with ovarian cancer may benefit from FDHT-PET and possibly from therapies targeted to the androgen receptor.

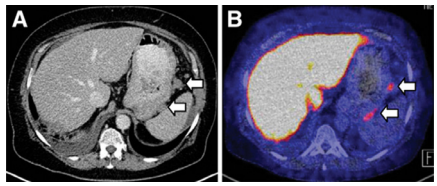

Figure 1 Metastatic ovarian cancer. Transaxial CT (A) and FES-PET/CT (B) images of a patient with focally increased FES uptake in the metastatic lesions between the stomach and spleen (arrows). Reprinted with permission.[10]

PET Imaging of Steroid Receptors in Endometrial Cancer

Patients with ERα-positive endometrial cancer have a higher clinical response rate and improved survival compared to the

patients with ERα-negative tumors,[14] supporting imaging ERα as a potential molecular predictive biomarker for prognosis.

The study by Tsujikawa et al[15] demonstrated that FES-PET and FDG-PET were useful for the differential diagnosis of benign and malignant uterine tumors; high FDG uptake/low FES uptake indicates malignant tumors, and low FDG uptake/high FES uptake indicates benign tumors. In a follow up study,[16] the authors reported that the mean SUV ratio of FDG to FES correlated with the degree of aggressiveness in terms of FIGO stage and histologic grade in endometrial cancer. High-risk carcinoma demonstrated a significantly greater FDG-to-FES ratio (mean ± standard deviation: 3.6 ± 2.1) than did low-risk carcinoma (1.3 ± 0.5, $P < 0.01$) and endometrial hyperplasia (0.3 ± 0.1, $P < 0.005$). Receiver operating characteristic analysis showed that the most accurate diagnostic PET parameter for predicting high-risk and low-risk carcinomas was the FDG-to-FES ratio. The optimal FDG/FES cutoff value of 2.0 provided 73% sensitivity, 100% specificity, and 86% accuracy in differentiating malignant tumors from benign lesions. These results support the notion that endometrial carcinoma reduces estrogen dependency with accelerated glucose metabolism as it progresses to a higher stage or grade; accordingly, FDG-to-FES ratio may be considered an index reflecting tumor aggressiveness.

In a similar study in patients with mesenchymal uterine tumors, Zhao et al[17] demonstrated that FES-PET and FDG-PET are useful noninvasive biomarkers for the assessment of tumor hormone receptor expression, glucose metabolism, and proliferation, and for differential diagnosis of uterine leiomyoma and sarcoma. Positive correlations were found between SUV for FES and immunohistochemistry scores of ERα, progesterone receptors ($P < 0.001$), and isoform progesterone receptorsβ ($P < 0.005$). In addition, positive correlations were found between SUV for FDG and glucose transporter 1 (GLUT-1) and a marker of cell proliferation (Ki-67) ($P < 0.001$) expressions. Moreover, the FDG-to-FES ratio correlated with Ki-67, GLUT-1, and the ERβ subtype in uterine sarcoma (Fig. 2). These results indicate that PET tracers are useful noninvasive biomarkers for the assessment of tumor hormone-receptor expression, glucose metabolism, and proliferation, and for possible distinction between benign and malignant lesions.

PET Imaging of HER Receptors in Ovarian Cancer

The four members of the human epidermal growth factor receptor family: HER1, HER2, HER3, and HER4, play a central role in the pathogenesis of multiple cancers, and hence serve as drug targets and biomarkers for anticancer treatment. HER2 is expressed in many tissues, and controls cell growth, survival, and differentiation via signal transduction pathways. It plays a major role in facilitating tumorigenesis and excessive/uncontrolled cell growth.[18] Overexpression of HER2 occurs in up to 20%-30% of mucinous ovarian cancers, and is associated with poor survival in advanced epithelial ovarian cancer.[19] Targeting of HER2 with the monoclonal antibody trastuzumab is a well-established therapeutic strategy for HER2-positive breast cancer. Several PET tracers with ^{89}Zr- and ^{64}Cu-labeled antibodies have been developed, with ^{89}Zr-trastuzumab and ^{64}Cu-DOTA-trastuzumab being the two most widely utilized. While clinical data is not yet available in patients with ovarian cancer, the preclinical studies are promising. Studies in HER2-overexpressing ovarian cancer xenografts models[20,21] demonstrated that ^{89}Zr-trastuzumab and ^{64}Cu-DOTA-trastuzumab uptake was reduced after treatment with an HSP 90 inhibitor, known to down-regulate the expression of HER2. This suggests that PET imaging detects HER2-positive ovarian cancer, and may

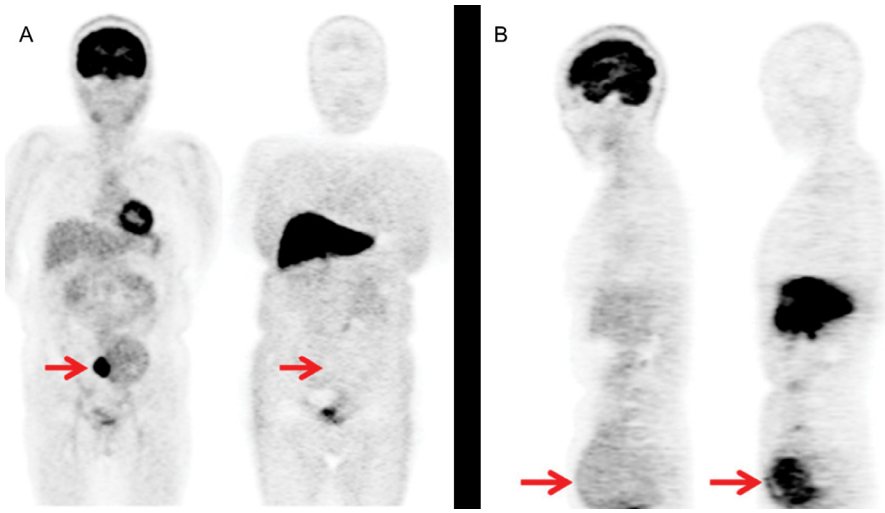

Figure 2 (A) Leiomyosarcoma. Body FDG-PET (left) and FES-PET (right) images of a 56-year-old woman with uterine leiomyosarcoma (red arrows). The SUV for FDG and FES, and FDG/FES ratio were 12.0, 0.9, and 13.3, respectively. Low uptake of FES significantly correlated with low expression of ERα (not shown). (B) Leiomyoma. Body FDG-PET (left) and FES-PET (right) images of a 49-year-old woman with uterine leiomyoma (red arrows). The SUV for FDG and FES, and FDG/FES ratio were 1.9, 6.2, and 0.3, respectively. High uptake of FES correlated with high expression of ERα (not shown). Reprinted with permission.[17]

have an important role in monitoring tumor status during HER2-targeting therapy.

Similar to HER2, HER3 has been implicated in cancer progression and drug resistance, given its unique functionality through dimerization with other HER receptors. Approximately 16% of ovarian tumors show overexpression of HER3 protein compared to normal ovarian samples.[22] The overexpression of HER3 is strongly associated with poor overall prognosis of ovarian cancer. The development of lumretuzumab (RG7116), a humanized monoclonal HER3 targeting antibody, labeled with ^{89}Zr, allows for assessment of HER3 expression noninvasively. A pilot PET study of 20 patients with histologically confirmed HER3 overexpressing solid tumors including ovarian cancer[23] demonstrated ^{89}Zr-RG7116 specific uptake in HER3-positive metastatic disease. This PET tracer has the potential to be used for prediction and monitoring response to HER3-directed therapy, with further studies required to fully assess its role in ovarian cancer.

PET Imaging of Somatostatin Receptors

Neuroendocrine tumors (NETs) are rare neoplasms characterized by overexpression of somatostatin receptors (SSTRs). Somatostatin is a peptide hormone which binds to SSTRs, and regulates neurotransmission, hormone secretion, and cell proliferation. SSTRs has been targeted for imaging, most recently with ^{68}Ga for PET imaging (^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-TATE, and ^{68}Ga-DOTA-NOC). Most NETs are well differentiated, and are not well visualized on FDG-PET requiring ^{68}Ga-DOTA-peptides for accurate assessment. In addition, ^{68}Ga-DOTA-peptides imaging provide an indirect measure of tumor cell differentiation, offering information on disease extension and tumor cell receptor expression status, particularly relevant before starting targeted radionuclide therapy.

PET Imaging of SSTRs in Cervical Cancer

A potential role of SSTRs-PET agents is in the evaluation of a rare subtype of cervical cancer, small cell neuroendocrine carcinoma. Cervical neuroendocrine carcinoma represent only about 2% of all cervical malignancies, and are associated with a poor prognosis[24] given its propensity to spread distantly via lymphatic and hematogenous dissemination. Whole-body imaging with SSTRs-PET agents has been proposed to assist in the evaluation of locoregional disease and distant spread of cervical NETs for which structural imaging is often unremarkable.[25] This potential is illustrated by the use ^{68}Ga-DOTATATE PET/CT in a patient with small NET of the cervix, which demonstrated focal uptake at the primary tumor site and in a solitary pelvic bone metastasis, confirmed by biopsy.[25] This study illustrates the potential utility of SSTRs-PET as a useful imaging modality for early detection and treatment in these patients.

PET Imaging of Cell Proliferation Rate

Rapid and uncontrolled cell proliferation is the primary hallmark of cancer and usually indicative of tumor aggressiveness, and is thus considered an important biomarker for tumor prognosis. FDG is not considered a cell proliferative tracer, and its uptake reflects not only cell proliferation, but other molecular mechanisms and cellular components with the most important being expression of GLUT-1 and hexokinase, number of viable tumor cells, microvessel density, and presence of inflammatory cells.[26] Several DNA precursors have been investigated for imaging the rate of cell proliferation, the most widely used being 3′-Deoxy-3′-[^{18}F]fluorothymidine (FLT), a pyrimidine analogue of the naturally occurring nucleoside thymidine. The cellular uptake of FLT occurs through a combination of passive diffusion and facilitated transport by type 1 equilibrate nucleoside transporters (ENT1).[27,28] Thus, FLT accumulates in proliferating tissues and malignant tumors, but is only minimally incorporated into DNA (<2%); therefore, it is not a direct measure of cell proliferation. In vitro studies indicated that FLT uptake is closely related to TK1 activity and respective protein levels, and is therefore considered to reflect TK1 activity and, hence, S-phase fraction rather than DNA synthesis. Potential limitations of FLT are high bone marrow and liver activity, possible early increase of uptake with some cytostatic agents, and false-negative results in tumors that mainly depend on the de novo thymidine synthesis pathway.[29,30] Furthermore, it has been shown that FLT is a less sensitive diagnostic tool due to its lower tumor-to-nontumor uptake ratios compared with FDG; but has been proposed as a useful tool in monitoring response to therapy,[31] however, validation with larger clinical studies is required.

PET Imaging of Cell Proliferation Rate in Cervical Cancer

Although concurrent chemoradiotherapy is the standard treatment for bulky or locally advanced cervical cancer, it increases the incidence of hematologic toxicity.[32,33] A proposed strategy for reducing hematologic toxicity in cervical cancer patients is to identify active bone marrow within the radiation field in order to avoid/decrease radiation to these regions using an intensity modulation radiation therapy[34] (Fig. 3). McGuire et al studied 18 patients (six with cervical cancer and twelve with head and neck cancers) and found that by reducing the radiation dose to functional bone marrow, identified by FLT-PET, a higher proportion of patients completed a full course of treatment and/or the overall toxicity was reduced without compromising treatment planning goals.[35] In a recent small study,[36] FDG and FLT uptake was compared for detection of active bone marrow within the pelvic bone for sparing during radiotherapy. While there was a significant overlap between FLT and FDG results, FLT had a higher interpatient consistency and tendency to identify bone marrow. The authors concluded that despite agreement between the tracers, FLT showed less individual variation providing a superior imaging choice for bone marrow sparring strategies. In summary, FLT has shown a promising role in proliferative imaging in cervical cancer for bone marrow sparing radiation planning.

PET Imaging of Cell Proliferation Rate in Endometrial Cancer

Uterine leiomyomas are the most common benign neoplasms arising from the smooth muscle layer of the uterus. The most

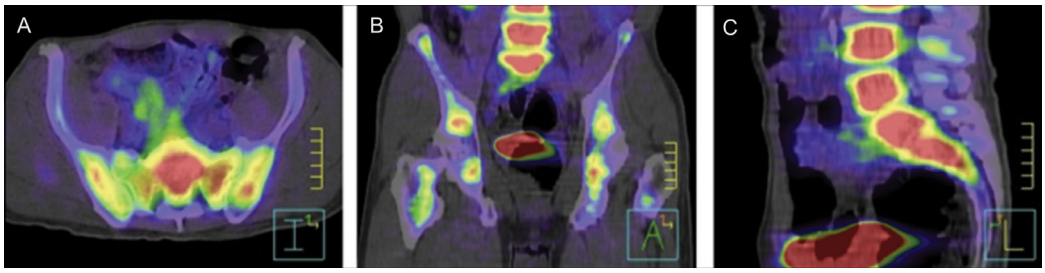

Figure 3 Cervical cancer. Co-registered FLT-PET and CT images in transaxial (left), coronal (middle), and sagittal (right) demonstrated FLT uptake in the bone marrow. Purple represents the lowest uptake and red the highest uptake. Reprinted with permission.[34]

commonly used PET tracer, FDG, demonstrates increased uptake in approximately 10% and 1.2% of leiomyomas in premenopausal and postmenopausal women, respectively.[37] FLT has been evaluated to differentiate malignant from benign leiomyomas by Yamane et al.[38] In their study of 15 patients (nine premenopausal and six postmenopausal), they demonstrated that FDG and FLT have similar sensitivity (100%) and negative-predictive value (100%) for malignancy, while specificity, positive predictive value, and accuracy of FLT were higher than those of FDG. Specificity, positive predictive value and accuracy were 90%, 83.9%, and 93.3%, respectively for FLT and were 70%, 62.5%, and 80%, respectively for FDG. In addition, differences in SUV_{max} between malignant and benign lesions were significant for FLT ($P < 0.01$), but not for FDG. Moreover, FLT showed better and significant linear correlation with the labeling index of Ki-67 compared with FDG ($R^2 = 0.91$, $P < 0.001$ vs. $R^2 = 0.26$, $P = 0.06$) (Fig. 4). The study suggests that negative findings on FDG-PET or FLT-PET may rule out the possibility of malignancy for patients with suspected leiomyosarcoma diagnosed by conventional MR methods, which has important clinical implications, as benign leiomyomas can resemble malignant tumors.

PET Imaging of Cell Proliferation Rate in Ovarian Cancer

It has been shown that FDG-PET is more sensitive than contrast-enhanced CT in identifying primary tumors and metastasis in ovarian cancer,[39,40] but suffers from limitations including variable degree of FDG uptake in epithelial ovarian carcinomas, and physiological uptake in the ovaries, most commonly in corpus luteal cysts. In a small pilot study of patients (n = 6) with ovarian cancer who underwent FLT before debulking surgery,[41] higher FLT uptake in malignant (mean $SUV_{max} = 4.85$, range 1.7-8.8) compared with benign lesions (1.65, range 1.4-1.9) and normal ovarian tissue (1.12, range 0.6-1.5) was noted. The mitotic index, as determined by Ki-67 staining, was higher in malignant lesions (18.89, range 11.97-27.19) compared to benign (0.59, range 0.23-0.95) and normal tissue (0.45, range 0.06-1.20). The authors found higher TK-1 expression in malignant (35.52, range 5.21-106.62) compared to benign lesions (8.71, range 4.74-12.67) and normal ovarian tissue (9.79, range 0.85-39.46). The authors noted an increasing trend between FLT uptake and Ki-67 mitotic index in malignant lesions.

The role of FLT has also been evaluated to predict response to treatment in several types of cancers.[29,42,43] These studies demonstrated reduction in cell proliferation rate that preceded changes in tumor volume. In a small study (n = 3) of recurrent ovarian cancer patients treated with gemcitabine-based chemotherapy, tumor FLT uptake decreased earlier than the FDG uptake and was better correlated with a reduction in tumor size, as measured by subsequent CT.[43]

The mammalian target of rapamycin (mTOR) plays a central role in regulating cell growth and proliferation. The mTOR inhibitor everolimus has been shown to inhibit human ovarian cancer cell growth, enhance the effect of cisplatin, and delay tumor progression in an ovarian cancer xenograft model.[44] The ability of FLT was evaluated for monitoring early response to treatment with everolimus in an animal model of cisplatin-resistant ovarian tumor. The reduced FLT uptake appears to occur early and precede tumor volume response. The authors concluded that early treatment monitoring by FLT may provide an important diagnostic tool in future preclinical or clinical trials evaluating treatment of cisplatin-resistant ovarian tumors by mTOR inhibitors.[42]

Further studies are needed to determine whether FLT is specific enough to distinguish between malignant and benign lesions, to assess its role in treatment planning, and to serve as an early biomarker of response to therapy in genealogical cancers.

PET Imaging of Tumor Hypoxia

It is well-known that hypoxic cells are more resistant to radiation than well-oxygenated cells. Radiotherapy may fail to achieve local control due to the presence of tumor hypoxia (pO2 <10 mm Hg), which decreases the availability of oxygen free radicals necessary to induce sufficient DNA damage to cause cell death. There is also evidence that hypoxia increases resistance to chemotherapy, likely related to decrease in proliferating cells since most anticancer drugs are most effective against rapidly proliferating cells. Polarographic oxygen electrodes are considered to be the gold standard for detection of hypoxia. However, this technique is invasive, technically difficult to perform, evaluates only readily accessible lesions and is sample dependent, and thus, cannot readily address tumor heterogeneity, an important feature of solid tumors. The PET imaging of hypoxia has several advantages compared with the polarographic oxygen

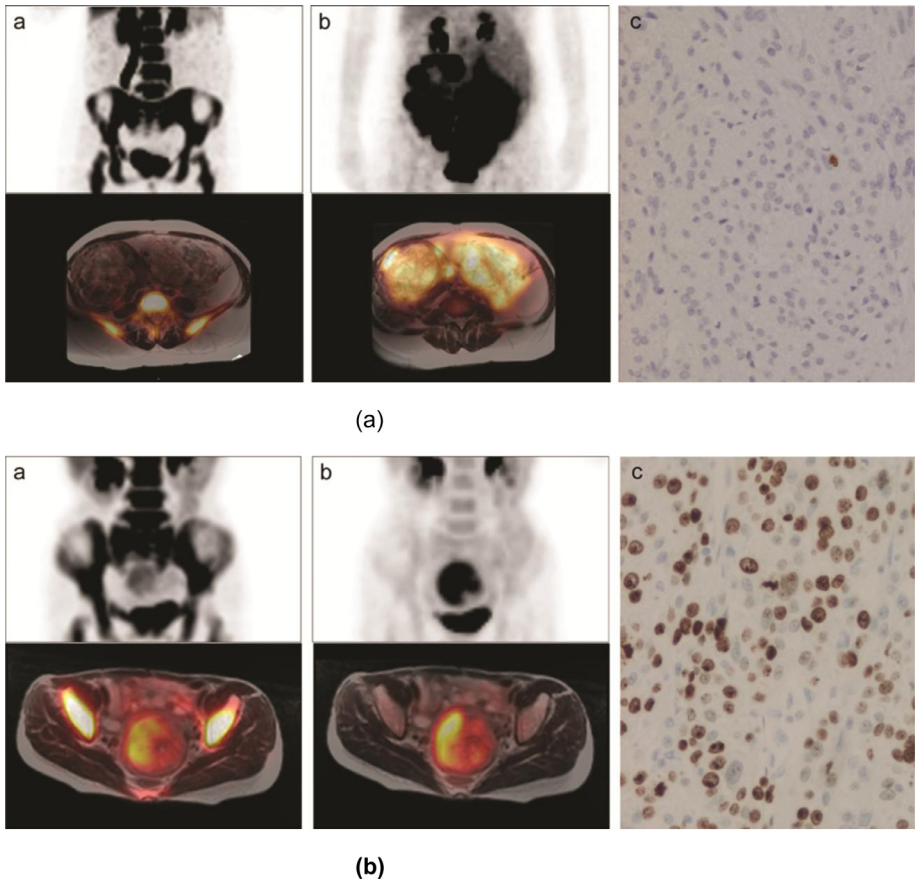

Figure 4 (A) Leiomyoma. Maximum-intensity reprojection and transaxial PET images fused with MRI acquired with FLT (a) and FDG (b), and Ki-67 immunohistochemical staining (c). These images show no apparent FES uptake (SUV_{max} of 1.8), but high FDG uptake (SUV_{max} of 14.8) in the leiomyoma. The Ki-67 labeling index was low (1.7%). (B) Leiomyosarcoma. Maximum-intensity reprojection and transaxial PET images fused with MRI acquired with FLT (a) and FDG (b), and Ki-67 immunohistochemical staining (c). The images show increased FLT uptake (SUV_{max} of 3.9) and FDG uptake (SUV_{max} of 6.5). The Ki-67 labeling index was high (53.4%). Reprinted with permission.[38]

electrode probe and can directly address intratumoral heterogeneity. Alternative noninvasive methods such as PET imaging allow for serial evaluations and can evaluate the entire tumor, addressing tumor heterogeneity. In addition, it can evaluate multiple lesions throughout the body, even areas inaccessible to probe insertion. There are essentially two groups of hypoxia PET tracers, fluorine labeled nitroimidazoles and copper labeled diacetyl-bis(N4-ethylthiosemicarbazone) (ATSM) analogues. Hypoxia imaging with PET is based mostly on ^{18}F-labeled 2-nitroimidazole compounds, which covalently bind to cellular macromolecules in hypoxic conditions as a result of multistep intracellular electron reduction of the parent compound. When hypoxia is present, further reductive metabolism gives rise to more or less stable intracellular hydroxylamine derivatives, which are trapped intracellularly and can be detected with PET.[45,46]

The main limitations of the 2-nitroimidazoles tracer class are relatively low uptake within the tumor and the slow accumulation in hypoxic tissues showing no hypoxia-specific signal until several hours postinjection, thus, making successful evaluation of hypoxic lesions a challenge. ^{18}F-fluoromisonidazole (FMISO) is the most widespread nitroimidazole compound used for hypoxia imaging. The tracer is highly lipophilic, which facilitates its diffusion across cell membranes but results in slow clearance of the tracer from normoxic tissue, making the tumor-to-blood ratio rather low. Therefore, long intervals between tracer injection and imaging, usually greater than 2 hours, are required for optimal discrimination between hypoxia and normoxic tissue.[47] Several other nitroimidazol hypoxia compounds including [^{18}F]FETA, [^{18}F]FAZA, [^{18}F]FETNIM, [^{18}F]EF1, [^{18}F]EF3, and [^{18}F]EF5 have been developed in hopes of addressing limitations of FMISO.

Cu-ATSM is part of the dithiosemicarbazones group, and demonstrates some pharmacokinetic advantages compared to nitroimidazoles. Cu-ATSM has faster pharmacokinetics allowing imaging earlier after injection compared with FMISO (30 minutes after injection for Cu-ATSM vs. 2-4 hours for FMISO). Additionally, the different radioisotopes of copper used to label ATSM provide a great deal of versatility: [^{60}Cu] (t1/2 = 23.4 min, β+ = 81%), [^{61}Cu] (t1/2 = 3.4 h, β+ = 62%), [^{62}Cu] (t1/2 = 9.7 min, β+ = 97.5%), and [^{64}Cu] (t1/2 = 12.7 h, β+ = 17%, $\beta-$ = 40%).[48] ^{64}Cu-ATSM is the most commonly used copper isotope with a half-life of 12.7 hours, which makes it well-suited for PET studies. This radiotracer has been studied as both a diagnostic and therapeutic

radionuclide given its' unique decay prolife (β+: 18%, β−: 38%, and electron capture: 44%). The PET images of ^{64}Cu-ATSM are of very high quality since it has a β+ maximum energy of 0.66 MeV, similar to ^{18}F of 0.63 MeV.[49] The utility of FMISO and Cu-ATSM for selecting the most appropriate treatment plan and improving patient outcomes has yet to be established.

PET Imaging of Hypoxia in Cervical Cancer

Tumor hypoxia is an important feature of cervical cancer. Multiple studies using intratumoral pO2 demonstrated hypoxic changes in about half of the cervical cancer patients.[50-53] These studies demonstrated that patients with nonhypoxic tumors have better prognosis than those with hypoxic tumors.[54] Although the hypoxia imaging tracer, FMISO, has proven useful in the assessment and prediction of outcome of different cancers, there are only a small number of studies in cervical cancer. In a small longitudinal, multiparametric MRI and PET study of patients with cervical cancer (n = 13), Georg et al[55] observed that the topographic location of hypoxic subvolumes, as assessed by FMISO, changed during radiotherapy. The variation in hypoxic regions during the treatment course may indicate the necessity of dose adjustment and a more personalized treatment approach during therapy. A pilot study of patients (n = 16) with cervical cancer that underwent MRI, FMISO-PET, and/or FDG-PET demonstrated that all tumors displayed imaging characteristics concordant with cervix cancer with morphologically visible tumor on MRI and increased FDG and FMISO uptake.[56] In all patients, the extent of hypoxia by FMISO was independent of tumor volume. In the 11 patients with complete imaging data sets, a voxel-by-voxel analysis showed only weak correlations between the MRI, FDG, and FMISO parameters, indicating that each imaging biomarker provides complementary information on tumor biology and heterogeneity that may be used to improve management of these patients.

The radiotracer FAZA is a second generation 2-nitroimidazole with superior pharmacokinetics compared to FMISO, providing an improved tumor-to-background ratio.[57] Its major disadvantage is its elimination via the urinary system, resulting in high tracer activity in the ureters and bladder, which makes delineation of tumor sites adjacent to the urinary system difficult. The feasibility of FAZA was evaluated by Schuetz et al[58] in patients (n = 15) with cervical cancer before, during and after combined radiochemotherapy and MRI-guided brachytherapy. Five patients had increased tumor uptake of FAZA prior to radiochemotherapy and four patients before brachytherapy. One of the five patients with a FAZA positive scan had incomplete remission 3 months after radiotherapy and one had regional recurrence. Four of the 10 patients with FAZA negative scans developed distant metastases. The authors concluded that FAZA imaging was feasible, however, its predictive and prognostic value in cervical cancer remains to be clarified. A more recent study[59] of 27 patients with cervical cancer presented encouraging results with hypoxia volume detected with FAZA-PET in the majority of cervical tumors and the extent of hypoxia varied markedly between tumors (Fig. 5).

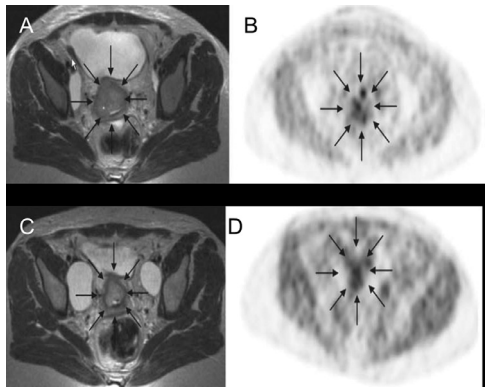

Figure 5 Cervical cancer. Transaxial MRI (left) and FAZA-PET (right) images before therapy (A-B) and during radiotherapy (C-D) in a patient with FIGO stage IIb cervical cancer. Arrows indicate the tumor on the MRI and the hypoxic areas within the tumor. Reprinted with permission.[58]

Vercellino et al[60] evaluated FETNIM for imaging hypoxia in cervical cancer, and compared its uptake with FDG in a small number of patients. The authors reported that high FETNIM uptake (tumor-to-muscle ratio >3.2) and high hypoxia marker values (osteopontin levels >144 ug/L) were associated with worse prognosis, shorter progression-free interval and lower overall survival (OS). The authors found no significant correlation between FETNIM uptake, FDG uptake or blood levels of osteopontin. FETNIM tumor uptake was difficult to discriminate from adjacent normal soft tissues, limiting its use in defining the hypoxic volume. Furthermore, furosemide was needed to reduce the image artifact related to high urine activity within the urinary bladder and improve image quality.

One of the promising agents currently under study for imaging of hypoxia is Cu-ATSM. Cu-ATSM is a neutral lipophilic molecule with high cell membrane permeability and, thus, diffuses readily from the bloodstream to surrounding cells. Inside the cell, it undergoes reduction only in hypoxic cells and becomes trapped within those cells, but washes out rapidly from normoxic cells without any change. Cu-ATSM is insignificantly excreted by the urinary tract, which makes it ideal for the evaluation of pelvic organs. The most commonly used, ^{60}Cu-ATSM and ^{64}Cu-ATSM, provide favorable tumor-to-background ratio.

Dehdashti et al[61] demonstrated that the pretreatment tumor hypoxia assessed by ^{60}Cu-ATSM in patients (n = 14) with advanced cervical cancer is predictive of response to subsequent therapy. Tumor ^{60}Cu-ATSM uptake was inversely correlated with progression free survival (PFS) and OS. An arbitrarily selected tumor-to-muscle uptake (T/M) ratio of >3.5 discriminated hypoxic tumors from normoxic tumors, and tumors likely to develop recurrence. There was no significant difference in tumor FDG uptake between patients with hypoxic tumors and those with normoxic tumors. In addition, tumor FDG uptake did not correlate with ^{60}Cu-ATSM uptake (r = 0.04; P= 0.80). These findings later were confirmed in a larger number of patients with

advanced cervical cancer.[62] Thirty-eight women with biopsy-proved cervical cancer underwent ^{60}Cu-ATSM before the initiation of radiotherapy and chemotherapy. The study confirmed PFS and cause-specific survival were significantly better in patients with a ^{60}Cu-ATSM T/M of $\leq$3.5 ($P = 0.006$ and $P = 0.04$, respectively). The 3-year progression-free survival of patients with normoxic tumors (T/M of $\leq$3.5) was 71%, and that of patients with hypoxic tumors (T/M of $>$ 3.5) was 28% ($P = 0.01$). The T/M threshold of 3.5 was the best discriminator of patients likely to develop a recurrence from those unlikely to develop a recurrence. Similarly, no correlation was seen between tumor FDG uptake and ^{60}Cu-ATSM uptake. In addition, there was no significant difference in tumor FDG uptake between patients with hypoxic tumors and those with normoxic tumors ($P = 0.9$). The authors concluded that pretherapy ^{60}Cu-ATSM provides clinically important information about tumor oxygenation that was predictive of outcome in this patient population.

In a subsequent study,[63] ^{60}Cu-ATSM was compared with ^{64}Cu-ATSM in patients with cervical cancer. The authors demonstrated that image quality with ^{64}Cu-ATSM was better because of lower noise. In addition, they found that the pattern and magnitude of tumor uptake of ^{60}Cu-ATSM and ^{64}Cu-ATSM on studies separated by 1-9 days were similar. Recently, a multicenter trial (ACRIN 6682) with ^{64}Cu-ATSM in patients with cervical cancer to confirm its role in predicting prognosis has been completed and the data is under evaluation. Representative images of a patient undergoing ^{64}Cu-ATSM-PET/CT are illustrated in Figure 6.

Grigsby et al[64] evaluated the association of ^{60}Cu-ATSM uptake with the expression of hypoxia-related tumor molecular markers: vascular endothelial growth factor (VEGF), cyclo-oxygenase-2, epidermal growth factor receptor (EGFR), carbonic anyhdrase IX (CA-9), and apoptotic index in patients (n = 15) with cervical cancer. The authors found that overexpression of tumor molecular markers and apoptosis occurred in patients with hypoxic tumors. In addition, a significant correlation between ^{60}Cu-ATSM uptake and the clinical presence of FDG positive lymph nodes was noted (6/6 hypoxic patients vs 3/9 normoxic patients, $P = 0.0098$).

PET Imaging of Angiogenesis

Angiogenesis, the formation of new blood vessels, is of critical importance for tumor growth and metastasis, and has been targeted for imaging for tumor diagnosis, and assessment of treatment response. The process of angiogenesis is multifaceted controlled by numerous important pathways including VEGF, the platelet derived growth factor, the fibroblast growth factor, and tyrosine kinase inhibitors.[65] Examples of angiogenesis imaging biomarkers are integrin and vascular endothelial growth factor receptor 2. In view of current antiangiogenic treatment strategies, the noninvasive visualization and characterization of tumor angiogenesis are very desirable.

PET Imaging of Angiogenesis in Ovarian Cancer

VEGF has been implicated in angiogenesis and tumor progression in epithelial ovarian cancer,[66,67] and directly correlated with the extent of disease and inversely with PFS.[68,69] Therapies targeting antigenic pathways in ovarian cancer have been explored, and their therapeutic value is under evaluated. In the meta-analysis of 12 studies of antiangiogenic agents in ovarian cancers,[70] the overall analysis revealed that antiangiogenesis therapies (Bevacizumab, Trebananib, Pazopanib, Cediranib, and Nintedanib) were significantly associated with improvements in PFS (hazards ratio, 0.66; 95% confidence interval, 0.58-0.75; $P < 0.01$) and OS (hazards ratio, 0.89; 95% confidence interval, 0.82-0.97; $P = 0.01$) in the total population. However, VEGF-directed therapies in epithelial ovarian cancer with bevacizumab, a

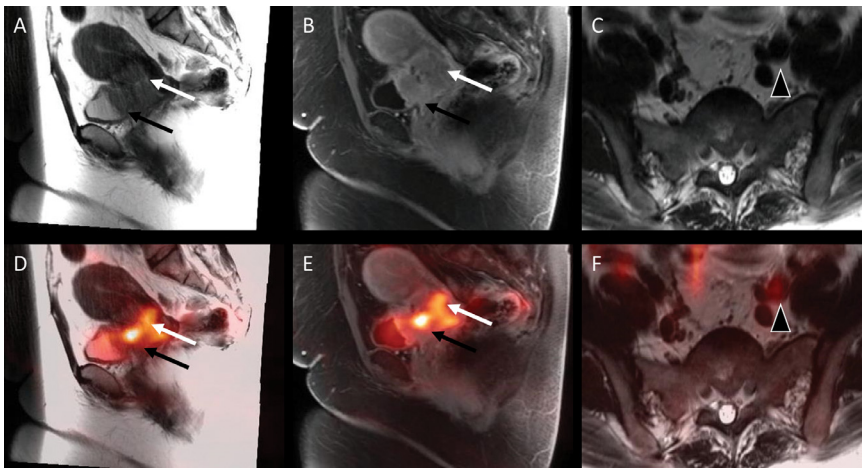

Figure 6 Cervical cancer. Pelvic MR (upper) and fused ^{64}Cu-ATSM-PET and MR images (lower). Sagittal T2-weighted (A), sagittal T1-weighted postcontrast (B) and transaxial T2-weighted (C) images. Fused ^{64}Cu-ATSM-PET with same sequences MR images (D-F) in a 33-year-old woman with newly diagnosed squamous cell carcinoma of the cervix. The images demonstrate a ^{64}Cu-ATSM avid mass centered within the anterior cervix, which extends to and involves the lower third of the uterine body (white arrows) invading the posterior bladder wall by the mass (black arrows). Avid lymphadenopathy is also noted (arrow heads).

humanized anti-VEGF monoclonal antibody, and pazopanib, a VEGF receptor tyrosine kinase inhibitor were not associated with improvements in OS and PFS benefit was limited. Furthermore, patients with recurrent ovarian cancer derived greater OS benefit from the antiangiogenesis therapies. The authors raised the possibility of using specific biomarker signatures to stratify patients with ovarian cancer according to the expected benefit of antiangiogenesis therapy. Radiolabeled bevacizumab has been used to visualize and quantify VEGF-A using the PET isotope, ^{89}Zr-bevacizumab, in xenograft model of ovarian cancer.[71] While preclinical studies are promising as an early predictive biomarker for bevacizumab efficacy, ^{89}Zr-bevacizumab has not been tested in ovarian cancer patients.

PET Imaging of Poly(ADP-ribose) Polymerase

The nuclear enzyme poly(ADP-ribose) polymerase 1 (PARP-1) is the most abundant isoform of the PARP enzyme family, and plays a crucial role in cell signaling, DNA damage response, and modulates a variety of other important biological pathways. The therapeutic potential of PARP inhibitors are being explored for cancer treatment since they enhance the effect of anticancer drugs and decrease angiogenesis. Poly (ADP-ribose) polymerase inhibitors (PARPi) are a promising group of drugs for treatment of epithelial ovarian cancer; however, the response to PARPi therapy is variable, and tools for predicting patient response are limited. Current methods to determine PARP-1 expression are based on immunohistology which requires invasive procedures by biopsy or surgery to obtain tumor specimens. The immunohistochemistry of PARP-1 has been shown to be highly variable in patients with ovarian,[72] breast,[73] and prostate cancer,[74] and yield mixed results in regard to prognosis and outcome. Therefore, there is a need for a biomarker capable of assessing PARP-1 in vivo that could enable patient selection for PARPi therapy.

PET Imaging PARP in Ovarian Cancer

[^{18}F]FluorThanatrace ([^{18}F]FTT) is a radiolabeled small-molecule PARPi that has shown to correlate with PARP-1 expression through a receptor-ligand.[73,75] In addition, similar correlation with PARP-1 expression has been found with [^{125}I]KX1, an iodinated analogue of [^{18}F]FTT.[76] In a study,[77] Makvandi et al quantified PARP-1 expression in primary ovarian and metastatic disease (n = 20) using [^{18}F]FTT. They found a spectrum of tumor [^{18}F]FTT uptake and PARP-1 expression by fluorescent immunohistochemistry (f-IHC) and [^{125}I]KX1 autoradiography, demonstrating direct evidence for the wide range of PARP-1 expression in ovarian cancer. The authors reported positive correlations between PARP-1 f-IHC and [^{18}F]FTT uptake ($r^2 = 0.60$, $r = 0.77$) and PARP-1 f-IHC and [^{125}I]KX1 autoradiography ($r^2 = 0.79$, $r = 0.89$). There was no correlation between FDG and [^{18}F]FTT, PARP-1 f-IHC, or [^{125}I]KX1 autoradiography, supporting distinct and different molecular imaging targets for [^{18}F]FTT and FDG, and suggesting that FDG and FFT provide different and complementary information. Additional studies are needed to further evaluate [^{18}F]FTT as a biomarker to stratify patients for PARPi therapy and assess its effectiveness in patients with ovarian cancer.

Summary

The role of FDG in the evaluation of gynecological tumors has been well-established and described by other authors in this special issue. This chapter provides an overview of non-FDG PET tracers, targeting various biological metabolic processes in gynecological cancers. Given the expected advances in targeted therapy and precision medicine, we anticipate witnessing the use of a wide range of novel radiotracers in these patients to unravel the molecular, genetic and clinical phenotype complexities involved in disease progression, leading to better identification of more effective prognostication and targeted therapies. Future investigations are needed to further evaluate clinical applications of these novel non-FDG tracers and determine their benefit in gynecological cancers.

References

1. Natarajan A, Mayer AT, Xu L, et al: Novel radiotracer for immunoPET imaging of PD-1 checkpoint expression on tumor infiltrating lymphocytes. Bioconjug Chem 26:2062-2069, 2015
2. Hanahan D, Weinberg RA: Hallmarks of cancer: The next generation. Cell 144:646-674, 2011
3. Peterson LM, Mankoff DA, Lawton T, et al: Quantitative imaging of estrogen receptor expression in breast cancer with PET and 18F-fluoroestradiol. J Nucl Med 49:367-374, 2008
4. Linden HM, Dehdashti F: Novel methods and tracers for breast cancer imaging. Semin Nucl Med 43:324-329, 2013
5. Gustafsson JA: Estrogen receptor beta—a new dimension in estrogen mechanism of action. J Endocrinol 163:379-383, 1999
6. Hasan J, Ton N, Mullamitha S, et al: Phase II trial of tamoxifen and goserelin in recurrent epithelial ovarian cancer. Br J Cancer 93:647-651, 2005
7. Argenta PA, Thomas SG, Judson PL, et al: A phase II study of fulvestrant in the treatment of multiply-recurrent epithelial ovarian cancer. Gynecol Oncol 113:205-209, 2009
8. Papadimitriou CA, Markaki S, Siapkaras J, et al: Hormonal therapy with letrozole for relapsed epithelial ovarian cancer. Long-term results of a phase II study. Oncology 66:112-117, 2004
9. Bowman A, Gabra H, Langdon SP, et al: CA125 response is associated with estrogen receptor expression in a phase II trial of letrozole in ovarian cancer: Identification of an endocrine-sensitive subgroup. Clin Cancer Res 8:2233-2239, 2002
10. van Kruchten M, de Vries EF, Arts HJ, et al: Assessment of estrogen receptor expression in epithelial ovarian cancer patients using 16alpha-18F-fluoro-17beta-estradiol PET/CT. J Nucl Med 56:50-55, 2015
11. Yoshida Y, Kurokawa T, Tsujikawa T, et al: Positron emission tomography in ovarian cancer: 18F-deoxy-glucose and 16alpha-18F-fluoro-17beta-estradiol PET. J Ovarian Res 2:7, 2009
12. Antunes IF, van Waarde A, Dierckx RA, et al: Synthesis and evaluation of the estrogen receptor beta-Selective Radioligand 2-(18)F-Fluoro-6-(6-Hydroxynaphthalen-2-yl)Pyridin-3-ol: Comparison with 16alpha-(18)F-Fluoro-17beta-Estradiol. J Nucl Med 58:554-559, 2017
13. Talbot JN, Gligorov J, Nataf V, et al: Current applications of PET imaging of sex hormone receptors with a fluorinated analogue of estradiol or of testosterone. Q J Nucl Med Mol Imaging 59:4-17, 2015
14. Singh M, Zaino RJ, Filiaci VJ, et al: Relationship of estrogen and progesterone receptors to clinical outcome in metastatic endometrial carcinoma: A Gynecologic Oncology Group Study. Gynecol Oncol 106: 325-333, 2007

15. Tsujikawa T, Yoshida Y, Mori T, et al: Uterine tumors: pathophysiologic imaging with 16alpha-[18F]fluoro-17beta-estradiol and 18F fluorodeoxyglucose PET—initial experience. Radiology 248:599-605, 2008
16. Tsujikawa T, Yoshida Y, Kudo T, et al: Functional images reflect aggressiveness of endometrial carcinoma: Estrogen receptor expression combined with 18F-FDG PET. J Nucl Med 50:1598-1604, 2009
17. Zhao Z, Yoshida Y, Kurokawa T, et al: 18F-FES and 18F-FDG PET for differential diagnosis and quantitative evaluation of mesenchymal uterine tumors: Correlation with immunohistochemical analysis. J Nucl Med 54:499-506, 2013
18. Neve RM, Lane HA, Hynes NE: The role of overexpressed HER2 in transformation. Ann Oncol 12(Suppl 1):S9-S13, 2001
19. Berchuck A, Kamel A, Whitaker R, et al: Overexpression of HER-2/neu is associated with poor survival in advanced epithelial ovarian cancer. Cancer Res 50:4087-4091, 1990
20. Oude Munnink TH, Korte MA, Nagengast WB, et al: (89)Zr-trastuzumab PET visualises HER2 downregulation by the HSP90 inhibitor NVP-AUY922 in a human tumour xenograft. Eur J Cancer 46:678-684, 2010
21. Niu G, Li Z, Cao Q, et al: Monitoring therapeutic response of human ovarian cancer to 17-DMAG by noninvasive PET imaging with (64)Cu-DOTA-trastuzumab. Eur J Nucl Med Mol Imaging 36:1510-1519, 2009
22. Rajkumar T, Stamp GW, Hughes CM, et al: c-erbB3 protein expression in ovarian cancer. Clin Mol Pathol 49:M199-M202, 1996
23. Bensch F, Lamberts LE, Smeenk MM, et al: (89)Zr-Lumretuzumab PET imaging before and during HER3 antibody lumretuzumab treatment in patients with solid tumors. Clin Cancer Res 23:6128-6137, 2017
24. Miller B, Dockter M, el Torky M, Photopulos G: Small cell carcinoma of the cervix: A clinical and flow-cytometric study. Gynecol Oncol 42: 27-33, 1991
25. Damian A, Lago G, Rossi S, et al: Early detection of bone metastasis in small cell neuroendocrine carcinoma of the cervix by 68Ga-DOTATATE PET/CT Imaging. Clin Nucl Med 42:216-217, 2017
26. Buck AK, Reske SN: Cellular origin and molecular mechanisms of 18F-FDG uptake: Is there a contribution of the endothelium. J Nucl Med 45:461-463, 2004
27. Kostakoglu L: Novel PET radiotracers for potential use in management of lymphoma. PET Clin 7:83-117, 2012
28. Plotnik DA, Emerick LE, Krohn KA, et al: Different modes of transport for 3H-thymidine, 3H-FLT, and 3H-FMAU in proliferating and nonproliferating human tumor cells. J Nucl Med 51:1464-1471, 2010
29. Dittmann H, Dohmen BM, Kehlbach R, et al: Early changes in [18F]FLT uptake after chemotherapy: An experimental study. Eur J Nucl Med Mol Imaging 29:1462-1469, 2002
30. McKinley ET, Ayers GD, Smith RA, et al: Limits of [18F]-FLT PET as a biomarker of proliferation in oncology. PLoS One 8:e58938, 2013
31. Tehrani OS, Shields AF: PET imaging of proliferation with pyrimidines. J Nucl Med 54:903-912, 2013
32. Torres MA, Jhingran A, Thames Jr HD, et al: Comparison of treatment tolerance and outcomes in patients with cervical cancer treated with concurrent chemoradiotherapy in a prospective randomized trial or with standard treatment. Int J Radiat Oncol Biol Phys 70:118-125, 2008
33. Abu-Rustum NR, Lee S, Correa A, et al: Compliance with and acute hematologic toxic effects of chemoradiation in indigent women with cervical cancer. Gynecol Oncol 81:88-91, 2001
34. McGuire SM, Menda Y, Ponto LL, et al: A methodology for incorporating functional bone marrow sparing in IMRT planning for pelvic radiation therapy. Radiother Oncol 99:49-54, 2011
35. McGuire SM, Menda Y, Ponto LLB, et al: Spatial mapping of functional pelvic bone marrow using FLT PET. J Appl Clin Med Phys 15:129-136, 2014
36. Wyss JC, Carmona R, Karunamuni RA, et al: [(18)F]Fluoro-2-deoxy-2-d-glucose versus 3′-deoxy-3′-[(18)F]fluorothymidine for defining hematopoietically active pelvic bone marrow in gynecologic patients. Radiother Oncol 118:72-78, 2016
37. Nishizawa S, Inubushi M, Kido A, et al: Incidence and characteristics of uterine leiomyomas with FDG uptake. Ann Nucl Med 22:803-810, 2008
38. Yamane T, Takaoka A, Kita M, et al: 18F-FLT PET performs better than 18F-FDG PET in differentiating malignant uterine corpus tumors from benign leiomyoma. Ann Nucl Med 26:478-484, 2012
39. 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
40. 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
41. Richard SD, Bencherif B, Edwards RP, et al: Noninvasive assessment of cell proliferation in ovarian cancer using [18F] 3′deoxy-3-fluorothymidine positron emission tomography/computed tomography imaging. Nucl Med Biol 38:485-491, 2011
42. Aide N, Kinross K, Cullinane C, et al: 18F-FLT PET as a surrogate marker of drug efficacy during mTOR inhibition by everolimus in a preclinical cisplatin-resistant ovarian tumor model. J Nucl Med 51: 1559-1564, 2010
43. Tsuyoshi H, Morishita F, Orisaka M, et al: 18F-fluorothymidine PET is a potential predictive imaging biomarker of the response to gemcitabine-based chemotherapeutic treatment for recurrent ovarian cancer: preliminary results in three patients. Clin Nucl Med 38:560-563, 2013
44. Mabuchi S, Altomare DA, Cheung M, et al: RAD001 inhibits human ovarian cancer cell proliferation, enhances cisplatin-induced apoptosis, and prolongs survival in an ovarian cancer model. Clin Cancer Res 13:4261-4270, 2007
45. Lee ST, Scott AM: Hypoxia positron emission tomography imaging with 18f-fluoromisonidazole. Semin Nucl Med 37:451-461, 2007
46. Lopci E, Grassi I, Chiti A, et al: PET radiopharmaceuticals for imaging of tumor hypoxia: A review of the evidence. Am J Nucl Med Mol Imaging 4:365-384, 2014
47. Koh WJ, Rasey JS, Evans M, et al: Imaging of hypoxia in human tumors with [F-18]fluoromisonidazole. Int J Radiat Oncol Biol Phys 22: 199-212, 1992
48. Lapi SE, Lewis JS, Dehdashti F: Evaluation of hypoxia with copper-labeled diacetyl-bis(N-methylthiosemicarbazone). Semin Nucl Med 45:177-185, 2015
49. Vavere AL, Lewis JS: Cu-ATSM: A radiopharmaceutical for the PET imaging of hypoxia. Dalton Trans 43:4893-4902, 2007
50. Nordsmark M, Bentzen SM, Rudat V, et al: Prognostic value of tumor oxygenation in 397 head and neck tumors after primary radiation therapy. An international multi-center study. Radiother Oncol 77:18-24, 2005
51. Hicks RJ, Rischin D, Fisher R, et al: Utility of FMISO PET in advanced head and neck cancer treated with chemoradiation incorporating a hypoxia-targeting chemotherapy agent. Eur J Nucl Med Mol Imaging 32:1384-1391, 2005
52. Hockel M, Knoop C, Schlenger K, et al: Intratumoral pO2 predicts survival in advanced cancer of the uterine cervix. Radiother Oncol 26: 45-50, 1993
53. Fyles AW, Milosevic M, Wong R, et al: Oxygenation predicts radiation response and survival in patients with cervix cancer. Radiother Oncol 48:149-156, 1998
54. Hockel M, Schlenger K, Aral B, et al: Association between tumor hypoxia and malignant progression in advanced cancer of the uterine cervix. Cancer Res 56:4509-4515, 1996
55. Georg P, Andrzejewski P, Baltzer P, et al: Changes in tumor biology during chemoradiation of cervix cancer assessed by multiparametric MRI and hypoxia PET. Mol Imaging Biol 20:160-169, 2018
56. Pinker K, Andrzejewski P, Baltzer P, et al: Multiparametric [18F]Fluorodeoxyglucose/ [18F]Fluoromisonidazole positron emission tomography/ magnetic resonance imaging of locally advanced cervical cancer for the non-invasive detection of tumor heterogeneity: A pilot study. PLoS One 11:e0155333, 2016
57. Busk M, Horsman MR, Jakobsen S, et al: Imaging hypoxia in xenografted and murine tumors with 18F-fluoroazomycin arabinoside: a comparative study involving microPET, autoradiography, PO2-polarography, and fluorescence microscopy. Int J Radiat Oncol Biol Phys 70:1202-1212, 2008
58. Schuetz M, Schmid MP, Potter R, et al: Evaluating repetitive 18F-fluoroazomycin-arabinoside (18FAZA) PET in the setting of MRI guided adaptive radiotherapy in cervical cancer. Acta Oncol 49:941-947, 2010

59. Han K, Shek T, Vines D, et al: Measurement of tumor hypoxia in patients with locally advanced cervical cancer using positron emission tomography with (18)F-Fluoroazomyin Arabinoside. Int J Radiat Oncol Biol Phys 102:1202-1209, 2018
60. Vercellino L, Groheux D, Thoury A, et al: Hypoxia imaging of uterine cervix carcinoma with (18)F-FETNIM PET/CT. Clin Nucl Med 37:1065-1068, 2012
61. Dehdashti F, Grigsby PW, Mintun MA, et al: Assessing tumor hypoxia in cervical cancer by positron emission tomography with 60Cu-ATSM: Relationship to therapeutic response-a preliminary report. Int J Radiat Oncol Biol Phys 55:1233-1238, 2003
62. Dehdashti F, Grigsby PW, Lewis JS, et al: Assessing tumor hypoxia in cervical cancer by PET with 60Cu-labeled diacetyl-bis(N4-methylthiosemicarbazone). J Nucl Med 49:201-205, 2008
63. Lewis JS, Laforest R, Dehdashti F, et al: An imaging comparison of 64Cu-ATSM and 60Cu-ATSM in cancer of the uterine cervix. J Nucl Med 49:1177-1182, 2008
64. Grigsby PW, Malyapa RS, Higashikubo R, et al: Comparison of molecular markers of hypoxia and imaging with (60)Cu-ATSM in cancer of the uterine cervix. Mol Imaging Biol 9:278-283, 2007
65. Albini A, Tosetti F, Li VW, et al: Cancer prevention by targeting angiogenesis. Nat Rev Clin Oncol 9:498-509, 2012
66. Xu L, Yoneda J, Herrera C, et al: Inhibition of malignant ascites and growth of human ovarian carcinoma by oral administration of a potent inhibitor of the vascular endothelial growth factor receptor tyrosine kinases. Int J Oncol 16:445-454, 2000
67. Manenti L, Riccardi E, Marchini S, et al: Circulating plasma vascular endothelial growth factor in mice bearing human ovarian carcinoma xenograft correlates with tumor progression and response to therapy. Mol Cancer Ther 4:715-725, 2005
68. Duncan TJ, Al-Attar A, Rolland P, et al: Vascular endothelial growth factor expression in ovarian cancer: A model for targeted use of novel therapies. Clin Cancer Res 14:3030-3035, 2008
69. Goodheart MJ, Ritchie JM, Rose SL, et al: The relationship of molecular markers of p53 function and angiogenesis to prognosis of stage I epithelial ovarian cancer. Clin Cancer Res 11:3733-3742, 2005
70. Li J, Li S, Chen R, Yu H, et al: The prognostic significance of anti-angiogenesis therapy in ovarian cancer: A meta-analysis. J Ovarian Res 8:54, 2015
71. Nagengast WB, de Vries EG, Hospers GA, et al: In vivo VEGF imaging with radiolabeled bevacizumab in a human ovarian tumor xenograft. J Nucl Med 48:1313-1319, 2007
72. Hjortkjaer M, Waldstrom M, Jakobsen A, et al: The prognostic value of BRCA1 and PARP expression in epithelial ovarian carcinoma: Immunohistochemical detection. Int J Gynecol Pathol 36:180-189, 2017
73. Edmonds CE, Makvandi M, Lieberman BP, et al: [(18)F]FluorThanatrace uptake as a marker of PARP1 expression and activity in breast cancer. Am J Nucl Med Mol Imaging 6:94-101, 2016
74. Zhou D, Xu J, Mpoy C, et al: Preliminary evaluation of a novel (18)F-labeled PARP-1 ligand for PET imaging of PARP-1 expression in prostate cancer. Nucl Med Biol 66:26-31, 2018
75. Zhou D, Chu W, Xu J, et al: Synthesis, [(1)(8)F] radiolabeling, and evaluation of poly (ADP-ribose) polymerase-1 (PARP-1) inhibitors for in vivo imaging of PARP-1 using positron emission tomography. Bioorg Med Chem 22:1700-1707, 2014
76. Makvandi M, Xu K, Lieberman BP, et al: A radiotracer strategy to quantify PARP-1 expression in vivo provides a biomarker that can enable patient selection for PARP inhibitor therapy. Cancer Res 76:4516-4524, 2016
77. Makvandi M, Pantel A, Schwartz L, et al: A PET imaging agent for evaluating PARP-1 expression in ovarian cancer. J Clin Invest 128:2116-2126, 2018