Review

Application of FDG-PET in Cervical Cancer and Endometrial Cancer: Utility and Future Prospects

YUYA NOGAMI, MIHO IIDA, KOUJI BANNO, IORI KISU, MASATAKA ADACHI, KANAKO NAKAMURA, KIYOKO UMENE, KENTA MASUDA, EIICHIRO TOMINAGA, KYOKO TANAKA and DAISUKE AOKI

Department of Obstetrics and Gynecology, School of Medicine, Keio University, Tokyo, Japan

Abstract. *Positron-emission tomography (PET), a diagnostic imaging technique using an agent labeled with a positron-emitting radionuclide, may facilitate improved diagnosis and treatment in gynecological fields. A combined PET/computerized tomography (CT) scan can identify the precise anatomical location of a lesion based on accumulation of ^{18}F-fluoro-D-glucose (FDG). FDG-PET and PET/CT have been used for detecting metastatic lesions and predicting prognosis in uterine cancer. PET has higher reliability in diagnosing lymph node metastases of uterine cancer than CT or MRI, and is considered most useful among non-invasive diagnostic imaging methods. Accumulation of FDG in lesions is indicative of a poor prognosis. Due to its limited spatial resolution, PET is not suitable has lower utility for detecting small lesions, and is not suitable for early-stage screening, and diagnosing primary lesions. Further improvements in diagnostic technology, including PET/MRI, investigation of new positron tracers, and analysis of data from various combinations of tracers are likely to make PET particularly useful for diagnosis and therapeutic strategy planning.*

Positron-emission tomography (PET) is a diagnostic imaging technique based on the use of a positron-emitting radionuclide. The first PET scanner was produced experimentally in 1975 by Phelps *et al*. (1). PET utilizes detection of enhanced glucose metabolism in malignant tumors based on the uptake of ^{18}F-fluoro-D-glucose (FDG) for functional diagnosis of malignant tumors. Thus, PET differs from other diagnostic imaging techniques such as

Correspondence to: Dr. Kouji Banno, Department of Obstetrics and Gynecology, School of Medicine, Keio University, Shinanomachi 35 Shinjuku-ku, Tokyo 160-8582, Japan. Tel: +81 333531211, Fax: +81 332261667, e-mail: kbanno@z7.keio.jp

ultrasound tomography, computed tomography (CT), and magnetic resonance imaging (MRI), which detect structural changes (2). FDG-PET has mainly been used for examination of tumors such as lymphoma, melanoma, lung cancer, breast cancer and colon cancer, but its use has recently expanded to other tumors, including gynecological tumors. The 2008 annual report of the U.S. National Oncologic PET Registry (NOPR) indicated that out of 81,951 PET studies conducted in 1,368 U.S. facilities, 8,362 studies (10.2%) were performed on gynecological tumors (3). These included 4,509 studies on ovarian cancer (53.9%), 2,869 on endometrial cancer, and 984 on cervical cancer (3). Therapeutic strategies were changed in 38% of the cases based on PET results, indicating the importance of PET in diagnosis and treatment. The clinical utility of PET was advanced by production of an experimental PET/CT scanner by Kinaham *et al*. in 1999 (4), since it allowed precise anatomical locations of FDG-accumulating lesions to be identified. In the present article, clinical applications and future prospects of FDG-PET and FDG-PET/CT in cervical and endometrial cancer are reviewed.

Diagnosis with PET and PET/CT

FDG-PET. Diagnostic imaging using PET can be facilitated using agents labeled with ^{11}C, ^{15}O, and ^{18}F. Among these agents, FDG shows high accumulation in tissues with enhanced glucose metabolism and is taken up into cells by a glucose transporter (5). FDG is phosphorylated by hexokinase into FDG-6-phosphate, which is very slowly metabolized by enzymes in the glycolysis pathway and has very low membrane permeability, preventing its diffusion out of cells. Thus, FDG accumulates in brain cells, cardiac muscle, and tumors, where large amounts of glucose are taken-up and activity of glucose-6-phosphatase is low. In contrast to glucose, FDG is excreted through the kidney or urinary system (5). Since a malignant tumor has enhanced glucose metabolism and takes-up FDG similarly to glucose,

FDG accumulation based on an uptake index, the standardized uptake value (SUV), can be used in PET identification of malignant lesions. One limitation of this approach is that FDG also accumulates at inflamed sites, at which glucose metabolism is also increased, and an active inflammatory site may give a false-positive result (6). The advantages of PET are that the whole body can be examined in a single scan with high safety and low invasiveness (6). The disadvantages include lack of anatomical location information and low spatial resolution (6) of approximately 3-5 mm, which only allows tumors of approximately 10 mm or more to be detected (7). PET had been thought to be unsuitable for gynecological tumors because the bladder is near the uterus and the ovary generates an artifact; however, improved image processing technology and introduction of PET/CT has resolved this problem and markedly improved the diagnostic accuracy.

PET/CT. A combined PET/CT scan was described by Kinaham *et al*. in 1999 (4). This method allows simultaneous imaging of anatomic and metabolic information and is rapidly becoming an essential diagnostic tool for planning the therapeutic strategy for a malignant lesion (8). Several PET/CT studies have reported variable but generally favorable results of patient-based sensitivity of 73-77%, specificity of 56-97%, and accuracy of 68-89% in cervical cancer (9, 10), and sensitivity of 50-63%, specificity of 87%, and accuracy of 78-83% in endometrial cancer (11, 12). For example, Kitajima *et al*. evaluated FDG-PET alone, contrast-enhanced CT alone, and FDG-PET/contrast-enhanced CT for diagnosis of recurrent uterine cancer (50 cases of cervical cancer, 40 cases of endometrial cancer) and found that PET/CT outperformed FDG-PET by 10% in sensitivity, 20% in specificity, and 16% in accuracy, showing the higher diagnostic accuracy of PET/CT (13).

False-positive and false-negative findings in PET. As described above, a malignant tumor has greater glucose consumption than normal tissue due to increased glucose transport and delayed de-phosphorylation in the cytoplasm (4). Therefore, PET can determine the location and activity of a lesion based on FDG accumulation. However, if a non-malignant tissue also has active glucose metabolism, FDG may also accumulate in this region and a false-positive result will be obtained in PET (14). In the gynecological field, false-positive PET findings have been reported for endometriosis cysts, uterine fibroids, and in the uterine endometrium during menstrual and ovulatory periods, and for lesions with intense inflammation (15). In PET/CT in 285 women, Lerman *et al*. found SUVs (mean±SD) as high as 5±3.2 (range=2.3-16.6) and 3.7±0.9 (range=1.1-5.4) in the uterine endometrium during menstrual and ovulatory periods, respectively (16). Thus, PET for a uterine lesion should be

avoided during these periods. In contrast, SUVs up to 3.0 were found in post-menopausal women receiving hormonal therapy. For accurate diagnosis with PET, diseases that may cause false-negative findings must also be taken into account. Murakami *et al*. found that urinary tract tumor, scirrhous stomach cancer, bronchovesicular carcinoma, and hepatocellular cancer often give false-negative results in PET (14). A tumor of less than 1 cm in size also often gives a false-negative result because of the partial volume effect and the low spatial resolution of PET (4-5 mm) (14).

SUV in PET. SUV is the ratio of tracer concentration in the region of interest (ROI) to the overall tracer concentration, with the assumption that the tracer is uniformly-distributed in the body and is not eliminated (17). If a person has high body fat, correction with body weight only leads to overcorrection. SUV also varies depending on the setting of the ROI because tissues in a tumor are not uniform and glucose metabolism is similarly uneven. Use of the maximum-pixel SUV within an ROI encompassing the tumor or the mean SUV within the ROI also influences the calculation of the SUV (17). For these reasons, SUV is only a semi-quantitative index for comparison of cases. However, it is generally thought that an SUV of 2.5-4.0, or higher indicates a malignant lesion. SUV has also become increasingly important because many studies have shown that the SUV in FDG-PET/CT is a prognostic factor in cancer.

FDG-PET in Cervical Cancer

Diagnosis of the primary tumor. FDG-PET has low efficacy in screening for early-stage cervical cancer and cannot be used for this purpose. Diagnostic imaging generally plays a small role in cervical cancer because inspection and cytodiagnosis are straightforward in the uterine cervix and early detection of cervical cancer is clinically important (18). In preoperative FDG-PET in patients with cervical cancer, Ohno *et al*. found that primary tumors of intra-epithelial cancer, minimally-invasive cancer, and invasive cancer could be identified, but that abnormal accumulation could not be detected in cases of histological stage Ib or IIa (19). PET showed favorable sensitivity of 85-92% for detection of primary lesions in patients with stage Ib or higher disease and most primary tumors 2 cm or more in size can be detected (19). PET can also be used for detection of endocervical adenocarcinoma (20). Collectively, these results indicate that PET has poor efficacy for detection of small lesions, including early cancer, due to its limited spatial resolution (21).

Detection of lymph node metastases. Lymph node metastasis is not included in the conventional International Federation of Gynecology and Obstetrics (FIGO) staging system, but requires early detection and treatment and is an important

prognostic factor. The most reliable diagnostic and therapeutic method is systematic lymph node dissection. However, this procedure is technically challenging and has postoperative complications and risks, and thus non-invasive methods for detection of lymph node metastases are required (22). Conventional CT and MRI can identify enlargement of lymph nodes that may be caused by metastasis, but the diagnostic accuracy is unsatisfactory (22). In contrast, several reports have shown that PET is useful for evaluation of lymph node metastasis (23-28).

A meta-analysis by Havrilesky *et al*. published in 2005 showed that FDG-PET had a sensitivity of 79% and specificity of 99% for preoperative diagnosis of pelvic lymph node metastases (23). These results are favorable in comparison to the sensitivity of 47% with CT, and sensitivity of 72% and specificity of 96% with MRI found by Scheidler *et al*. for diagnosis of lymph node metastases (22). For para-aortic lymph node metastasis, FDG-PET has a sensitivity of 84% and specificity of 95% (23). The diagnostic accuracy of FDG-PET/CT for detection of lymph node metastases of cervical cancer is listed in Table I. Choi *et al*. compared the preoperative diagnostic accuracy of FDG-PET/CT to that of MRI, and found sensitivity of 57.6% *vs*. 30.3%, specificity of 92.6% *vs*. 92.6%, and accuracy of 85.1% *vs*. 72.7% (9). In a prospective study of FDG-PET/CT for detection of pelvic lymph node metastases in 120 patients with stage Ib or higher cervical cancer, Loft *et al*. found a sensitivity of 75%, specificity of 96%, positive predictive value of 75%, and negative predictive value of 96% (24). These values were 100%, 99%, 94%, and 100%, respectively, for detection of para-aortic lymph node metastases, indicating even greater reliablity; and 100%, 94%, 63%, and 100%, respectively, for detection of distant metastases (24). Yildirim *et al*. (25) and Sironi *et al*. (10) also found that FDG-PET/CT is significantly superior to CT and MRI for detecting pelvic lymph node metastases and para-aortic lymph node metastases. Thus, addition of FDG-PET/CT findings to FIGO staging is likely to improve the precision of the preoperative diagnosis and treatment planning.

Despite these favorable results, FDG-PET/CT can also give false-negative findings. In 38 cases of para-aortic lymph node metastases from primary stage Ib2 cervical cancer that underwent chemoradiation treatment, Boughanim *et al*. found three cases (8%) that were false-negatives on FDG-PET/CT (26). Thus, an incorrect therapy plan would have resulted from dependence on FDG-PET/CT findings only, without performance of systematic lymph node dissection. Importantly, the three false-negative metastatic lymph nodes were large enough to be macroscopically visible, including two of size greater than 5 mm (26). This study suggests that FDG-PET/CT is not superior to systematic lymph node dissection, even in cases of advanced cancer. Chao *et al*. stated that in early stage cancer that may be curable by surgery,

systematic lymph node dissection performed for metastatic diagnosis, as well as treatment, should not be replaced by FDG-PET/CT performed only for metastatic diagnosis (27).

Collectively, the above results indicate that FDG-PET/CT is the most reliable non-invasive diagnostic imaging method for detection of metastatic lymph nodes and is essential for cervical cancer staging as a means to detect distant metastases, including lymph node metastases. A prospective study showed that lymph node metastases detected with FDG-PET/CT can be a prognostic factor for recurrence-free survival, indicating the practical value of FDG-PET lymph node staging (28). However, FDG-PET/CT may also give false-negative findings for metastatic lymph nodes and further prospective studies are required in regard to this concern.

Detection of recurrent lesions. Diagnosis of pelvic recurrence with CT and MRI has generally been found to be difficult in prospective studies. This is particularly true after surgery, at which time CT and MRI cannot identify the anatomical location or may locate a fibrosing or necrotic lesion or an inflammatory change. However, CT or MRI data along with PET evidence of FDG uptake allow for better identification of a recurrent lesion. Mittra *et al*. examined FDG-PET/CT for evaluation of recurrent cervical cancer and obtained values for sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 93%, 93%, 93%, 86%, and 96%, respectively, for the detection of local recurrence at the primary site; and 96%, 95%, 95%, 96%, and 95%, respectively, for detection of distant metastases (29). These results suggest that PET/CT is extremely useful for identification of recurrent cervical cancer and localization of distant metastases (29).

Prediction of therapeutic effects and prognosis. The prognosis of cervical cancer is determined by the tumor size, histological type, FIGO stage, pelvic and para-aortic lymph node metastasis, presence of lymphovascular invasion, and presence of uterus invasion, each of which is determined histopathologically after surgery. Preoperative prediction of prognosis with FDG-PET/CT would be extremely useful in planning the therapeutic strategy. Several studies have investigated associations between prognosis and FDG accumulation in primary cervical cancer, lymph nodes, and the uterine body (30-34). Kidd *et al*. (30) measured pre-treatment SUV values in 287 patients and found that SUV was the only significant independent factor associated with overall survival in a Cox proportional-hazards model including tumor volume, lymph node metastasis and prognosis: the overall survival rates at five years were 95% for SUV ≤ 5.2, 70% for SUV >5.2 and ≤ 13.3, and 44% for SUV>13.3 ($p<0.0001$) (30). Xue *et al*. reported 5-year disease-free survival rates of 71% and 52% in patients with SUV <10.2 and ≥ 10.2 respectively (31). Singh *et al*. (32)

Table I. *Diagnostic accuracy of ^{18}F-fluoro-D-glucose - positron-emission tomography (FDG-PET)/computerized tomography (CT) for cervical cancer lymph node metastases.*

Reference	Number of patients	Lymph node	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
Yildrim *et al*. (25)	16	PAN	50%	83.3%	75%	50%	83.3%
Loft *et al*. (24)	120	PLN	75%	96%	NA	75%	96%
		PAN	100%	99%	NA	94%	96%
Sironi *et al*. (10)	47	PAN	72%	99.7%	99.6%	81%	99.5%
Choi *et al*. (9)	22	PLN	57.6%	92.6%	85.1%	NA	NA
Havrilesky *et al*. (23)	200	PLN	79%	99%	NA	NA	74%
		PAN	84%	95%	NA	NA	74%

PLN: Pelvic lymph node, PAN: para-aortic lymph node, NA: not available.

evaluated 47 patients with FIGO stage IIIb cervical cancer before therapy and found 3-year survival rates of 73% for those with no lymph node metastasis, 58% for those with only pelvic lymph node metastases, 29% for those with pelvic and para-aortic lymph node metastases, and 0% for those with pelvic, para-aortic, and supraclavicular lymph node metastases. These studies indicate that SUV in FDG-PET/CT is a predictor of a poor prognosis.

Roles of FDG-PET in Endometrial Cancer

Diagnosis of the primary tumor. In pre-menopausal women, increased FDG uptake in the endometrium may be associated with malignancy, but may also be physiological (16). PET has limited spatial resolution and low detectability of small lesions, and thus cannot be used in screening for early detection of cancer. PET/CT can differentiate accumulation in the digestive tract from that in the uterus, and can indicate faint malignant accumulation; however, this method is far inferior to MRI for sensitivity and detection of lesions (21). Thus, the excellent spatial resolution of MRI, CT, and ultrasonography makes these methods more suitable for initial diagnosis, and PET has a limited role in evaluation of the primary tumor.

Detection of lymph node metastasis. In October 2009, the FIGO Gynecologic Cancer Staging system underwent major revisions, with the location of lymph node metastasis introduced into staging of endometrial cancer (35). In the FIGO 1988 staging, all lymph node metastasis-positive cases were classified into stage IIIc, while in the new staging, cases with pelvic lymph node metastases are classified into stage IIIc1 and those with para-aortic lymph node metastases into stage IIIc2. Thus, diagnosis of lymph node metastasis including location is now required. PET/CT will be important for this diagnosis, which is difficult based on size only.

Kitajima *et al*. investigated 62 pathologically metastatic-positive lymph nodes in 10 patients with endometrial cancer

and found that overall sensitivity, specificity, and accuracy of PET/CT in node-based analysis were 53.3%, 99.6%, and 97.8%, respectively (11, 38) (Table II). These results illustrate the high specificity of preoperative lymph node diagnosis with PET/CT. Park *et al*. compared PET/CT and MRI for detectability of lymph node metastases in 53 patients with endometrial cancer, and found that PET/CT had better sensitivity and specificity than MRI for both pelvic and para-aortic lymph node metastases (12). However, detectability of lymph node metastases is closely associated with node size, and Kitajima *et al*. (11) and Sironi *et al*. (10) found that detectability using PET was extremely low for a node with diameter of 5 mm or less. Thus, PET cannot detect micrometastases. However, PET can depict systemic lesions with good contrast and is useful for detecting metastases at unusual sites, such as supraclavicular or mediastinum lymph nodes, bone, and intramuscular metastases, which are often overlooked in gynecological tumor staging.

Detection of recurrent lesions. FDG-PET is useful for detection of recurrent lesions in endometrial cancer. Saga *et al*. performed 30 postoperative FDG-PET examinations to evaluate recurrence in 21 patients with endometrial cancer and found that FDG-PET had a better diagnostic ability (sensitivity 100%, specificity 88.2%) compared with CT/MRI alone and tumor markers (36). Belhocine *et al*. found that the sensitivity, specificity, and accuracy of FDG-PET in detecting recurrent lesions were 96%, 78%, and 90%, respectively, and concluded that FDG-PET is useful for accurate localization of suspected recurrences and for detection of asymptomatic recurrent disease (37). A recent report using PET/CT (38) found more favorable diagnostic accuracy (sensitivity 91-100%, specificity 83-100%, accuracy 92-97%) than that for PET-alone, indicating that PET/CT is a superior modality for assessment of recurrence. Endometrial Cancer Treatment Guidelines of Japan Society of Gynecologic Oncology (JGOG) recommend diagnostic imaging including PET for verification when recurrence is

Table II. *Diagnostic accuracy of 18F-fluoro-D-glucose - positron-emission tomography (FDG-PET)/ computerized tomography (CT) for endometrial cancer lymph node metastases.*

Reference	Number of patients	Lymph node	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
Kitajima *et al*. (11)	40	PAN+PLN	53%	99.6%	97.8%	NA	NA
Park *et al*. (12)	53	PLN	83%	91%	NA	36%	99%
		PAN	57%	88%	NA	57%	88%

PLN: Pelvic lymph node, PAN: para-aortic lymph node, NA: not available.

suspected and for detection of lesions of other diseases, but imaging (except for routine chest radiography) is not recommended in the asymptomatic stage or in follow-up (35). This is due to the high cost of imaging and because early detection of a recurrent lesion is not clearly linked to improved prognosis. This may be altered if therapies are developed that link early detection of recurrence to improved overall and progression-free survival.

Prediction of therapeutic effects. With recent advances in the efficacy of anti-tumor drugs, imaging is playing an increasingly larger role in determining whether the response to chemotherapy at an early stage warrants a revision of the therapeutic plan (39). Treatment response assessment is usually conducted by measuring the size of the tumor. However, reduction of glucose metabolism precedes a decrease in tumor size, and thus PET is expected to play a major role in response assessment (39). Assessment of viability after therapy also allows for additional treatment to be performed. In FDG-PET performed before and after chemotherapy in 21 patients, Nishiyama *et al*. found that the change in FDG accumulation was associated with treatment response, with a sensitivity of 90% and specificity of 80% for differentiation of responders from non-responders using a cut-off based on the percentage change in SUV after treatment (40). Further studies of the association of FDG accumulation with prognosis are needed to establish the utility of PET in treatment assessment.

Chung *et al*. followed-up 61 patients with endometrial cancer for a median duration of 31 months post-treatment and found that SUV_{max} values were inversely associated with disease-free survival and that SUV was a predictor of a poor prognosis (41). A Kaplan-Meier survival curve showed a significant difference in disease-free survival ($p<0.001$, hazard ratio=12.96) between groups of patients with SUV_{max} <4.25 and ≥4.25 . In multivariate analyses, post-treatment SUV_{max} ($p=0.001$, hazard ratio=1.199) and serous adenocarcinoma histology ($p=0.028$, HR 5.594) were significantly associated with recurrence (41). These results suggest that SUV of FDG-PET/CT is a prognostic factor in endometrial cancer. The wide variety of available therapies is likely to make early treatment response assessment increasingly important and use of PET is likely to expand for this purpose (39).

PET/MRI

PET/MRI has advantages of high soft-tissue contrast and no X-ray exposure compared to PET/CT and X-ray CT and is expected to play an increasingly important role in diagnosis. PET/MRI has increased diagnostic accuracy over each modality alone because abnormal accumulation that is difficult to detect with PET may be clearer with the added information provided by MRI (42-46). Simultaneous PET and MRI also shortens the scan time and gives higher image registration accuracy that may allow measurement of scientific parameters similar to that in NMR spectroscopy (47). In endometrial cancer, MRI provides important information on the extent of the primary tumor and PET/MRI is useful for early diagnosis of cancer with intimal thickening and advanced cancer with muscle invasion. For the primary tumor, the diagnostic accuracy varies depending on the size of the tumor, but PET/MRI is useful for evaluating tumors with diameters of at least 10-12 mm (48, 49). PET/MRI also has high sensitivity in detection of cervical cancer and can measure in detail the local extent of uterine body invasion, vaginal invasion, and parametrial invasion of cervical cancer, which is difficult using PET/CT. For lymph nodes, the diagnostic accuracy varies depending on the node size, as in endometrial cancer, but enlarged lymph nodes of at least 10-12 mm in diameter can be detected with high accuracy (9, 10). Diagnosis of distant metastases and recurrent tumors, and treatment response assessment with PET/MRI have yet to be reported, but PET/MRI is likely to be an increasingly useful methodology.

New PET Examinations

For gynecological malignancies, the usefulness of FDG-PET has been reported in ovarian, cervical, and endometrial cancer. FDG-PET is particularly useful for planning a therapeutic strategy based on diagnosis of distant metastases, and for diagnosis of recurrence after treatment, treatment

response, and lymph node metastases. However, FDG-PET has difficulty evaluating the local extent of disease before treatment and in diagnosis of lymph node metastases of less than 5 mm, with high false-positive and false-negative rates. Thus, FDG-PET is currently used as a supplement for conventional diagnostic imaging techniques.

Improved PET requires new agents, including candidates such as methionine and choline, and use of tracers other than ^{18}F (^{11}C, ^{13}N, ^{15}P) (50). Tsujikawa *et al.* performed PET scans with 16α-[^{18}F]fluoro-17β-estradiol (FES) to detect estrogen receptor (ER) expression and FDG, and found that the FDG to FES accumulation ratio was correlated with the aggressiveness of endometrial cancer (50). FES is an 18F-labeled compound of estradiol, which has the highest physiological activity among estrogens, and is likely to be useful for diagnosis of estrogen-dependent diseases and evaluation of the response to hormonal therapies. ER is distributed widely in the body as two sub-types: ERα and ERβ. FES has higher affinity for ERα, which typically exists in the mammary gland and uterus. FES-PET for response assessment in hormonal therapy for breast cancer has been reported in Europe and the U.S.

FES-PET of uterine cancer shows estrogen-dependent growth similar to that in breast cancer and is useful for differential diagnosis of benign and malignant uterine tumors when coupled with glucose metabolism evaluation using FDG-PET. That is, high glucose metabolism and low ER expression occur in malignant tumors such as endometrial cancer and uterine sarcoma, and low glucose metabolism and high ER expression are seen in benign tumors such as endometrial hyperplasia and uterine fibroid (50). Semi-quantification of tumor uptake of FDG and FES as SUVs indicated that a ratio of uptake of FDG to that of FES of 2 or more has an accuracy of detection of uterine sarcoma of 91.3% (51). Thus, combining FES-PET and FDG-PET and utilizing female hormone dependence and glucose metabolism may permit differentiation of benign from malignant gynecological diseases. In general, PET performed with a combination of tracers may allow for better understanding of the biological characteristics of tumors and allow for differential diagnosis and more effective personalized therapy.

SUV$_{max}$ for Prediction of Poor Prognosis

High SUV$_{max}$ values on FDG-PET are related to poor prognosis in many types of cancer. To investigate whether pre-treatment SUV$_{max}$ is useful as a biomarker for lymph node metastasis, pelvic recurrence, and prognosis, Kidd *et al.* analyzed the medical records of 287 patients with cervical cancer and concluded that SUV$_{max}$ was the only independent prognostic factor (p=0.0027) and was useful for predicting the response to treatment (30). Moreover, SUV$_{max}$ was found not to be associated with patient characteristics including

histological type, tumor stage, age, and tumor volume. However, since accumulation of FDG requires a certain number of tumor cells, the FDG-PET signal depends on the tumor diameter and differentiation. For solid tumors such as squamous cell carcinoma and poorly-differentiated adenocarcinoma, FDG-PET can detect 100% of tumors with a diameter of 10 mm or more, almost 50% with a diameter of 5-9 mm, and almost none with a diameter of less than 5 mm (30). G1 highly differentiated adenocarcinoma may form a duct that leads to reduction of the detection rate, since accumulation of FDG in this type of cancer does not always agree with indices of prognosis and malignancy (23). Thus, although SUV is a useful prognostic factor, it is only semi-quantitative and the prognosis should be based on SUV and other findings. SUV$_{max}$ has also been widely used for prognostic prediction in cervical cancer, but only in a few studies in endometrial cancer and ovarian cancer.

Conclusion

PET is a useful technique in cervical cancer and endometrial cancer. In types of both cancer, the primary tumor diagnostic performance of PET is inferior to that of CT or MRI, but PET is particularly useful for the detection of lymph node metastases, distant metastases, and recurrence. However, more evidence for the reliability of PET assessment of treatment response and degree of malignancy is required in studies using improved diagnostic technology. At present, PET is used as a supplement to conventional diagnostic imaging such as MRI and ultrasound. However, the importance of PET in cervical cancer and endometrial cancer is likely to increase with improved visualization of treatment response and degree of malignancy. These changes may occur through the use of PET/CT and PET/MRI, which have much a higher diagnostic accuracy than PET alone, and through the use of combinations of tracers, including FES.

References

1 Phelps ME, Hoffman EJ, Mullani NA and Ter-Pogossian MM: Application of annihilation coincidence detection to transaxial reconstruction tomography. J Nucl Med *16*: 210-224, 1975.

2 Riegger C, Koeninger A, Hartung V, Otterbach F, Kimmig R, Forsting M, Bockisch A, Antoch G and Heusner TA: Comparison of the diagnostic value of FDG-PET/CT and axillary ultrasound for the detection of lymph node metastases in breast cancer patients. Acta Radiol *53*: 1092-1098, 2012.

3 Hillner BE, Siegel BA, Shields AF, Liu D, Gareen IF, Hunt E and Coleman RE: Relationship between cancer type and impact of PET and PET/CT on intended management: Findings of the National Oncologic PET Registry. J Nucl Med *49*: 1928-1935, 2008.

4 Kinahan PE, Townsend DW, Beyer T and Sashin D: Attenuation correction for a combined 3D PET/CT scanner. Med Phys *25*: 2046-2053, 1998.

5 Inoue T, Oriuchi N, Kunio M, Tomiyoshi K, Tomaru Y, Aoyagi K, Amano S, Suzuki H, Aoki J, Sato T and Endo K: Accuracy of standardized uptake value measured by simultaneous emission and transmission scanning in PET oncology. Nucl Med Commun *20*: 849-857, 1999.

6 Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, Angioli R, Tateo S, Mangili G, Katsaros D, Garozzo G, Campagnutta E, Donadello N, Greggi S, Melpignano M, Raspagliesi F, Ragni N, Cormio G, Grassi R, Franchi M, Giannarelli D, Fossati R, Torri V, Amoroso M, Crocè C and Mangioni C: Systematic pelvic lymphadenectomy *vs*. no lymphadenectomy in early-stage endometrial carcinoma: Randomized clinical trial. J Natl Cancer Inst *100*: 1707-1716, 2008.

7 Kitchener H, Swart AM, Qian Q, Amos C and Parmar MK: Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): A randomised study Lancet *373*: 125-136, 2009.

8 Kitajima K, Murakami K, Yamasaki E, Kaji Y, Fukasawa I, Inaba N and Sugimura K: Diagnostic accuracy of integrated FDG-PET/contrast-enhanced CT in staging ovarian cancer:comparison with enhanced CT. Eur J Nucl Med Mol Imaging *35*: 1912-1920, 2010.

9 Choi HJ, Roh JW, Seo SS, Lee S, Kim JY, Kim SK, Kang KW, Lee JS, Jeong JY and Park SY: Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: A prospective study. Cancer *106*: 914-922, 2006.

10 Sironi S, Buda A, Picchio M, Perego P, Moreni R, Pellegrino A, Colombo M, Mangioni C, Messa C and Fazio F: Lymph node metastasis in patients with clinical early-stage cervical cancer: Detection with integrated FDG PET/CT. Radiology *238*: 272-279, 2006.

11 Kitajima K, Murakami K, Yamasaki E, Fukasawa I, Inaba N, Kaji Y and Sugimura K: Accuracy of ^{18}F-FDG PET/CT in detecting pelvic and paraaortic lymph node metastasis in patients with endometrial cancer. Am J Roentgenol *190*: 1652-1658, 2008.

12 Park JY, Kim EN, Kim DY, Suh DS, Kim JH, Kim YM, Kim YT and Nam JH: Comparison of the validity of magnetic resonance imaging and positron emission tomography/computed tomography in the preoperative evaluation of patients with uterine corpus cancer. Gynecol Oncol *108*: 486-492, 2008.

13 Kitajima K, Murakami K, Yamasaki E, Domeki Y, Tsubaki M, Sunagawa M, Kaji Y, Suganuma N and Sugimura K: Performance of integrated FDG PET/contrast-enhanced CT in the diagnosis of recurrent colorectal cancer: Comparison with integrated FDG PET/non-contrast-enhanced CT and enhanced CT. Eur J Nucl Med Mol Imaging *36*: 1388-1396, 2009.

14 Shida M, Murakami M, Tsukada H, Ishiguro Y, Kikuchi K, Yamashita E, Kajiwara H, Yasuda M and Ide M: F-18 Fluorodeoxyglucose uptake in leiomyomatous uterus. Int J Gynecol Cancer *17*: 285-290, 2007.

15 Liu Y: Benign ovarian and endometrial uptake on FDG PET-CT: Patterns and pitfalls. Ann Nucl Med *23*: 107-112, 2009.

16 Lerman H, Metser U, Grisaru D, Fishman A, Lievshitz G and Even-Sapir E: Normal and abnormal ^{18}F-FDG endometrial and ovarian uptake in pre- and postmenopausal patients: assessment by PET/CT. J Nucl Med *45*: 266-271, 2004.

17 Sakamoto S, Murakami K and Hiroyuki K: Application of PET/CT fused images in the diagnosis of colorectal cancer. Nihon Rinsho *69*: 299-305, 2011 (in Japanese).

18 Higashiyama S, Kawabe J, Hayashi T, Kurooka H, Oe A, Kotani J, Kawamura E and Shiomi S: A case of cavernous hemangioma in which malignancy was preoperatively excluded by FDG-PET. Ann Nucl Med *22*: 327-330, 2008.

19 Ohno Y, Nishio M, Koyama H, Fujisawa Y, Yoshikawa T, Matsumoto S and Sugimura K: Comparison of quantitatively analyzed dynamic area-detector CT using various mathematic methods with FDG PET/CT in management of solitary pulmonary nodules. Am J Roentgenol *200*: 593-602, 2013.

20 Yasuda S and Ide M: PET and cancer screening. Nihon Hoshasen Gijutsu Gakkai Zasshi *61*: 759-765, 2005(in Japanese).

21 Kitajima K, Murakami K, Kaji Y and Sugimura K. Spectrum of FDG PET ICT findings of uterine tumors. Am J Roentgenol *195*: 737-743, 2010.

22 Scheidler J, Hricak H, Yu KK, Subak L and Segal MR: Radiological evaluation of lymph node metastases in patients with cervical cancer. A meta-analysis. JAMA *278*: 1096-1101, 1997.

23 Havrilesky LJ, Kulasingam SL, Matchar DB and Myers ER: FDG-PET for management of cervical and ovarian cancer. Gynecol Oncol *97*: 183-191, 2005.

24 Loft A, Berthelsen AK and Roed H: The diagnostic value of PET/CT scanning in patients with cervical cancer: A prospective study. Gynecol Oncol *106*: 29-34, 2007.

25 Yildirim Y, Sehirali S and Avci ME: Integrated PET/CT for the evaluation of para-aortic nodal metastasis in locally advanced cervical cancer patients with negative conventional CT findings. Gynecol Oncol *108*: 154-159, 2008.

26 Boughanim M, Leboulleux S and Rey A: Histologic results of para-aortic lymphadenectomy in patients treated for stage B2/II cervical cancer with negative 18F -fluorodeoxyglucose positron emission tomography scans in the para-aortic area. J Clin Oncol *26*: 2558-2561, 2008.

27 Chao A, Ho KC and Wang CC: Positron emission tomography in evaluating the feasibility of curative intent in cervical cancer patients with limited distant lymph node metastases. Gynecol Oncol *110*: 172-178, 2008.

28 Kidd EA, Siegel BA and Dehdashti F. Lymph node staging by positron emission tomography in cervical cancer: Relationship to prognosis. J CIin Oncol *28*: 2108-2113, 2010.

29 Mittra E, El-Maghraby T and Rodriguez CA: Efficacy of ^{18}F-FDG PET/CT in the evaluation of patients with recurrent cervical carcinoma. Eur J Nucl Med Mol lmaging *36*: 1952-1959, 2009.

30 Kidd EA, Siegel BA and Dehdashti F: The standardized uptake value for F-18 fluorodeoxyglucose is a sensitive predictive biomarker for cervical cancer treatment response and survival. Cancer *110*: 1738-1744, 2007.

31 Xue F, Lin LL and Dehdashti F: F-18 Fluorodeoxyglucose uptake in primary cervical cancer as an indicator of prognosis after radiation therapy. Gynecol Oncol *101*: 147-151, 2006.

32 Singh AK: FDG-PET lymph node staging and survival of patients with FIGO stage IIIb cervical carcinoma. Int J Radiat Oncol Bio Phys *56*: 489-493, 2003.

33 Lee YY, Choi CH, Kim CJ, Kang H, Kim TJ, Lee JW, Lee JH, Bae DS and Kim BG: The prognostic of the SUV max (maximum standardized uptake value) for F-18 fluorodeoxy-glucose) of the cervical tumor in PET imaging for early cervical cancer: Preliminary results. Gynecol Oncol *115*: 65-68, 2009.

34 Yen TC: Standardized uptake value in paraaortic lymph node is a significant prognostic factor in patients with primary advanced squamous cervical cancer. Eur J Nucl Med Mol Imaging *35*: 493-501, 2008.

35 Endometrium cancer treatment guidelines. Japan Society of Gynecologic Oncology. Supported by Japan Society of Obstetrics and Gynecology, Japan Association Obstetricians and Gynecologists, Gynecological Malignancy Chemotherapy Research Organization.

36 Saga T, Higashi T, Ishimori T, Mamede M, Nakamoto Y, Mukai T, Fujita T, Togashi K, Yura S, Higuchi T, Kita M, Fujii S and Konishi J: Clinical value of FDG-PET in the follow up of post-operative patients with endometrial cancer. Ann Nucl Med *17*: 197-203, 2003.

37 Belhocine T, De Barsy C, Hustinx R and Willems-Foidart J: Usefulness of ^{18}F-FDG PET in the post-therapy surveillance of endometrial carcinoma. Eur J Nucl Med Mol Imaging *29*: 1132-1139, 2002.

38 Kitajima K, Murakami K, Yamasaki E, Kaji Y, Shimoda M, Kubota K, Suganuma N and Sugimura K: Performance of integrated FDG-PET/contrast-enhanced CT in the diagnosis of recurrent pancreatic cancer: Comparison with integrated FDG-PET/non-contrast-enhanced CT and enhanced CT. Mol Imaging Biol *12*: 452-459, 2010.

39 Nishizawa S, Inubushi M and Okada H: Physiological 18F-FDG uptake in the ovaries and uterus of healthy female volunteers. Eur J Nucl Med Mol Imaging *32*: 549-556, 2005.

40 Nishiyama Y, Yamamoto Y, Kanenishi K, Ohno M, Hata T, Kushida Y, Haba R and Ohkawa M: Monitoring the neoadjuvant therapy response in gynecological cancer patients using FDG PET. Eur J Nucl Med Mol Imaging *35*: 287-295, 2008.

41 Chung HH, Kim JW, Kang KW, Park NH, Song YS, Chung JK and Kang SB: Post-treatment [^{18}F]FDG maximum standardized uptake value as a prognostic marker of recurrence in endometrial carcinoma. Eur J Nucl Med Mol Imaging *38*: 74-80, 2011.

42 Pichler BJ, Judenhofer MS and Wehrl HF: PET/MRI hybrid imaging: devices and initial results. Eur Radiol *18*: 1077-1086, 2008.

43 Boss A, Bisdas S, Kolb A, Hofmann M, Ernemann U, Claussen CD, Pfannenberg C, Pichler BJ, Reimold M and Stegger L: Hybrid PET/MRI of intracranial masses: initial experiences and comparison to PET/CT. J Nucl Med *51*: 1198-1205, 2010.

44 Boss A, Stegger L, Bisdas S, Kolb A, Schwenzer N, Pfister M, Claussen CD, Pichler BJ and Pfannenberg C: Feasibility of simultaneous PET/MR imaging in the head and upper neck area. Eur Radiol *21*: 1439-1446, 2011.

45 Park H, Wood D, Hussain H, Meyer CR, Shah RB, Johnson TD, Chenevert T and Piert M: Introducing parametric fusion PET/MRI of primary prostate cancer. J Nucl Med *53*: 546-551, 2012.

46 Buchbender C, Heusner TA, Lauenstein TC, Bockisch A and Antoch G: Oncologic PET/MRI, part 1: tumors of the brain, head and neck, chest, abdomen, and pelvis. J Nucl Med *53*: 928-938, 2012.

47 Yamamoto S, Watabe H, Kanai Y, Watabe T, Aoki M, Sugiyama E, Kato K and Hatazawa J: Development of a flexible optical fiber based high resolution integrated PET/MRI system. Med Phys *39*: 6660-6671, 2012.

48 Horowitz NS, Dehdashti F, Herzog TJ, Rader JS, Powell MA, Gibb RK, Grigsby PW, Siegel BA and Mutch DG: Prospective evaluation of FDG-PET for detecting pelvic and para-aortic lymph node metastasis in uterine corpus cancer. Gynecol Oncol *95*: 546-551, 2004.

49 Chao A, Chang TC, Ng KK, Hsueh S, Huang HJ, Chou HH, Tsai CS, Yen TC, Wu TI and Lai CH: ^{18}F-FDG PET in the management of endometrial cancer. Eur J Nucl Med Mol Imaging *33*: 36-44, 2006.

50 Tsujikawa T, Yoshida Y, Kudo T, Kiyono Y, Kurokawa T, Kobayashi M, Tsuchida T, Fujibayashi Y, Kotsuji F and Okazawa H: Functional images reflect aggressiveness of endometrial carcinoma: Estrogen receptor expression combined with ^{18}F-FDG PET. J Nucl Med *50*: 1598-1604, 2009.

51 Zhao Z, Yoshida Y, Kurokawa T, Kiyono Y, Mori T and Okazawa H: ^{18}F-FES and ^{18}F-FDG PET for differential diagnosis and quantitative evaluation of mesenchymal uterine tumors: Correlation with immunohistochemical analysis. J Nucl Med *54*: 499-506, 2013.