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Positron Emission Tomography in Gynecologic Cancer

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Most positron emission tomography (PET) imaging studies in gynecologic cancer are performed using ^{18}F-fluorodeoxyglucose (FDG). It contributes valuable information in primary staging of untreated advanced cervical cancer, in the post-treatment surveillance with unexplained tumor marker (such as squamous cell carcinoma antigen [SCC-Ag]) elevation or suspicious of recurrence, and restaging of potentially curable recurrent cervical cancer. Its value in early-stage resectable cervical cancer is questionable. In ovarian cancer, FDG-PET provides benefits for those with plateaued or increasing abnormal serum CA 125 (>35 U/mL), computed tomography and/or magnetic resonance imaging (CT-MRI) defined localized recurrence feasible for local destructive procedures (such as surgery, radiotherapy, or radiofrequency ablation), and clinically suspected recurrent or persistent cancer for which CT-guide biopsy cannot be performed. The role of FDG-PET in endometrial cancer is relatively less defined because of the lack of data in the literature. In our prospective study, FDG-PET coupled with MRI-CT may facilitate optimal management of endometrial cancer in well-selected cases. The clinical impact was positive in 29 (48.3%) of the 60 scans, 22.2% for primary staging, 73.1% for post-therapy surveillance, and 57.1% after salvage therapy, respectively. Scant studies have been reported in the management of vulvar cancer using FDG-PET. More data are needed. Gestational trophoblastic neoplasia is quite unique in biological behavior and clinical management. Our preliminary results suggest that FDG-PET is potentially useful in selected gestational trophoblastic neoplasia by providing a precise metastatic mapping of tumor extent upfront, monitoring response, and localizing viable tumors after chemotherapy. The evaluation of a diagnostic tool, such as PET, is usually via comparing the diagnostic efficacy (sensitivity, specificity, etc), by using a more sophisticated receiver operating curve method, or the proportion of treatment been modified. Evaluating PET by clinical benefit is specific to the individual tumor and an attractive new endpoint.

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Positron emission tomography (PET) is a biologic imaging modality that can use a variety of radioactive substances for images. Studies have shown that the level of ^{18}F-fluorodeoxyglucose (FDG) uptake in tumors has clinical and biological information.[1-3] FDG uptake reflects the culmination of complex and incompletely understood biologic characteristics that affect glycolysis in a specific tumor. Most studies suggest that higher FDG uptake is correlated with more clinically aggressive behavior.[4-6]

Normally, FDG is excreted through bowel and genitourinary tract within 1 h after intravenous injection. The use of FDG may result in bowel, ureter, and bladder activity, which can limit interpretation of the PET imaging in gynecologica cancers. Technical modifications to limit this background activity include intravenous hydration with diuretic therapy, continuous bladder irrigation, and mechanical bowel preparation. Additionally, premenopausal patients may demonstrate increased ovarian FDG uptake at midfollicular cycle and increased endometrial uptake during menstruating and ovulating phase of the cycle, which must be taken into clinical consideration and re-

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quires repeat PET imaging in the early follicular phase of the menstrual cycle.[7]

Most scans in previous PET studies were performed approximately 1 h after tracer injection, partly because of the 110-min physical half-life of ^{18}F. Studies from our group using dual-phase PET (adding 3-h delayed images to the 40-min scans) in cervical cancer found that combined analysis of early and late images was significantly superior to the 40-min scans in detecting metastasis in untreated advanced primary as well as recurrent cervical cancer patients.[8,9] We recommend that if any equivocal or suspicious lesions (≥grade 2) are detected by initial PET imaging, additional delayed images should be acquired 3 h subsequent to FDG administration. However, the advantages of an additional delayed image were limited in endometrial cancer.[10] The most important role for adding a delayed image was to rule in an equivocal lesion, to rule out the physiologic uptake of bowel or genitourinary tract, or to rule out a benign lesion caused by inflammation or tissue reaction.

Carcinoma of Uterine Cervix

Cervical cancer is the second most common malignant disease among women and also the leading cause of cancer-related death among women in developed countries. Approximately 85% to 90% of cervical cancers are squamous cell, and most of the remaining 10 to 15% are adenocarcinoma.[11-14]

The definitive treatment and prognosis for patients with cervical cancer is markedly affected by the extent of disease at the time of diagnosis. When cancer is confined to the cervix or adjacent vagina, radical surgery or radiotherapy alone could obtain similar survival rates.[11-13] When there is regional spread or bulky (≥4 cm) tumor, multimodality therapy will be necessary.[14-17] The clinical staging system provided by the International Federation of Gynecology and Obstetrics (FIGO) is widely used. FIGO stage is determined clinically, on the basis mainly of the size of the tumor in the cervix or its extension into the pelvis. The results from other diagnostic modalities, such as ultrasonography, CT, or MRI, do not alter the FIGO staging of the disease.[18] The main routes of tumor spread of cervical cancer may be through paracervical lymphatics to pelvic and then to extra-pelvic lymph nodes (LNs) or hematogeneous dissemination to visceral organs locally or at distant sites. The FIGO clinical stage correlates with the prognosis and with pelvic control rates but underestimates the pathological extent of the disease in 17% to 32% of FIGO stages IB and 50 to 67% of FIGO stages II to IV.[12,19]

Several factors, such as stage, volume and grade of tumor, histologic type, lymphatic spread, and vascular invasion, influence prognosis.[11-14] Among them, para-aortic LN metastases are associated with poorer progression-free interval and survival.[11,20] Prognosis of recurrent cervical cancer is poor.[21-26] Treatment options for recurrent cervical cancer after radical surgery or irradiation remain limited and controversial. Those extended beyond local recurrences usually are considered incurable except solitary lung[11,12,22,27] or isolated para-aortic LN metastasis.[28] Even for those with local recurrences and pelvic sidewall free, pelvic exenteration often is necessary for a secondary cure if adjuvant or primary radiotherapy or concurrent chemoradiation treatment has been administered initially.[11,29-32] As many as 40% of exenterations are abandoned because of peritoneal, nodal, or pelvic sidewall disease found during exploratory laparotomies.[30] Obviously, if PET can identify those characteristics precluding exenteration attempts, then futile exploration can be avoided. Besides, early detection and precise assessment of the recurrence is crucial for appropriate salvage treatment.

Role of Imaging

MRI/CT studies have been used widely in staging and restaging cervical cancer. However, the suboptimal accuracy because small or normally sized LN metastases may be missed (false-negative), whereas an enlarged reactive LN may be a false-positive.[33,34] It is crucial to distinguish malignancy from benign inflammatory processes in previously treated regions. Unfortunately, MRI/CT scans have limitations in differentiating tumor infiltration from posttreatment inflammation or fibrosis/scarring. FDG-PET has improved the accuracy of detection and staging from 8% to 43% over conventional workups in patients with lung, colorectal cancer, lymphoma, melanoma, breast cancer, and thyroid cancer, depending on the clinical question.[1-7]

PET in Primary Staging

The clinical value of FDG-PET for primary staging seems promising in locally advanced previously untreated cervical cancer. Rose and coworkers[35] reported a prospective surgical-pathological study of locally advanced cervical cancer (n = 32), in which abdominal and pelvic PET scanning had a sensitivity (SN) of 75%, specificity (SP) of 92%, positive predictive value (PPV) of 75%, and a negative predictive value (NPV) of 92% for para-aortic LN metastasis. Grigsby and coworkers[36] retrospectively investigated 101 consecutive patients with carcinoma of the cervix undergoing primary chemoradiation. CT demonstrated abnormally enlarged pelvic LNs in 20% and para-aortic LNs in 7%, whereas PET detected abnormal FDG uptake at pelvic LN in 67% and para-aortic LNs in 21% and supraclavicular LNs in 8%. The 2-year progression free rates were 64% for CT (−), PET (−); 18% for CT (−), PET (+); and 14% for CT (+), PET (+) ($P < 0.0001$). In a preliminary report of a prospective randomized study, we found a 19% change of treatment plan in the additional PET arm in untreated cervical cancer patients with MRI-defined positive pelvic node metastasis undergoing chemoradiation.[37] We as well as others also confirm the sensitivity of FDG-PET in detection para-aortic LN metastasis.[9,38]

Reinhardt and coworkers[39] reported another prospective surgical-pathological study of 35 FIGO stage IB-II cervical cancer patients who underwent radical hysterectomy and had a preoperative abdominal and pelvic FDG-PET and MRI. On a patient basis, node staging resulted in a SN of 91% with PET and 73% with MRI. On a LN sites basis, PET achieved a PPV of 90% and MRI of 64% ($P < 0.05$). Sugawara and

coworkers reported 86% of SN in 7 cervical cancer patients (stage IB-IIB) with known LN metastasis (1 by surgical, 6 by clinical follow-up.[40] In contrast, Williams and coworkers[41] retrospectively reviewed 18 cases with gynecologic malignancies and MRI, CT, and PET scans before LN dissection, 16 among whom had cervical cancers (14 primary, 2 recurrent). SN and SP rates were suboptimal (SN: MRI, 53.7%; CT, 48.1%; PET, 24.5%). Narayan and coworkers[42] compared PET and CT/MRI in 27 surgically staged cervical cancer patients. PET detected only 57% of confirmed para-aortic LN metastasis. In a prospective surgical-pathological study from our group (unpublished), patients with untreated stage IA2-IIA, adeno-adenosquamous carcinoma or nonbulky (≤4 cm) squamous cell carcinoma, and MRI-defined negative for nodal metastasis were enrolled. All patients had a preoperative dual-phase FDG-PET and ^{99m}Tc-Sulfur colloid lymphoscintigraphy as well as intraoperative sentinel LN detection at radical surgery. The gold standard of LN metastasis is histological. A sample size of 120 patients was calculated to fit study aims (diagnostic efficacy of PET and sentinel LN sampling). An interim analysis was performed when 60 patients were accrued. There were 16.7% (10/60) pelvic LN metastases and 1.67% (1/60) para-aortic LN metastasis identified histologically. FDG-PET demonstrated the para-aortic LN metastasis (1/1) but failed to detect any tumor deposits (0/10) in the pelvic LN. This study shows that dual-phase FDG-PET has little value in primary nonbulky stage IA2-IIA and MRI defined LN-negative cervical cancer.

PET in Post-Treatment Surveillance or Restaging of Tumor Recurrence

Serum tumor markers such as squamous cell carcinoma antigen (SCC-Ag), CEA have been used in combination with CT-MRI for posttherapy surveillance.[43-47] A few retrospective studies have investigated FDG-PET as routine posttreatment surveillance or to determine whether various clinical situations suspicious of recurrence are true recurrences.[48-51] These studies are difficult to interpret because of a poorly defined high-risk group or suspicious of recurrence. Grigsby and coworkers[52] analyzed pre- and post-treatment PET scans in 76 cervical cancer patients. Among the 11 patients who developed new abnormal FDG uptakes, there were no survivors at 2 years. Ryu and coworkers[53] performed PET as routine post-therapy surveillance, in which 80 of 249 patients showed positive PET scanning, yet only 28 had recurrence confirmed (false positive rate of 65%). We have prospectively investigated the role of PET in 27 patients with unexplained elevation of SCC-Ag levels (MRI and/or CT normal or inconclusive). PET findings were positive for 19 of them, of which 17 were confirmed to have recurrences (Fig. 1), and such expedited detection of recurrent cervical cancer led to positive effects on patient survival.[54]

In another prospective trial (n = 40), we evaluated the diagnostic efficacy and benefit of PET restaging in documented recurrent cervical cancer. A total of 55% patients had treatment modified as the result of PET findings. For those receiving primary surgery, a significantly better 2-year overall survival rate was noted for study patients when compared with a group of historical controls who were restaged without PET.[55] We also investigated the prognostic features of recurrent cervical cancer patients, in which study a serum level of SCC-Ag greater than 4 ng/mL at relapse, primary radiation, and presence of symptoms at recurrence were significant predictors of poor survival. A scoring system using these 3 covariates defined 3 distinct prognostic groups.[56] Our results suggest that we may select appropriate candidates for PET scanning using this risk-score, and PET scans may offer maximal benefits with precise restaging information.

FDG-PET has been used to assess response to neoadjuvant chemotherapy.[57] PET with other radiotracers such as Cu-60 has also been used to monitor early response to radiotherapy.[58] Both were found useful.

Since the introduction of PET/CT, improvements of anatomical localization of the FDG functional images in many malignancies been reported. The experience in the utility of PET/CT in cervical cancer has been limited. However, further progress is likely.[59,60]

Ovarian Cancer

Ovarian cancer is one of the most common gynecologic malignancies, with a prevalence of 30 to 50 per 100,000 women, accounting for half of all deaths related to female genital cancer.[11,61,62] Improvement has been noted in 5-year survival rate during the past 40 years; mortality has remained fairly constant at approximately 60%. The poor prognosis is related to the absence of symptoms in most patients with early stage disease. Thus, 70% to 75% of patients are diagnosed with advanced disease (stage III/IV), and their overall survival is relatively poor.[62] CA125 is an important tumor marker for epithelial ovarian cancer, despite its limited accuracy in predicting malignancy (only 50% of stage I ovarian cancer is associated with a preoperative level of >35 U/mL), differentiation between ovarian and nonovarian primary, a significant number of patients still have persistent disease at second-look laparotomy with normalization of a previously elevated serum CA 125, and CA 125 also fails to provide information on tumor localization.[11,62-64]

For ovarian cancer, the overall and progression-free survivals are closely related to the initial stage when diagnosed. Morphologic imaging modalities have played a major role to delineate disease status before surgical exploration. CT and MRI were considered to be useful for predicting probability of optimal cytoreduction in those apparently advanced ovarian cancer patients.[65,66] Although some investigators regard FDG-PET information useful in differential diagnosis of malignancy, most of the studies of this purpose proved to be of little value.[67-71] Potential advantages of PET/CT[60,72,73] include increased lesion contrast, anatomic localization of lesions, and differentiation of neoplastic disease process from post-treatment fibrosis.

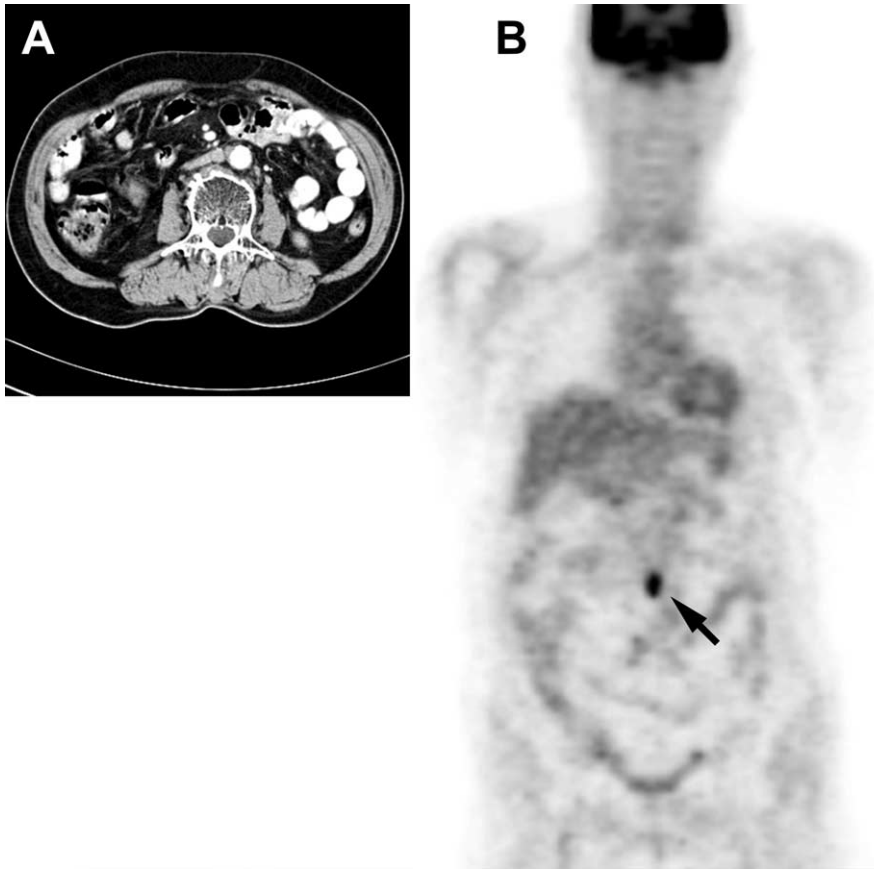

Figure 1 This patient was a 69-year-old woman. She had a past history of cervical cancer (moderate differentiated squamous cell carcinoma) IIb in April 1999 and had concurrent chemoradiation therapy (CCRT). In April 2002, she had her first recurrence at para-aortic lymph node (PALN) and had curative intent CCRT treatment. In February 2004, she had unexplained tumor marker SCC-Ag elevation (3.13 ng/dL and 4.15 ng/dL at 1 month apart) (A). The PET scan showed re-recurrence at PALN (B, coronal section with arrow). She thus had palliative treatment. She is now alive with disease.

PET for Staging/Metastatic Survey

Apparent early stage ovarian cancer has a high prevalence of subclinical disease, which accounts for its relatively high recurrence rate. Yoshida and coworkers reported improved staging with PET over CT imaging alone.[74] However, other studies have demonstrated inability to detect small macroscopic disease (< 0.5 cm) with both CT and PET[75,76] Therefore, these authors have stressed that PET findings are not sufficient to allow accurate staging and that surgical staging will remain the standard. In our experience, PET allows us to identify suboptimal > 1 cm residual disease as well as smaller lesions primarily in the para-aortic and pelvic nodal regions, but it has not been as helpful for identifying peritoneal disease (unpublished).

Evaluation of Response to Chemotherapy

Except for a minority of patients with early-stage low-grade tumors, adjuvant chemotherapy after surgery is commonly used. During chemotherapy patients routinely are monitored at various intervals to ensure they are responding favorably. Serial CA-125 levels are measured with or without clinically or radiologically measurable disease for monitoring response to treatment.[62-65]

It has been demonstrated that ovarian cancer xenografts demonstrate FDG uptake in viable cells in contrast to necrotic cells.[77] Additionally, in vitro, cytotoxic therapy is associated with decreased FDG uptake, suggesting its potential utility to determine tumor response to chemotherapy.[78] Serial PET scans have not been used routinely to determine response to therapy in ovarian cancer because of its high cost. They have, however, been used at the completion of a planned course of therapy for patients with a complete clinical response. Reports of the use of neoadjuvant chemotherapy for patients with advanced stage ovarian cancer has increased in the literature. This approach has been advocated by some to increase optimal resectability and decrease operative morbidity with cytoreductive surgery.[79] Assessing patients following neoadjuvant chemotherapy has included both CT and CA-125. PET may potentially have a role in determining tumor response and respectability.[80]

Evaluating the Patient in Clinical Complete Response

After front-line therapy for ovarian cancer, which typically involves 6 to 8 cycles of platinum and taxane-based chemotherapy, the majority of patients (70-80%) experience a clinical,

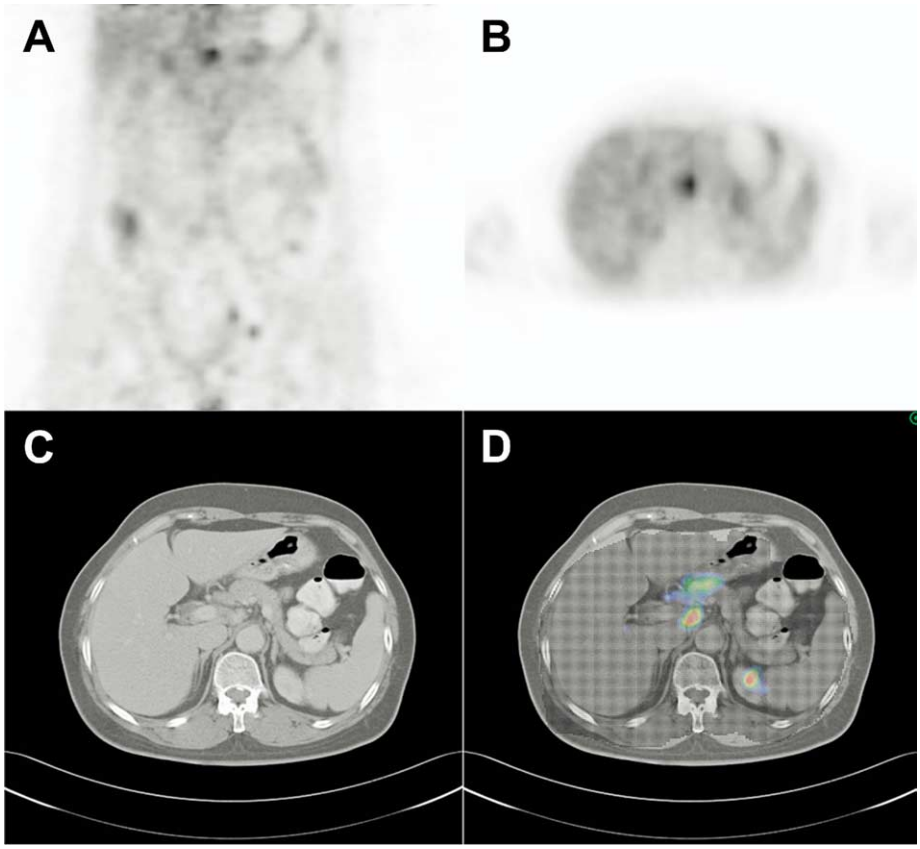

Figure 2 This patient was a 52-year-old woman with stage IIIc ovarian cancer developed unexplained serum tumor marker CA 125 elevation (16.2 U/mL and 39.5 U/mL at 1 month apart) 7 years after initial clinical complete response the first-line chemotherapy. The ^{18}F-FDG-PET scan revealed lymph node metastases to celiac trunk (A, coronal section; B, transaxial section; C, CT of abdomen; D, PET fusion with CT) and proved histopathologically (A).

radiologic, and biochemical complete response. However, normal CA-125 levels are associated with persistent disease in 36% to 73% of cases.[65,81-84] Reassessment, including physical examination, serum CA-125 levels, and imaging studies such as CT, MRI, or ultrasound are needed to determine the disease status if chemotherapy could be stopped or some forms of consolidation, are necessary. CT has a very low sensitivity (approximately 10%) for persistent disease with CA-125 level.[85] Since the mid-1960s, second-look surgery (laparotomy) has been used as the gold standard to evaluate response in clinical trials. However, second-look surgery has been used less because of the lack of survival advantage.

Kim and coworkers compared the results of PET scanning with second-look laparotomy after primary chemotherapy.[86] Overall, no significant difference was noted for the patients who underwent second-look laparotomy or PET imaging alone 30.6 months versus 28.8 months, respectively. These results suggest it may be possible to use PET to triage the likelihood of patients in this population having persistent disease.

Evaluating the Patient With Suspected Recurrence

Elevated CA-125 values often are seen in the absence of clinical or radiological evidence of disease.[87] The appropriate management of this clinical situation is controversial, and some have suggested observation only (awaiting pathological confirmation of recurrence or clinical evidence of progression), whereas others have suggested interventions, such as initiation of tamoxifen.[88,89] PET has demonstrated abnormal imaging in this patient population and has been used to confirm recurrent disease and to initiate chemotherapy.[90,91] Zimney and coworkers reported 54 patients with ovarian cancer who were felt to be clinically without evidence of disease or in whom disease recurrence was suspected.[92] Among those with suspected recurrence, FDG-PET had a SN of 94%, SP 75%, PPV of 98%, and NPV of 50% and accuracy of 93%. However, the SN of PET was 96% if suspicion of recurrent disease was based on CA-125 alone. PET evidence of recurrent ovarian cancer preceded conventional diagnosis by 6 months. Others compared the diagnostic accuracy of FDG-PET, CA-125, and CT/MRI in those suspected recurrent ovarian cancer.[93,94] Both CA-125 and FDG-PET had higher SN and SP than CT/MRI. FDG-PET provided anatomic localization of the recurrence obviously not obtained by CA-125 alone. Wilder and coworkers described a high likelihood of recurrence with progressive elevations of the CA-125, which remained in the normal range (<35 U/mL).[95] Kurokawa and coworkers reported a patient whose recurrent ovarian cancer was diagnosed on PET, which was confirmed on MRI 2 weeks later.[96] However, despite these favorable results, Cho and

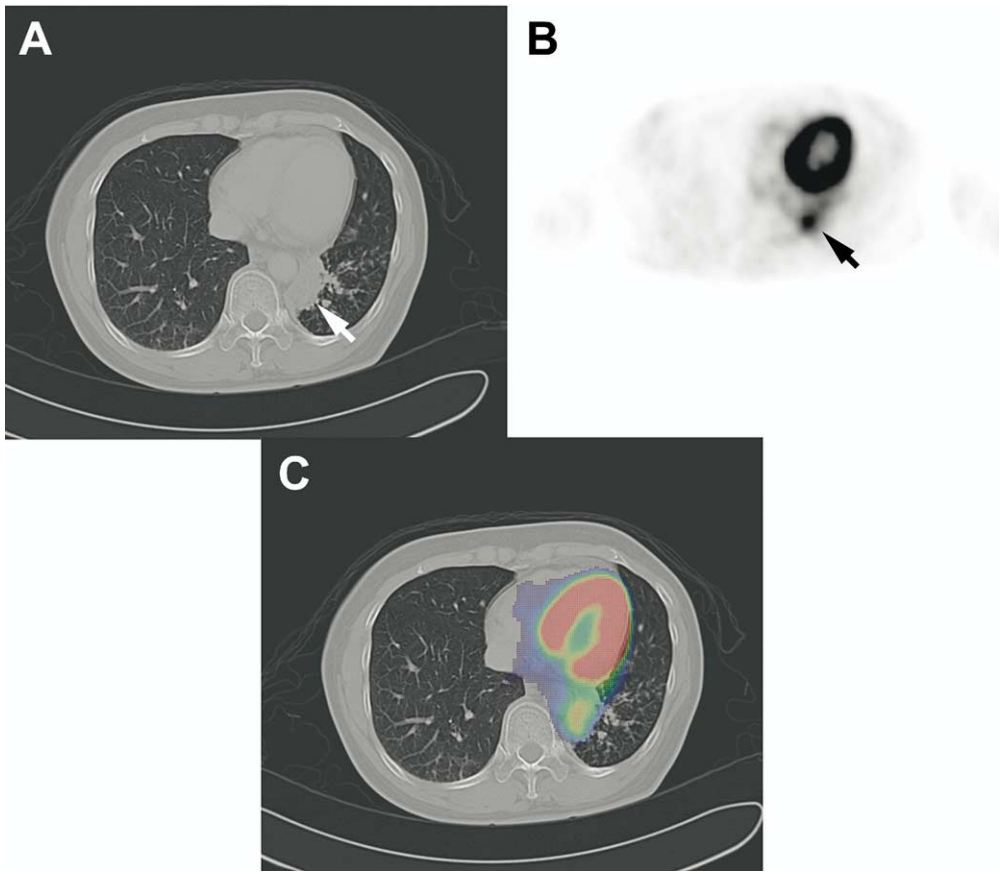

Figure 3 This patient was a 54-year-old woman with stage IIIc endometrioid adenocarcinoma of uterus. She was found to have lung metastasis during her periodic surveillance by CT scan (A, arrow). The ^{18}F-FDG-PET scan and image fusion suggested an inflammatory focus (SUVmax: 1.38) rather than a metastatic lesion in left lung (B and C with arrow). She did not receive any treatment and was well after clinical follow up for at least 18 months.

coworkers reported that FDG-PET was inferior to CT in the assessment of early recurrent ovarian carcinoma.[97]

Overall, the SN of PET for recurrent disease has been shown to be quite high, but most patients already had elevated CA-125, abnormal examination or abnormal imaging, so that PET was confirmatory of patient status. However, there is no evidence that an early institution of salvage therapy improves overall survival.

Evaluating the Patient With Recurrent Disease for Secondary Cytoreductive Surgery

As noted previously, the optimal management of these patients is controversial. Theoretically, earlier detection of recurrent disease should allow secondary cytoreduction while the patient has a high performance status and localized disease, features that are associated with more optimal secondary debulking and improved survival. Bristow and coworkers reported the use of PET-CT in 22 patients with increased CA-125 levels and negative or nondiagnostic conventional CT.[98] PET-CT was able to detect lesions in all these patients. At surgical reassessment, 18 of the 22 patients (81.8%) had greater than 1-cm disease (range, 1.5–3.2 cm; median, 2.3 cm). Among these 18, optimal cytoreduction (<1 cm) was accomplished in 15 (83.3%), and 13 (72.2%) were resected to no residual disease. Sometimes the use of PET may avoid an unnecessary exploration for secondary cytoredution when it obviously impossible (Fig. 2).

Conclusion and Potential Future Applications of PET in Ovarian Cancer

At this time, PET has little clinical application for the diagnosis of a pelvic mass. These patients will likely be evaluated surgically for definitive diagnosis or with close clinical and imaging follow-up. In terms of staging and metastatic survey, PET could be good for nodal disease but miss small peritoneal disease, and it may have some role for identifying incompletely staged patients who may have para-aortic nodal metastasis.

PET may be useful in determining response to chemotherapy. However, patients with minimal residual disease after optimal primary cytoreductive surgery are mostly expected to have small volume macroscopic or microscopic disease, which is at less than the detection limit of PET. Therefore, PET will not be as accurate as second-look laparoscopy or laparotomy. In view of the morbidity of a surgical procedure PET may help define prognosis of patients following chemotherapy as suggested by the recent work of Kim and cowork-

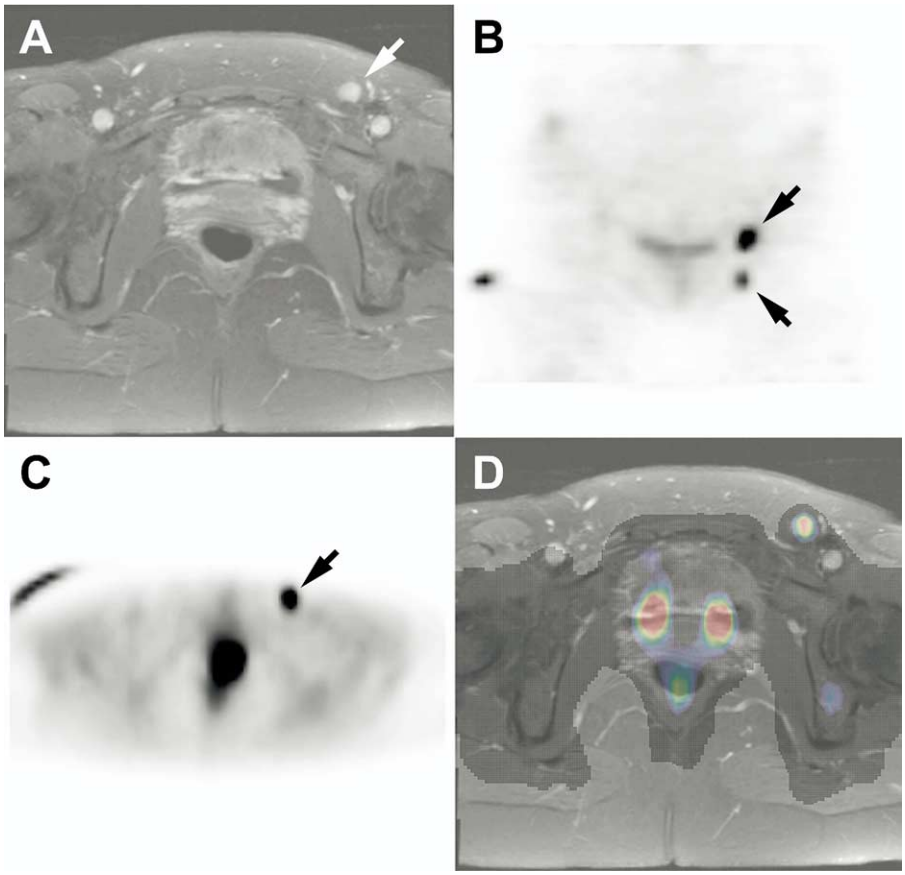

Figure 4 This patient was a 46-year-old woman with adenocarcinoma arising from the left Bartholin gland. She was found to have tumor at vulva, suspected left inguinal lymph node metastasis by MRI (1.1 cm in diameter, score 3; A). The ^{18}F-FDG-PET scan and image fusion suggested except for tumor itself, she also had left inguinal and left pelvic lymph nodes metastases (B, coronal section; C, transaxial section; D, image fusion). Histopathologic results showed inflammatory focus in the left inguinal lymph node.

ers in the diagnosis of recurrent disease,[86] PET appears to be less sensitive than CA-125 but more sensitive than CT. PET may play a role in determining recurrence and in triaging this population to initiate chemotherapy or secondary cytoreductive surgery.[88,90,99,100]

Endometrial Cancer

Endometrial cancer is a common gynecologic cancer. The FIGO staging is surgically determined. The overall survival rate of patients with endometrial cancer is expected to be high because most patients have early-stage disease at the time of diagnosis.[101,102] Unfortunately, the prognosis is poor in advanced or recurrent endometrial carcinoma, especially when extrapelvic sites were involved, previously irradiated or multifocal.[101-105]

Imaging studies such as MRI-CT usually are used to evaluate disease extension or post-therapy surveillance.[106,107] CA-125 measurement may play a role in predicting extrauterine spread of clinically localized endometrial cancer preoperatively or follow-up.[108-110] FDG-PET could be useful in the management of endometrial cancer. However, very limited information is available.[111-115] In the literature, 2 retrospective case series[111,112] investigated the role of PET for post-therapy surveillance, and a single prospective study evaluated the sensitivity and specificity of FDG-PET for detecting pelvic and para-aortic node metastasis preoperatively.[115] The diagnostic efficacy and benefit of FDG-PET in other settings of endometrial cancer is still uncertain.

In a prospective study, we evaluated the value of integrating whole-body FDG-PET into the management of endometrial cancer in comparison with conventional MRI-CT imaging alone.[10] All patients with histologically confirmed primary advanced (stage III/IV) or suspicious/documented recurrent endometrial cancer, with poor prognostic features (serum CA 125 $>$ 35 U/mL or unfavorable cell types), or surveillance after salvage therapy were eligible. Before FDG-PET scanning, each had received MRI-CT. The ROC method with calculation of AUC was used to compare the diagnostic efficacy. Forty-nine eligible patients were accrued, and 60 studies were performed (27 primary staging, 33 posttherapy surveillance or restaging on relapse). The clinical impact of FDG-PET scanning was classified as (1) negative: if PET led to unnecessary, additional invasive procedures; (2) no change: same findings as MRI-CT, the false-positive and false-negative FDG-PET findings did not affect surgical staging or treatment, or detecting an incurable relapse; or (3) positive: [i]

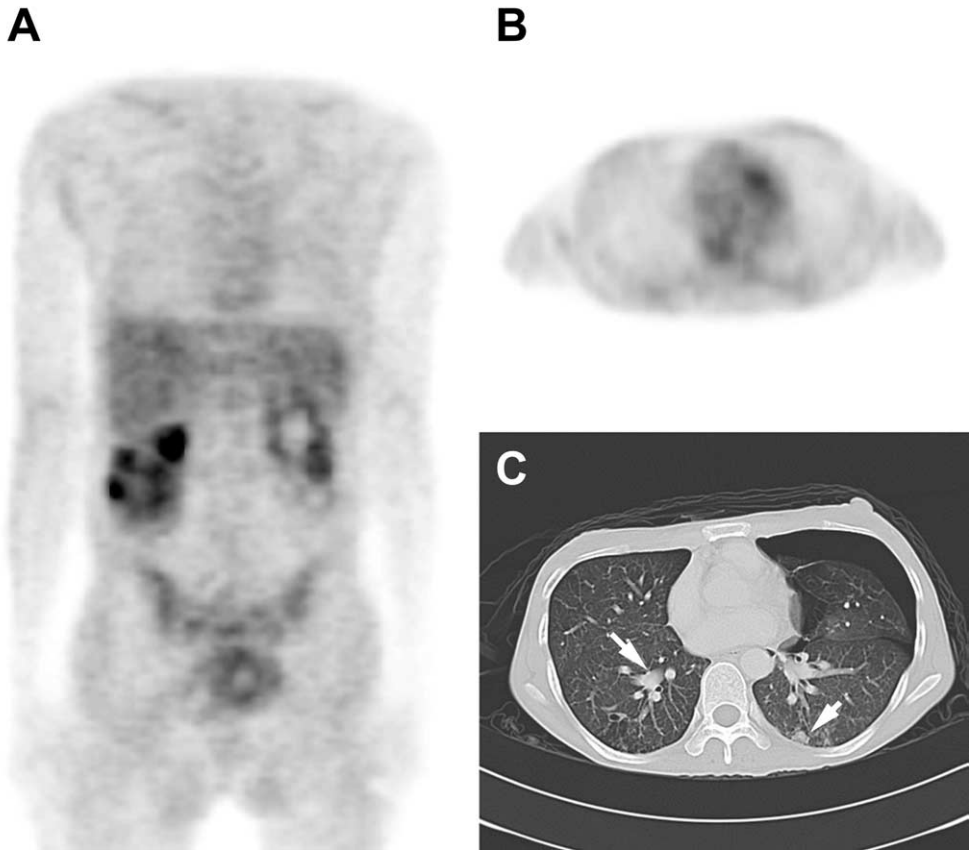

Figure 5 This patient was a 38-year-old woman with placental site trophoblastic tumor in August 2002. She had a whole-body CT scan because of an elevation of serum tumor marker β-HCG (372 mIU/mL) in September 2002. The ^{18}F-FDG-PET scan showed except tumor in uterus, no obvious FDG-avid lesion in whole body (A, coronal section; B, transaxial section). She had hysterectomy only. No further chemotherapy was given to her after operation. She is now alive without disease. Whole-body CT revealed except for tumor in uterus, bilateral multiple lung metastases were also observed (C, arrow).

treatment modified owing to correct staging with upstaged or down-staged against MRI-CT, [ii] confirmation of sole site involvement for distant recurrences (stick to curative treatment), [iii] early detection of curable recurrence or re-recurrence, [iv] deferring exploration for the false-positives of MRI-CT (Fig. 3), or [v] change to palliation avoiding a futile salvage attempt. Clinical impact was determined on the scan basis. The clinical impact was positive in 29 (48.3%) of the 60 scans. The SN of FDG-PET alone ($P < 0.0001$) or FDG-PET plus MRI-CT ($P < 0.0001$) was significantly higher than MRI-CT alone in overall lesion detection. FDG-PET plus MRI-CT was significantly superior to MRI-CT alone in overall lesion detection (AUC: 0.949 versus 0.872; $P = 0.004$), pelvic nodal/soft tissue ($P = 0.048$) or extrapelvic metastasis ($P = 0.010$), whereas FDG-PET alone was only marginally superior by AUC ($P = 0.063$). Whole-body FDG-PET coupled with MRI-CT facilitated optimal management of endometrial cancer in well-selected cases.

Vulvar Cancer

Vulvar cancer is a relatively rare female genital malignancy.[11] Owing to the rarity, efforts to optimize management is compromised by the small number of patients. The primary status of inguinal LN and presence of extravulvar lesions play an important role in stage, treatment, and prognosis of patients with vulvar cancer.[116-119] The groin LN metastasis is common even with superficial depth invasion.[118] However, it is still lacking an appropriate image modality to accurately detect the groin LNs and extravulvar metastasis.

Local vulvar recurrence is most likely and usually is amenable to further surgical excision, but regional and distant recurrences are difficult to detect and apply appropriate management and have poor prognosis.[11,119-123] It is interesting and important to know the exact sites of recurrent vulvar cancer for performing the tailored individual salvage or palliative treatment in such patients.

Very few studies have investigated the clinical impact of whole-body FDG-PET in vulvar cancer.[124] Cohn and coworkers reported a prospective series of 15 patients with primary vulvar squamous carcinoma of at least 2 cm in diameter and at least 1-mm invasion. FDG-PET was performed before groin dissection. Six patients has positive scan, suggesting 8 groins containing metastatic cancer. Pathologically, 5 patients had metastases in 9 groins, with

PET detecting 4 of 5 patients and 6 of 9 groins with disease. On the patient basis, PET had a SN of 80%, SP of 90%, PPV of 80%, and NPV of 90%. On a groin basis, they were SN of 67%, SP of 95%, PPV of 86%, and NPV of 86%.[124] In our experience (unpublished), precautions must be taken to avoid false-positive PET results attributable to inflammatory reaction, which can not be differentiated by dual-phase PET imaging technique (Fig. 4).

Gestational Trophoblastic Tumors or Neoplasia (GTTs/GTN)

GTT/GTN is one of the rare human malignancies that can be cured even in the presence of widespread metastases. GTN represents a range of tumors, including hydatidiform mole, invasive mole, choriocarcinoma, and placental site trophoblastic tumor (PSTT). Human chorionic gonadotropin (hCG) is an excellent tumor marker for GTN. It is also unique that the diagnosis of GTN could be based on clinical imaging and elevated serum hCG without histological verification. The hydatidiform mole needs no chemotherapy if the serum hCG values regressed well after removal. Almost 100% low-risk and nonmetastatic GTN could be cured with management under standard guidelines. The prognosis is good even for metastatic GTN. However, some of the high-risk and persistent/recurrent GTN harboring chemotherapy-resistant tumor cells remain a tough clinical problem, and PSTT represents a relative chemoresistant form of GTNs.[125-128] It is well recognized that GTN should be treated according the prognostic grouping. The WHO risk scoring system[129] which adopted the one designed by Bagshawe in 1976 is widely accepted.[130]

The diagnosis of GTN can be made without histologic examination. More often than not, tissue-proof of metastases is regarded unnecessary for its exquisite chemosensitivity and high vascularity. Chemotherapy usually will be instituted after the imaging studies except for those in which a complete response is confirmed. The commonly evaluated parameters for diagnostic accuracy of PET, including SN, SP, PPV, NPV, and accuracy, are not as applicable for GTN.

To the best of our knowledge, only case reports have studied the role of ^{18}F-FDG-PET in GTN, and the limited results appear to be promising.[131-135] After successfully localizing a chemotherapy-resistant pulmonary lesion by PET in a choriocarcinoma patient with an unexplained serum β-hCG elevation, we began a pilot study to evaluate the role of PET in GTN. Our preliminary results suggest five roles for PET in GTN.[136] The first was to discover chemotherapy-resistant lesions that can be removed by surgery and/or radiotherapy. The second was to rule out false-positive lesions found by a CT scan and thus avoiding unnecessary treatment (Fig. 5). The third was to define the tumor extent more precisely before starting treatment. The fourth was to confirm a complete treatment response in PSTT or recurrent/resistant GTN after salvage. However, for postmolar GTT with unexplained abnormal serum β-hCG regression, merely lung metastasis, or resistant to single agent chemotherapy PET might not be as useful.

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