Gynecologic Cancers

26

Seok-Ki Kim, Sung Eun Kim, June-Key Chung, and E. Edmund Kim

Introduction

Gynecologic cancers constitute approximately 20% of visceral cancers in women and are divided into three major types: ovarian, cervical, and endometrial cancers. The majority of gynecologic cancers require surgical removal, along with adjuvant radiotherapy or chemotherapy. The therapeutic option varies with the type and stage of cancer. Therefore, accurate staging is necessary for optimal treatment.

S.-K. Kim, M.D. (✉)
Department of Nuclear Medicine, National Cancer Center, Gyeonggi-do 410-769, South Korea
e-mail: skim@ncc.re.kr

S.E. Kim, M.D., Ph.D.
Department of Nuclear Medicine, Korea University College of Medicine, Guro Hospital, Seoul 152-703, South Korea
e-mail: seiong@korea.ac.kr

J.-K. Chung, M.D., Ph.D.
Department of Nuclear Medicine, Seoul National University College of Medicine, Seoul 110-744, South Korea
e-mail: jkchung@plaza.snu.ac.kr

E.E. Kim, M.D., M.S.
Departments of Nuclear Medicine and Diagnostic Radiology, The University of Texas MD Anderson Cancer Center and Medical School, 1515 Holcombe Blvd, Box 0059, Houston, TX 77030, USA

Graduate School of Convergence Science and Technology, Seoul National University, Seoul, South Korea
e-mail: kim@mdanderson.org

A variety of radiographic techniques are used for evaluating patients with suspected or diagnosed gynecologic malignancies. Unfortunately, morphologic imaging techniques are not optimal for diagnosis, staging, or identifying recurrent disease, when a specific tumor marker, such as serum CA-125, can hold some value for tracking status and heralding recurrence during postoperative patient management [1, 2].

The advent of positron emission tomography (PET) enables us to metabolically detect active gynecologic cancers with greater accuracy than anatomic imaging techniques. Furthermore, PET is more sensitive for the presence of active cancer than that determined by tumor markers, which, at present, are generally available [3]. Currently, most PET systems are installed as combined PET/computed tomography (CT) scanners that provide combined PET and CT images with acceptable precision. Anatomic information obtained from CT increases the usefulness of PET because the abdominopelvic cavity has complex spatial structures. As for other tumors, fluorine-18-fluorodeoxyglucose (^{18}F-FDG) is the most commonly used PET agent in gynecologic oncology today.

Ovarian Cancer

Ovarian carcinoma is the leading cause of death among women with gynecologic malignancies. There were 25,400 new reported cases of ovarian cancer, with 14,300 deaths attributed to this disease in the US in 1999 [4].

E.E. Kim et al. (eds.), *Clinical PET and PET/CT: Principles and Applications*,
DOI 10.1007/978-1-4419-0802-5_26,

Most ovarian tumors are first discovered when they are already in the advanced stage. Imaging techniques are relied on to identify the location of suspected lesions and to provide optimal treatment in the hope of reducing mortality. Ovarian cancer commonly seeds the peritoneal surfaces of the abdomen and pelvis and is often seen on the serosal and mesenteric surfaces of the large and small intestine, as well as the liver surface. The right and left hemidiaphragms are also common metastatic sites. Ovarian cancer recurs quite frequent despite successful implementation of cytoreductive surgery and chemotherapy, and 20–30% of early ovarian cancer and 50–75% of advanced ovarian cancer recurs although initial complete remission has taken place. Thus, exact diagnosis and early detection of recurrence are crucial to patient management. Ovarian cancer also has the potential to spread through the lymphatic vessels and commonly involves para-aortic lymph nodes without affecting the pelvic nodes. Ovarian cancer rarely metastasizes via the blood to the liver parenchyma, lungs, bones, or brain.

Although the disease usually spreads transperitoneally as tumor implant accompanying ascites, some tumor seedings are often not visible by conventional techniques such as sonography, CT, and MRI. The clinical requirements for PET imaging in patients with ovarian cancer are preoperative diagnosis and staging and differentiation between metastases and nonmalignant pathologic conditions. For pretreatment staging, FDG PET could be helpful in a limited patient group possessing high risks of ovarian cancer. Because it was recently discovered that PET/CT could provide additional anatomic information, PET/CT is expected to be used more for pretreatment staging than PET alone. In addition to staging, FDG PET could be useful for patients with a high suspicion of recurrence (i.e., rise of CA-125), especially in cases where conventional imaging techniques present no evidence of disease. FDG PET provides critical information for treatment planning such as recurrence site or pattern. FDG PET can evaluate treatment response early and show a close relationship with overall survival, although this has not been yet been determined using large scale clinical trials.

Differential Diagnosis of Adnexal Mass and Preoperative Evaluation

Although the CA-125 tumor marker is elevated in the majority of patients with advanced ovarian cancer, an established screening procedure for early detection of ovarian cancer is not yet available. A mass lesion of the ovary is usually detected during gynecologic examination, whereas imaging methods are necessary for evaluating the tumor status and spread. Chou et al. [5] reported a quite high diagnostic accuracy of about 90% for transvaginal color Doppler sonography, whereas the diagnostic roles of other imaging modalities have not been fully investigated. Grab et al. [6] compared diagnostic accuracy of sonography, MRI, and PET in the evaluation of adnexal masses. In a series with 101 patients, sonographic examination resulted in correct classification of 11 of 12 ovarian malignancies (sensitivity, 92%) but with a specificity of only 60%. With MRI and PET, specificities improved to 84% and 80% respectively, but sensitivities decreased. When all imaging modalities were combined, sensitivity and specificity were 92% and 85%, respectively, and accuracy was 86%. The combination of sonography with MRI and PET may improve accuracy in the differentiation of benign from malignant ovarian lesions. However, MRI, CT, and FDG PET have not been fully investigated in their role in the initial workup of all ovarian tumors. A study reported that ultrasonography, PET, and MRI were not helpful in selected women after the diagnosis of ovarian cancer [7]. However, Ju and Kim [8] reported that FDG PET/CT could be helpful in selected patients with clinically high suspicion of ovarian malignancy. They enrolled 101 patients according to CA-125 level, sonography finding, and menstrual status. In those patients, the sensitivity and specificity for ovarian cancer were 100% and 92.5%, respectively. FDG PET appeared to be more helpful in the differential diagnosis of solid ovarian mass rather than cystic ovarian mass.

The values and limitations of FDG PET in the diagnosis of suspected primary ovarian cancer have recently been detailed. It has been reported that most ovarian carcinomas show an increased

FDG uptake, whereas the borderline ovarian tumor shows mild FDG accumulation, which indicates the modest nature of borderline ovarian tumor [8]. Borderline ovarian tumor is one of the most important clinical disease entities, and prognosis is better than for other ovarian malignancy, although it might require laparotomy and surgical staging for diagnosis. However, low glucose metabolism of borderline tumors or early-stage ovarian cancers, together with high FDG uptake in inflammatory lesions, diminishes the sensitivity and specificity of FDG PET for the diagnosis of primary ovarian cancer [6].

Immunoscintigraphy has been thought to be the most specific imaging technique, however, it has not been accepted as a routine method for imaging. Krag [9] reported that in patients with ovarian cancer, immunoscinitigraphy had a sensitivity and specificity of 69% and 57%, respectively, for CT, 44% and 79%, respectively.

Preoperative Evaluation of Patients With a Pelvic Mass

The first report on FDG accumulation in ovarian cancer was by Hubner et al. [10]. They found a sensitivity of 93% and a specificity of 82% for assessing previous tumors. In the preoperative evaluation of patients with a pelvic mass, PET has been reported to have positive and negative predictive values (NPV) of 86% and 76%, respectively, for malignancy. Zimny et al. [11] evaluated FDG PET in 26 patients suspected of having ovarian cancer. Quantitative analysis revealed a mean standardized uptake value (SUV) of 6.8 ± 2.3 in primary ovarian carcinoma compared with 2.6 ± 1.2 in benign masses. The sensitivity, specificity, and diagnostic accuracy were 88%, 80%, and 85%, respectively.

FDG accumulation from an inflammatory lesion could cause additional issues in ovarian cancer, such as in other cancers. Schroder et al. [12] Reported on the preoperative detectability of FDG PET in ovarian carcinoma. With regard to metabolic differentiation of primary ovarian tumors, 24 of 28 the cases (85.8%) were correctly diagnosed using PET. The only false-positive findings resulted from an inflammatory adnexal mass, which illustrates the limitation of PET in distinguishing malignant from inflammatory processes (also showing an increased glucose metabolism). Römer et al. [13] conducted a study comprising 24 patients, four of 19 with a primary ovarian mass who had an inflammatory adnexal process, and showed an increased FDG uptake in all cases. Because of this fact, in their study, FDG PET showed a specificity of only 54%, whereas the sensitivity was 83%. Quantitative analysis of SUV, as recommended by the interdisciplinary consensus meeting, does not improve the diagnostic differentiation of inflammatory adnexal masses from malignant tumors.

Staging

Staging diagnosis is one of the major prognostic factors of ovarian cancer [14]. At diagnosis, approximately 70% of patients have tumors that have spread beyond the ovary and pelvis to the abdomen (stage III) or beyond (stage IV). Fewer than 20% of patients with advanced ovarian cancer (stage III and IV) live for 5 years after diagnosis [15]. CT and MRI are not reliable in evaluating tumor spread because lymph node metastases and smaller peritoneal implants can be missed.

At present, exploratory laparotomy is the "gold standard" in the staging of ovarian cancer. Staging laparotomy is required for histologic confirmation of the diagnosis, identification of tumor spread, and debulking of tumor masses prior to chemotherapy. Modern imaging techniques have been introduced for preoperative evaluation of the disease. Sonography, CT, and MRI, however, lack the potential for distinguishing benign reactive changes from cancer infiltration [16]. FDG PET can be clinically used for more complete staging of patients with primary or recurrent ovarian cancer.

Manuel et al. [17] evaluated the detectability of FDG PET prior to surgical exploration and correlated PET images with surgicopathologic findings in primary ovarian cancer. The sensitivity and specificity of FDG PET were 78% and

86%, respectively. On a region basis (the abdomen and pelvis were divided into five regions of interest) the sensitivity and specificity of PET were 43% and 92%, respectively, while CT or MRI was only 29% sensitive. PET is of limited value for the detection of microscopic seeding. A typical finding on FDG PET, in cases with peritoneal seeding, is diffused and increased uptake around the peritoneal pouch.

Extraperitoneal Metastasis

Another important strength of FDG PET is the ability of detecting distant metastasis. Although distant metastasis (except peritoneal spread) is not frequent in ovarian cancer, extraperitoneal involvement such as lymph node metastasis, and rarely solid organ metastasis, take place. In advanced cases, FDG PET could detect unexpected metastases to the supraclavicular lymph node or cardiophrenic lymph node. The clinical importance of this additional extraperitoneal metastasis remains to be clarified.

Recurrent Ovarian Carcinoma

To date, studies have focused on the role of FDG PET in patients with recurrent ovarian cancer. FDG PET can be helpful in detecting small recurrent lesions in patients in whom posttherapeutic alterations in anatomy may make it difficult to interpret conventional imaging studies. In recent reports [18–20], FDG PET was superior to conventional CT or MRI for detecting recurrent disease. The sensitivity was 83–91% versus 45–91%, and specificity was 66–93% versus 46–84% for PET and CT/MRI, respectively [18].

Posttreatment Surveillance Without the Evidence or Suspicion of Recurrence

Second-look laparotomy, defined as "a systematic surgical reexploration in asymptomatic patients who have no clinical evidence of tumor following initial surgery and completion of a planned program of chemotherapy for ovarian cancer" has been widely used to assess response to chemotherapy in clinical trials and standard management of ovarian cancer [21]. However, the second-look laparotomy does not affect survival. In patients with advanced disease, as many as 50% with negative results on second-look laparotomy following combination chemotherapy, have experienced a subsequent recurrence. This discouraging statistic suggests that, (1) even a thorough exploration does not reveal microscopic residuals in many patients, and (2) this group of patients should be strongly considered for adjuvant chemotherapy.

PET has been evaluated as a substitute for second-look surgery in ovarian cancer patients with a complete clinical, radiographic, and serologic response following primary surgery and chemotherapy [22]. Casey et al. [23] studied the role of PET with second-look laparotomy in seven patients. PET scans were consistent with the presence of tumors in all six patients with residual cancer, even though serum ovarian tumor markers remained below the normal threshold in three of the patients at the time of scanning. Whole-body PET would provide a sensitive noninvasive "second-look method" with little patient discomfort, with reasonably fast patient throughput and at a reasonable cost.

Although PET cannot rule out microscopic persistent or recurrent disease, a negative scan provides prognostic information. It has been demonstrated that patients with a longer relapse-free interval have a higher likelihood of benefiting from surgery. Furthermore, the response rate to re-treatment increases with the duration of the treatment-free interval. Patients with a 6-month treatment-free interval have potentially platinum-sensitive disease and patients with a treatment-free interval of longer than 24 months have the greatest likelihood of benefiting from re-treatment. Zimny et al. [24] reported that the median relapse-free interval was 20 months for negative PET scans compared with only 6 months for positive scans. Chung et al. [25] showed that the median duration of survival was 29.6 months with the second-look laparotomy and 30.9 months after PET ($p>0.05$) in patients on who PET was performed or second-look laparotomy after primary chemotherapy.

In comparing FDG PET with second-look laparotomy, the sensitivity for small residual lesions of FDG PET was not as sensitive as for second-look laparotomy [26, 27]. Therefore, we do not have enough evidence to recommend FDG PET as routine substitute for second-look laparotomy. The value of second-look laparotomy seems questionable in the aspects of safety and survival gain; and FDG PET is noninvasive and could evaluate unexpected extraperitoneal distant metastasis simultaneously. Therefore, FDG PET could be considered as a substitute for second-look laparotomy.

Cases With High Risk or Suspicion of Recurrence

FDG PET can more accurately detect recurrent lesions in the setting of suspicious recurrence is clinically high, such as unexplained high CA-125 levels, whereas the accuracy of FDG PET seems to be lower in the cases of low suspicious recurrence. The high accuracy of FDG PET with the addition of CA-125 suggests that this combination may have a significant role in the management of patients with ovarian cancer. The most appropriate biopsy site can be localized by PET prior to tissue changes detected by CT or MRI [18]. In a study by Zimny et al. [24] with 106 scans obtained from 54 patients, the overall sensitivity and specificity for detecting recurrent ovarian cancer were 83% and 83%, respectively. However, the diagnostic accuracy assessed by receiver operating characteristic analysis varied between the subgroups of patients enrolled in the study. PET was more accurate in patients with suspected recurrence with a diagnostic accuracy of 93% and sensitivity of 94% compared with 71% and 65% in patients judged as clinically free of disease [19]. More importantly, the analysis of patients with rising tumor marker CA-125 and negative or nondiagnostic findings of conventional imaging revealed a sensitivity of 96% with only one false-negative result [20]. In a report by Nakamoto et al. [26] on a patient-based analysis, overall sensitivity, specificity, and accuracy of conventional imaging modalities were 73%, 75%, and 73%, respectively, and these rates improved to 92%, 100%, and 94%, respectively, by considering both conventional imaging modalities and PET findings. Although FDG PET is useful in a setting of high CA-125, FDG PET alone might be more accurate than CA-125. The sensitivity and specificity of CT or MRI were 0.68 (range, 0.49–0.83) and 0.58 (range, 0.33–0.80), whereas those of CA-125 were 0.81 (range, 0.62–0.92) and 0.83 (range, 0.58–0.96), and those of FDG PET were 0.90 (range, 0.82–0.95) and 0.86 (range, 0.67–0.96) [19, 20].

Corresponding to the studies where the old PET scanner was used, many studies using newly developed PET/CT scanners were reported to show the same clinical effectiveness as the PET scanner [28–31] evaluated the lesion detectability and effectiveness in patients with recurrent ovarian cancer and compared CT with combined PET/CT. PET/CT identified additional lesions compared with CT in 12 or 15 patients (80%) and changed the management course in 11 of 15 patients (73%). The sensitivity, specificity, and accuracy using PET/CT in recent studies ranges from 88.2%–93.3%, 71.4%–96.9%, and 85.4%–91.2%, respectively [29, 32, 33].

Peritoneal Carcinomatosis

PET is of limited value for the detection of microscopic seeding. Typical findings of FDG PET in cases with peritoneal seeding are diffused increased uptake around the peritoneal pouch. However, it is sometimes difficult to differentiate abnormal uptake form the normal uptake pattern. Special attention is required to differentiate peritoneal seeding from increased bowel activity. Zimny et al. [11] reported that the sensitivity, specificity, and diagnostic accuracy were 50%, 95% and 80%, respectively, for evaluating peritoneal metastases. In other words, PET misses poorly localized microscopic spread disease [26]. Schroder et al. [12] reported that the sensitivity of FDG PET for the detection of peritoneal carcinomatosis was 72%, which is somewhat lower, but still higher than the 45% achieved with CT. MRI also is not a great improvement over CT because most metastases in the mesentery and the small intestine remain undetected by both methods.

FDG PET imaging of the abdomen and pelvis can be difficult because of the physiologic bowel uptake and bladder activity and the lack of anatomic landmarks. A new combined PET/CT scanning technique provides combined PET and CT images without the problem of organ motion, temporal differences, and patient positioning [31]. Although CT imaging compared with PET/CT might not be optimal for diagnostic aim, PET/CT obtains more anatomic information over CT, and is more advantageous than PET, especially in lesions with complex peritoneal location. PET/CT seems to be helpful in some types of ovarian cancers with moderate FDG accumulation, mucinous ovarian cancer, because CT could depict easily the FDG void cystic portion of mucinous portion of the tumor. But its utility for peritoneal carcinomatosis remains to be investigated [12, 34, 35].

Treatment Response Monitoring, Clinical Impact on Patient Management, and Cost Effectiveness

FDG PET is used for prediction for treatment response in ovarian cancer [36, 37]. As mentioned in the previously, FDG PET could be used as a substitute for the second-look laparotomy in patients with risk for surgery and can subsequently impact the clinical pathway.

FDG PET is helpful in detecting and staging recurrent ovarian cancer when applied in selecting the most appropriate treatment and avoiding second-look surgeries using the Monte Carlo simulation analysis [38, 39]. Assumptions in the management pathway were: (1) a PET-positive scans led to either laparoscopy or laparotomy, followed by chemotherapy (true-positive PET) or follow-up (false-positive PET); (2) a PET-negative scan resulted in continued follow-up (true-negative PET) or laparotomy (false-negative PET); and, (3) a laparotomy led to chemotherapy or follow-up. The number of unnecessary laparotomies was reduced from 70% to 5% using PET to manage the diagnostic evaluation. Cost savings per patient ranged from $1,941 to $11,766. Therefore, FDG PET can reduce unnecessary invasive staging procedures and management with PET in place of second-look surgery would yield substantial cost savings to the patient. Early detection of recurrence also could have a positive impact on cost effectiveness [38]. FDG PET could have an impact on the patient management pattern. As a result of FDG PET findings, the treatment management was changed in 24.7% to 58% of patients with ovarian cancer [26, 29, 30, 39].

FDG PET and CA-125 were compared as predictors to chemotherapy [39] with FDG PET being superior to CA-125 in prediction after chemotherapy. FDG PET could predict the effect of chemotherapy using pre- and postchemotherapy FDG PET imaging and was more accurate than the routinely used CA-125. More importantly, FDG PET following chemotherapy was related to survival, although CA-125 was not.

Indications in Ovarian Cancers

Initial Evaluation and Staging of Ovarian Tumor

There is no evidence for the usage of differential diagnosis of ovarian tumor, although FDG PET could be used for clinically and serologically suspicious ovarian tumor.

Although FDG PET alone has not been used routinely as a preoperative staging tool, it is useful combining CT and FDG PET in preoperative staging where PET/CT could be an optimal tool. Because initially advanced ovarian cancer has a possibility of extrapelvic or extra-abdominal metastatic lesion, FDG PET could be helpful.

Surveillance After Initial Treatment

FDG PET is recommended in cases with a high risk of recurrence, where CA-125 increased without explanatory lesions. Additionally, it is strongly recommended if other conventional imaging has a negative result. It is also recommended in patients with low risk, and if second-look laparotomy is planned, FDG PET should be considered as a noninvasive substitute, especially in inoperable cases.

Limitation in Ovarian Cancers

Distinguishing Malignant From Benign Lesions

The limitation of FDG PET is distinguishing malignant from inflammatory processes, which also show an increased glucose metabolism [17].

False-positive results for corpus luteum cyst, ovarian endometriosis, and gestational pouch were reported with a focally raised FDG uptake [14].

Type of Tumor

False-positive results were seen in benign serous cyst adenoma, endometriosis, and endometrioma, and false-negative PET results observed in a mesothelioma and a borderline serous tumor [8].

Tumor Size

Lesions smaller than 1 cm are quite difficult to identify not only because of the relatively poor spatial resolution but also the longer acquisition time of PET. Count recovery from small lesions may not be sufficient because of peristalsis of the alimentary tract and respiratory movement during image acquisition. Thus, even if PET findings are negative, small lesions may sometimes be detected by second-look laparotomy. However, follow-up patients typically receive chemotherapy for recurrence and systemic metastasis. Small lesions that cannot be detected on PET scans can be sensitive to drugs, while larger lesions are resistant to drugs because of possible penetration barriers. Therefore, if FDG PET reveals highly accumulated lesions remaining in a patient even after repeated chemotherapy, resection would be recommended. If PET findings are negative, chemotherapy can be proposed because some small lesions may remain. Thus, PET can be useful for therapeutic decision making [26].

Nonpathologic (Physiologic) Uptake

Physiologic uptakes in the stomach, colon, ureter, and bladder are sometimes difficult to differentiate from pathologic lesions. Such accumulation can mask abnormal uptake because of tiny disseminated lesions [26]. The combination of hydration, administration of a diuretic such as furosemide, and use of a Foley catheter with a drainage bag is an effective method of reducing physiologic uptake in the kidneys, ureter, and bladder, although reducing physiologic uptake in the colon is difficult [40].

The use of SUVs and SUV ratio can be helpful in the distinction between physiologic bowel activity and ovarian cancer metastatic to the bowel serosa. Manuel et al. [17] suggested that SUV and SUV ratio (cut-off value of 3.0 for SUV and 1.75 for SUV ratio) were significantly higher in cases of cancer metastasis to the bowel than those with no evidence of bowel metastases.

11C Methionine PET

Tumor imaging in the pelvis can be problematic because normal excreted activity in the urine may interfere with tumor identification. An essential amino acid, methionine, labeled with ^{11}C, has been found to be a valuable tracer for metabolic imaging of human cancer. High uptake of ^{11}C methionine may correlate with poor histologic grade of differentiation and high cell proliferation, which suggests that tissue uptake of methionine may reflect the biologic aggressiveness of cancer [41].

Lapela et al. [41] showed that it is possible to separate poorly differentiated from well-differentiated tumors. They tried to differentiate benign and malignant ovarian tumors. They reported that benign or borderline malignant tumors did not accumulate ^{11}C methionine, whereas all carcinomas had significant uptakes. The mean SUV of the primary carcinoma was 7.0 ± 2.2, and the mean Ki was 0.14 min^{-1}.

We found that ^{11}C methionine PET can be used to differentiate physiologic uptake of FDG from true lesion [42]. In a series of 16 gynecologic cancers, the higher diagnostic accuracy of the methionine PET(sensitivity = 80% [4/5cases],specificity = 100% [11/11 cases], and accuracy = 94% [15/16 cases]) than that of FDG PET (sensitivity = 40% [2/5 cases], specificity = 91% [10/11 cases], accuracy = 75% [12/16 cases]) was found for the detection of the recurrent gynecologic cancer in the pelvic region postoperatively.

Cervical Cancer

Uterine cervix carcinoma is estimated to be the second most frequently diagnosed cancer in women worldwide. Although the overall mortality from cervical cancer has decreased because of early detection and treatment of preinvasive disease, the mortality of invasive cervical cancer has not changed in the last 30 years.

The treatment and prognosis of invasive cervical cancer are determined by the stage of disease, volume of the primary tumor, grade of tumor, and presence of lymph node metastasis. Cross-sectional imaging modalities such as CT and MRI have proved to be useful for evaluating morphologic risk factors such as tumor size, depth of stromal invasion, stage of disease, and lymph node metastasis. An overall staging accuracy of 58–88% has been reported, but a low sensitivity of 44% was found. Neither tumor size nor early parametrial invasion can be evaluated reliably. MRI is now considered to be the most accurate imaging method for evaluation of tumor size and parametrial invasion. An overall staging accuracy of 80–92% has been shown, whereas 50% sensitivity for nodal metastasis is similar to that with CT [43].

Tumor volume can be overestimated as a result of paralesional edema. Small parametrial invasion and lymph node metastasis could be missed and tumor invasion or spread could be underestimated.

Preoperative Staging: Lymph Node Staging

Patients with an early stage of cervical cancer without lymph node metastasis are considered surgical candidates, whereas radiotherapy is often the preferred treatment when lymph node metastases are present [44]. Uterine cervical cancer metastasizes in a predictable pattern. The tumor usually spreads sequentially from the primary cervical lesion to the pelvic, para-aortic, and supraclavicular lymph nodes, and then ultimately to nonnodal distant metastatic sites such as the lung, liver, and bone. Metastasis to para-aortic lymph nodes in the absence of pelvic nodal metastasis is exceptionally uncommon [44, 45]. The status of lymph node metastasis is an important prognostic factor and crucial to creating a treatment plan. Conventional modalities such as CT and MRI have been used for noninvasive testing for lymph node staging.

Several reports have compared FDG PET with CT and surgical staging for detecting lymph node metastasis in patients with cervical cancer. Sugawara et al. [46] reported an 86% sensitivity of FDG PET for pelvic and para-aortic lymph node metastasis, as compared with a 57% sensitivity of CT in a study of 21 patients with cervical cancer with stages 1B to 4A. Grigsby et al. [47] reported that FDG PET detects abnormal lymph node regions more often than does CT. In 101 patients, CT demonstrated abnormally enlarged pelvic lymph nodes in 20 (20%) and para-aortic lymph nodes in seven (7%) of the 101 patients. PET demonstrated abnormal FDG uptake in pelvic lymph nodes in 67 (67%), in paraaortic lymph nodes in 21 (21%), and in supraclavicular lymph node in eight (8%) of the 101 patients. FDG PET could depict unexpected lesions that CT could not.

Reinhardt et al. [48] reported that node staging resulted in sensitivities of 91% with FDG PET and 73% with MRI and specificities of 100% with PET and 83% with MRI, respectively. The positive predictive value (PPV) of PET was 100%, and that of MRI was 67%. The metastatic involvement of lymph node sites was identified on PET with a PPV of 90%, and on MRI it was 64% ($p<0.05$). Earlier, Narayan et al. also reported similar results for accuracy (PET, 85% vs. MRI, 75%) [49]. A study by Williams et al. [50] reported the different result with others, but their study protocol of PET appeared suboptimal.

Para-aortic lymph nodes are out of the irradiation field in standard pelvic radiation treatment of uterine cervical cancer. If para-aortic lymph node metastasis is suspected, the irradiation of the para-aortic area is needed. The sensitivity and specificity of CT and MRI for para-aortic lymph node metastasis are not satisfactory. Rose et al. [51] reported

a sensitivity and specificity of 75% and 92%, respectively, for FDG PET in depiciting para-aortic lymph node metastasis in patients with more advanced stages (2B to 4A) before surgical staging lymphadenectomy. They observed a higher sensitivity of FDG PET for pelvic (100%) than for para-aortic (75%) lymph node metastases. Although the accuracy of FDG PET for para-aortic lymph node is not satisfactory, it seems to be the most accurate noninvasive method for assessing para-aortic status. Generally, FDG PET is a reliable alternative to conventional imaging for lymph node staging in patients with cervical cancer.

Recurrence

The recurrence rate of uterine cervical cancer is reported to be 6.5% following surgery and 26.2% after radiation therapy alone. About half of all cases of recurrent uterine cervical cancer are confined to the pelvic cavity, but some cases show metastatic lesions in the lymph nodes, lung, bone, and liver.

Radiologic studies such as intravenous renography, ultrasonography, CT and MRI are used to detect recurrent cervical cancer. It is difficult, however, for these imaging modalities to differentiate recurrent tumor from postoperative or radiation fibrosis, and to detect normal-sized metastatic lymph nodes and extrapelvic metastases. PET is effective in differentiating recurrence from scar tissue, and, in addition, can be used to obtain whole-body images to detect recurrence that was not clinically suspected.

Park et al. [52] reported the accuracy of CT and PET in the diagnosis of recurrent uterine cervical cancer in 36 patients. The sensitivity, specificity, and accuracy of CT were 78%, 83%, and 81%, respectively, while for PET, the corresponding figures were 100%, 94% ($p=0.0339$), and 97% ($p=0.0244$), respectively. Sun et al. [53] reported the sensitivity and specificity of 90% and 100%, respectively, with FDG PET in evaluation of recurrent ovarian cancer. PET could detect 7.9% of early recurrence in patients with clinically NED status.

Diagnostic accuracy of recent research using PET/CT is superior to PET (92.3% vs. 78.8%) [22, 26]. Sensitivity, specificity, and accuracy of the most recent study were 90.3%, 81.0%, 86.5%, respectively, and patient treatment plans changed following PET/CT in 23.1% of patients [54].

Treatment Response

Nakamoto et al. [55] reported a high sensitivity of FDG PET in monitoring therapeutic response of cervical cancer. In that study, FDG PET was performed prior to therapy and at a mean of 4.6 months after radiation in 20 patients with histologically proved uterine cervical cancer who were undergoing a "curative" course of radiation. FDG PET is a sensitive tool for detecting active cervical cancer following radiation therapy. The sensitivity, specificity, and accuracy were 100%, 60%, and 70%, respectively. With regard to the relatively low specificity, it is well known that FDG also accumulates in inflammatory foci, which can lead to false-positive findings.

Although PET would not completely replace monitoring of tumors using these modalities, this noninvasive technique could have a greater role for screening patients during follow-up because of its high sensitivity.

Prognosis

Grigsby et al. [47] reported that the findings on PET are a better predictor of survival than those on CT in patients with carcinoma of the cervix. The 2-year progression-free survival, based solely on para-aortic lymph node status, was 64% in CT-negative and PET-negative patients, 18% in CT-negative and PET-positive patients, and 14% in CT-positive and PET-positive patients ($p<0.0001$). A multivariate analysis demonstrated that the most significant prognostic factor for progression-free survival was the presence of positive para-aortic lymph nodes as detected using PET ($p=0.025$). Pinkus et al. [56] evaluated the prognostic value of FDG PET in patients with cervical cancer using a simple visual analysis

of primary tumor characteristics (scoring of heterogeneity, size, shape, and lymph node involvement). Only 8% of patients with a good prognosis by PET died, while 76% of patients with a poor prognosis by PET died within 2 years. The study extended the value of FDG PET in cervical cancer patients, powerfully separating patients who have an excellent prognosis from those with a poor prognosis who may require more aggressive initial treatment.

In a study of the prognostic value of SUV on FDG PET, squamous cell type uterine cervix cancer with high glucose metabolic activity results in a poor outcome. The survival of the high peak SUV group (> 13) was worse than the low peak SUV group (< 13). Two-year survival rates were 76.0% and 92.3% for the high and low peak SUV groups, respectively [57].

Indications in Cervical Cancers

(1) FDG PET is recommended for recurrent cervical cancer.
(2) FDG PET is recommended for lymph node staging for initial workup.

FDG PET is a more sensitive and specific noninvasive test for lymph node staging in pelvic and para-aortic lymph nodes than other conventional imaging. FDG PET could depict unexpected distant metastatic lesion in some advanced cases. This could potentially change the treatment plan.

(3) FDG PET could be helpful in the prediction of the prognosis and treatment effect but additional research is needed.

Limitations

Substantially increased uterine vascularity was generally observed in the secretory and menstrual phases using radionuclide imaging. In vivo FDG uptake could be altered by blood flow, transport, and hexokinase activity, therefore, FDG uptake in a normal uterus could be altered by the menstrual cycle phase. Preclinical studies have shown that FDG uptake in an estrogen-stimulated uterus is significantly greater than if no stimulation is present. Recently, a case of intrauterine accumulation of FDG during menstruation was reported [58].

Other Gynecologic Cancers

Endometrial Cancer

Endometrial cancer is one of the most common gynecologic malignancies and is predominant in postmenopausal women. Clinically, many endometrial cancers are found during the early stage of cancer because of clinical signs and symptoms such as vaginal bleeding, where the prognosis is known to be good. However, a considerable number of patients with advanced and relapsed disease reveal a poor prognosis.

As of yet, there is not sufficient data to validate the usefulness of FDG PET in detecting endometrial cancer. However, several studies have shown promising results that FDG PET is sensitive and specific in detection of recurrent or metastatic lesions. Nakahara et al. [59] reported on a case of endometrial cancer. FDG PET revealed heterogeneous and marked accumulation in the endometrium. Belhocine et al. [60] reported that feasibility of FDG PET for detecting early recurrence in endometrial cancer in 14 patients who showed no evidence of disease following treatment. Of the 14 patients, FDG PET diagnosed recurrence in two patients, where one of the two patients had a PET finding of enlarged hypermetabolic abdominal focus, although CT showed a negative result. The second patient had a single focus of hypermetabolic activity on the liver and a focal hypodensity in the same location on CT. Therefore, PET can be a useful method for detecting early recurrence in patients with endometrial cancer who showed no evidence of disease on conventional follow-up.

Uterine Sarcoma

FDG PET was useful in the diagnosis of sarcoma even though SUV was low. Umesaki et al. [61]

reported the cases of five sarcomas and evaluated the effectiveness of FDG PET for the diagnosis of uterine sarcoma in comparison with other diagnostic methods. PET examinations were 100% positive for the five sarcomas; MRI was 80% positive (four of five cases), and sonography was 40% positive (two of five cases). The mean SUV of the sarcomas was 4.5 ± 1.3.

Vulvar Cancer

Cohn et al. [62] undertook a prospective pilot study on the performance of FDG as a method for detection of groin metastases from vulvar cancer. Fifteen patients underwent PET prior to exploration of 29 groins. On a patient-by-patient basis, PET had a sensitivity of 80%, specificity of 90%, PPV of 80%, and NPV of 90% in demonstrating metastases. On a groin-by-groin basis, PET had a sensitivity of 67%, specificity of 95%, PPV of 86%, and NPV of 86%. The results of PET were relatively insensitive in predicting lymph node metastasis, and a negative study is not a reliable surrogate for a pathologically negative groin. However, the high specificity of PET suggests that it is useful in planning radiation therapy as an adjunct to lymphatic mapping and sentinel lymph node dissection.

References

1. Soper JT. Radiographic imaging in gynecologic oncology. Clin Obstet Gynecol. 2001;44:485–94.
2. Vardi J, Tadros G, Foemmel R, Shebes M. Plasma lipid-associated sialic acid and serum CA125 as indicators of disease status with ovarian cancer. Obstet Gynecol. 1989;73:379–83.
3. Gupta NC, Frank AR, Casey MJ. FDG PET imaging for post-treatment evaluation of patients with genitourinary malignancies. J Nucl Med. 1992;33:829.
4. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics. CA Cancer J Clin. 1999;49:8–31.
5. Chou CY, Chang CH, Yao BL, et al. Color Doppler ultrasonography and serum CA125 in the differentiation of benign and malignant ovarian tumors. J Clin Ultrasound. 1994;22:491–6.
6. Grab D, Flock F, Stohr I, Nussele K. Classification of asymptomatic adnexal masses by ultrasound, magnetic resonance imaging, and positron emission tomography. Gyncol Oncol. 2000;77:454–9.
7. Kawahara K, Yoshida Y, Kurokawa T, et al. Evaluation of positron emission tomography with tracer 18-fluorodeoxyglucose in addition to magnetic resonance imaging in the diagnosis of ovarian cancer in selected women after ultrasonography. J Comput Assist Tomogr. 2004;28:505–16.
8. Ju W, Kim SC. Discrepancy between magnetic resonance and 18F-fluorodeoxyglucose positron emission tomography imaging in a case of borderline ovarian tumor. Int J Gynecol Cancer. 2007;17:1031–3. Epub 2007 Mar 26.
9. Krag DN. Clinical utility of immunoscintigraphy in managing ovarian cancer. J Nucl Med. 1993;34:545–8.
10. Hubner KF, McDonald TW, Niethammer JG, et al. Assessment of primary and metastatic ovarian cancer by positron emission tomography using 2-[^{18}F]deoxyglucose. Gynecol Oncol. 1993;51:197–204.
11. Zimny M, Schroder W, Wolters S, et al. 18F-fluorodeoxyglucose PET in ovarian carcinoma: methodology and preliminary results. Nuklearmedizin. 1997;36:228–33.
12. Schroder W, Zimny M, Rudlowski C, et al. The role of 18F-fluoro-deoxyglucose positron emission tomography in diagnosis of ovarian cancer. Int J Cancer Oncol. 1999;9:117–22.
13. Romer W, Avril N, Dose J, et al. Metabolische Charakterisierung von Ovarialtumoren mit der Positronen-Emissions-Tomographie und F-18 Fluordeoxyglukose. Rofo. 1997;166:62–8.
14. Omura GA, Bradhy MF, Homesley HD, et al. Long-term follow-up and prognostic factor analysis in advanced ovarian carcinoma: the Gynecologic Oncologic Group experience. J Clin Oncol. 1991;9:1138–50.
15. Ozols RF. Chemotherapy of ovarian cancer. In: De Vita VT, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology, Updates, vol. 1. 2nd ed. Philidelphia: N.B. Lippincott; 1988. p. 1–12.
16. Bragg DG, Hricak H. Imaging in gynecologic malignancies. Cancer. 1993;71:1648–51.
17. Manuel M, Holschneider CH, Williams CM, et al. Correlation of FDG PET scans with surgicopathologic findings in ovarian cancers. J Nucl Med. 2002;43:29.
18. Delbeke D, Martin WH. Positron emission tomography imaging in oncology. Radiol Clin North Am. 2001;39:883–917.
19. Torizuka T, Nobezawa S, Kanno T, et al. Ovarian cancer recurrence: role of whole-body positron emission tomography using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose. Eur J Nucl Med. 2002;29:797–803.
20. Yen R-F, Sun S-S, Shen Y-Y, et al. Whole-body positron emission tomography with ^{18}F-fluoro-2-deoxyglucose for the detection of recurrent ovarian cancer. Anticancer Res. 2001;21:3691–4.
21. Barter J, Barnes W. Second-look laparotomy. In: Rubin S, Sutton G, editors. Ovarian cancer. New York: McGraw-Hill; 1993. p. 269–300.
22. Rose PG, Faulhaber P, Miraldi F, et al. Positron emission tomography for evaluating a complete clinical

response in patients with ovarian or peritoneal carcinoma: correlation with second-look laparotomy. Gynecol Oncol. 2001;82:17–21.
23. Casey MJ, Gupta NC, Muths CK. Experience with positrom emission tomography (PET) scans in patients with ovarian cancer. Gynecol Oncol. 1994;53:331–8.
24. Zimny M, Siggelkow W, Schroder W, et al. 2-[Fluorine-18]-fluoro-2-deoxy-D-glucose positron emission tomography in the diagnosis od recurrent ovarian cancer. Gynecol Oncol. 2001;83:310–5.
25. Chung J-K, Kang SB, Kim MH, et al. The role of 18F-FDG PET in patients with advanced epithelial ovarian carcinoma as a substitute for second-look operation. J Nucl Med. 2002;43:282.
26. Nakamoto Y, Saga T, Ishimori T, et al. Clinical value of positron emission tomography with FDG for recurrent ovarian cancer. AJR AM J Roentgeol. 2001;176:1449–54.
27. Karlan BY, Hoh C, Tse N, et al. Whole-body positron emission tomography with (fluorine-18)-2-deoxyglucose can detect metastatic carcinoma of the fallopian tube. Gynecol Oncol. 1993;49:383–8.
28. Mangili G, Picchio M, Sironi S, Viganò R, Rabaiotti E, Bornaghi D, Bettinardi V, Crivellaro C, Messa C, Fazio F. Integrated PET/CT as a first-line re-staging modality in patients with suspected recurrence of ovarian cancer. Eur J Nucl Med Mol Imaging. 2007;34:658–66. Epub 2006 Dec 20.
29. Chung HH, Kang WJ, Kim JW, Park NH, Song YS, Chung JK, Kang SB, Lee HP. Role of [^{18}F]FDG PET/CT in the assessment of suspected recurrent ovarian cancer: correlation with clinical or histological findings. Eur J Nucl Med Mol Imaging. 2007;34:480–6. Epub 2006 Nov 7.
30. Simcock B, Neesham D, Quinn M, Drummond E, Milner A, Hicks RJ. The impact of PET/CT in the management of recurrent ovarian cancer. Gynecol Oncol. 2006;103:271–6. Epub 2006 Apr 19.
31. Blodgett TM, Meltzer CC, Townsend DW, et al. PET/CT in restaging patients with ovarian carcinoma. J Nucl Med. 2002;43:310.
32. Nanni C, Rubello D, Farsad M, et al. (18)F-FDG PET/CT in the evaluation of recurrent ovarian cancer: a prospective study on forty-one patients. Eur J Surg Oncol. 2005;31:792–7.
33. García-Velloso MJ, Jurado M, Ceamanos C, Aramendía JM, Garrastachu MP, López-García G, Richter JA. Diagnostic accuracy of FDG PET in the follow-up of platinum-sensitive epithelial ovarian carcinoma. Eur J Nucl Med Mol Imaging. 2007;34:1396–405. Epub 2007 Feb 21.
34. Drieskens O, Stroobants S, Gysen M, et al. Positron emission tomography with FDG in the detection of peritoneal and retroperitoneal metastases of ovarian cancer. Gynecol Obstet Invest. 2003;55:130–4.
35. Turlakow A, Yeung HW, Salmon AS, et al. Peritoneal carcinomatosis: role of (18)F-FDG PET. J Nucl Med. 2003;44:1407–12.
36. Baum RP, Przetak C. Evaluation of therapy response in breast and ovarian cancer patients by positron emission tomography (PET). Q J Nucl Med. 2001; 45:257–68.
37. Smith GT, Hubner KF, McDonald T, et al. Cost analysis of FDG PET for managing patients with ovarian cancer. Clin Positron Imaging. 1999;2:63–70.
38. Smith GT, Hubner KF, McDonald T, et al. Avoiding second-look surgery and reducing costs in managing patients with ovarian cancer by applying F-18-FDG PET. Clin Positron Imaging. 1998;1:263.
39. Soussan M, Wartski M, Cherel P, Fourme E, Goupil A, Le Stanc E, Callet N, Alexandre J, Pecking AP, Alberini JL. Impact of FDG PET-CT imaging on the decision making in the biologic suspicion of ovarian carcinoma recurrence. Gynecol Oncol. 2008;108:160–5. Epub 2007 Oct 24.
40. Miraldi F, Vesselle H, Faulhaber PF, et al. Elimination of artifactual accumulation of FDG in PET imaging of colorectal cancer. Clin Nucl Med. 1998;23:3–7.
41. Lapela M, Leskinen-Kallio S, Varpula M, et al. Metabolic imaging of ovarian tumors with carbon-11-methioninre: a PET study. J Nucl Med. 1995;36: 2196–220.
42. Jeong HJ, Chung J-K, Paeng JC, et al. Usefulness of ^{11}C methionine PET in the pelvic region for evaluation of recurrent gynecologic cancer in postoperative state. J Nucl Med. 2002;43:283.
43. Hricak H, Yu KK. Raiology in invasive cervical cancer. AJR AM J Roentgeol. 1996;167:1101–8.
44. Eifel PJ, Berek JS, Thigpen JT. Cancer of the cervix, vagina, and vulva. In: De Vita VT, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 5th ed. Philidelphia: Lippincott-Raven; 1433. p. 1478–997.
45. Morice P, Sabourin JC, Pautier P, et al. Isolated paraaortic node involvement in stage IB/II cervical carcinoma. Eur J Gynaecol Oncol. 2000;21:123–5.
46. Sugawara Y, Eisbruch A, Kosuda S, et al. Escaluation of FDG PET in patients with cervical cancer. J Nucl Med. 1999;40:1125–31.
47. Grigsby PW, Siegel BA, Dehdashti F. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. J Clin Oncol. 2001; 19:3745–9.
48. Reinhardt MJ, Ehritt-Braun C, Vogelgesang D, et al. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and FDG PET. Radiology. 2001;218:776–82.
49. Narayan K, Hicks RJ, Jobling T, et al. A comparison of MRI and PET scanning in surgically staged locoregionally advanced cervical cancer: potential impact on treatment. Int J Gynecol Cancer. 2001;11:263–71.
50. Williams AD, Cousins C, Soutter WP, et al. Detection of pelvic lymph node metastases in gynecologic malignancy: a comparison of CT, MR imaging, and positron emission tomography. AJR AM J Roentgeol. 2001;177:343–8.
51. Rose PG, Adler LP, Rodriguez M, et al. PET for evaluating paraaortic nodal metastasis in locally advanced cervical cancer before surgical staging: a surgicopathologic study. J Clin Oncol. 1999;17:41–5.

52. Park DH, Kim KH, Park SY, et al. Diagnosis of recurrent uterine carvical cancer: computed tomography versus positron emission tomography. Korean J Radiol. 2000;1:51–5.
53. Sun SS, Chen TC, Yen RF, et al. Value of whole-body ^{18}F-fluoro-2-deoxyglucose positron emission tomography in the evaluation of recurrent cervical cancer. Anticancer Res. 2001;21:2957–62.
54. Chung HH, Jo H, Kang WJ, Kim JW, Park NH, Song YS, Chung JK, Kang SB, Lee HP. Clinical impact of integrated PET/CT on the management of suspected cervical cancer recurrence. Gynecol Oncol. 2007;104:529–34. Epub 2006 Oct 16.
55. Nakamoto Y, Eisbruch A, Achtyes ED, et al. Prognostic value of positron emission tomography using F-18-fluorodeoxyglucose in patients with cervical cancer undergoing radiotherapy. Gynecol Oncol. 2002;84:289–95.
56. Pinkus E, Miller TR, Grisby PW. Improved prognostic value of FDG PET in patients with cervical cancer using a simple visual analysis of tumor characteristics. J Nucl Med. 2002;43:28.
57. Jang HJ, Lee KH, Kim YH, et al. The role of FDG PET for predicting prognosis in squamous cell type uterine cervical carcinoma patients. J Nucl Med. 2002;43:28.
58. Yasuda S, Ide M, Takagi S, Shohtsu A. Intrauterine accumulation of F-18 FDG during menstruation. Clin Nucl Med. 1997;22:793–4.
59. Nakahara T, Fujii H, Ide M, et al. F-18 FDG uptake in endometrial cancer. Clin Nucl Med. 2001;26:82–3.
60. Belhocine TZ, Bolle KS, Willems-Foidart J. Usefulness of ^{18}F-FDG PET in the post-therapy surveillance of endometrial carcinoma. J Nucl Med. 2002;43:118–9.
61. Umesaki N, Tanada T, Miyama M, et al. Positron emission tomography 18F-fluorodeoxyglucose of uterine sarcoma: a comparison with magnetic resonance imaging and power doppler imaging. Gynecol Oncol. 2001;80:372–7.
62. Cohn DE, Dehdashti F, Gibb RK, et al. Prospective evaluation of positron emission tomography for the detection of groin node metastases from vulva cancer. Gynecol Oncol. 2002;85:179.