Whole-Body FDG-PET and PET/CT Imaging in Ovarian Cancer
By Karl F. Hubner, M.D.

Ovarian cancer afflicts 25,000 women in the U.S. every year, and this aggressive cancer caused about 14,000 deaths last year. Because of the extremely poor prognosis for advanced ovarian cancer, suspicious ovarian masses need prompt attention. “Missing” symptoms of ovarian cancer usually delay an early diagnosis. As a result, 75% of patients have stage III or IV disease at the time of initial diagnosis.3 The high probability of advanced disease demands accurate staging for appropriate treatment decisions.

Most ovarian cancers are serious carcinomas that typically involve both ovaries and have a tendency to spread along surfaces as silent occult metastatic peritoneal or bowel implants. Unfortunately, a sensitive, low-cost screening test for ovarian cancer, to detect early stage disease or residual microscopic disease, is not available.

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In high-risk women and for follow-up of patients with ovarian cancer, the mortality is poor, particularly in premenopausal women. Thirty-five percent of patients with residual disease have normal CA-125 levels.8

FOLLOW-UP TESTS

Diagnostic tests for follow-up of patients with ovarian cancer may include CT, MR, laparoscopy, and laparotomy. CT is 70% to 90% accurate for initial preoperative staging, and MR detect 40% to 50%, and ultrasound 60% to 90%, of recurrent disease.

Hysterectomy, salpingo-oophorectomy, and pelvic and aortic lymph node resection are used for treating early-stage ovarian cancer. The role of laparoscopy and surgical exploration that should be used to complete the surgical therapy fields. A recent report from the Johns Hopkins Medical Institutions underscores this expectation; it documents an overall patient-based accuracy for PET/CT in finding recurrent lesions > 1 cm at 82% with a sensitivity of 83% and a specificity of 94% (p = 0.046).

Other improvements in diagnostic approaches for ovarian cancer will arise from new developments in PET tracer chemistry. Initial results obtained with carbon-11 labeled methionine and carbon-11 labeled choline in gynecologic tumors are promising.

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FDG-PET

PET with FDG, the most common radio-tracer in oncology, is a unique imaging technique for localizing metabolically active, i.e., viable cancer tissue. The basis for its use is the fact that FDG uptake reflects changes in metabolic behavior of cells that have become malignant. FDG is a non-specific radiotracer; its uptake by a particular tissue simply corresponds to the amount of glucose used to sustain metabolism. Various dedicated positron imaging devices as well as gamma cameras fit for positron imaging in coincidence mode are commercially available. In addition, advanced hybrid PET/CT imaging systems introduced in 2000 permit fusion of emission and transmission images. First results obtained with PET/CT in ovarian cancer are promising and suggest that this new approach could have a significant impact on patient management, reducing morbidity and the expenses of surgical exploration. Most PET studies in oncology are done as whole-body scans and are evaluated by visual interpretation. Various relative uptake scales or activity concentration ratios can be applied for semiquantitative analyses, however.

FDG accumulation can be expressed by the standardized uptake value (SUV), calculated by using a calibration factor and correcting ‘PET counts’ for body weight as well as injected dose. Plotting time activity curves or graphical data analyses introduced by Patlak is also possible; but the latter option is generally reserved for research applications and is rarely used in routine clinical PET examinations.

FDG UPTAKE PATTERNS

Ovarian cancer tends to spread early by direct extension and later by intraperitoneal seeding, lymphatic invasion, and hematogenous routes. FDG-PET and PET/CT studies on ovarian cancer are showing an increasing use since the early 1990s. In a recent American study based on FDG-PET in 51 patients, mostly with recurrent ovarian cancer, the sensitivity was 90% and the specificity 75%, respectively, and the accuracy of non-specific FDG uptake in normal tissues and ovarian tumors was 86%. The authors also concluded that FDG-PET may be useful in monitoring treatment response. A recent study from the Netherlands showed that FDG-PET may be applied in patients with elevated CA-125 and a negative CT scan.

However, earlier results by Zimber et al., Römer et al., Fenchel et al., Kubisch-Huch et al., and Grab et al. suggested a range of 50% to 86% in specificity. A low negative predictive value for PET raises some concern, also expressed by Römer et al. who studied 24 patients prospectively for the presence of ovarian cancer and found a specificity of only 54%. Cho et al. concluded that PET was not as effective in detecting recurrent ovarian cancer as PET/CT imaging in small lesions. Hans and Kubisch-Huch, in a discussion of PET/CT applications, recom-mended exercising caution regarding the clinical use of FDG-PET in gynaecological cancer.

In contrast, Pichon et al. demonstrated a lesion-based sensitivity and specificity of 83% and 92% when using PET information in combination with CT. Nakamoto et al. combined PET findings with histological results from conventional imaging modalities and obtained similar results.

SHORTCOMINGS AND CAVEATS

Discordant results regarding the specificity of FDG-PET for ovarian cancer are due to differences in patient selection (inhomogeneity), tumor size, effectiveness of surgery or chemotherapy, and/or definition of outcome or survival indicators. Special attention to the natural course of this disease, more experience with false-negative and false-positive results, awareness of non-specific FDG uptake in normal tissues, and good technical quality of FDG-PET studies should improve the specificity for ovarian cancer. Image de-registration using conventional methods that depend on software, or the use of hybrid PET/CT fusion technology, add a new level of sophistication to PET in oncology and should improve sensitivity and specificity.

Several investigators have reported false-positive and false-negative findings on FDG-PET. False-positive results include mucus adenocarcinomas, endometrial and follicular cysts, corpus luteum cysts, fibromas, cystadenofibromas, misinterpreted gastrointestinal tract activity, salpingo-oophoritis and coexisting peritonitis, teratomas, dermoid cysts, tubo-ovarian abscesses, benign throma, and schwannoma which are included in the rubric of false positives. False-negative results include well-differentiated serous/mucinous cystadenocarcinomas, disseminated carcinomatosis, and PTa adenocarcinomas.

FDG-PET results with PET/CT are not only related to low metabolic activity of some neoplastic or benign, especially inflammatory, processes, but are also due to the limitations of the spatial resolution obtainable with PET. The modality is unlikely to detect metastases smaller than 5 mm in size and can also miss small retroperitoneal lymph nodes and sheets of tumor in carcinomatosis peritonei. Hübner et al. suggested that an SUV cut-off at 3.25 might help distinguish between benign and malignant ovarian lesions. In contrast, Römer et al. could not find a statistically significant difference between SUVs of ovarian cancer and inflammatory/infectious processes, and they achieved the same sensitivity and specificity of 83% and 54% with and without SUV information. When infectious processes were excluded from the analysis, however, SUV values could improve specificity. Koyama et al. used SUV calculations successfully for distinguishing malignant from benign uterine and ovarian tumors.

DISCUSSION

PET using F-18 FDG is probably not needed for the initial diagnosis of ovarian cancer, but is useful in localizing recurrent or metastatic cancer with a high degree of accuracy and has a significant impact on patient management. For 30% to 40% of patients, FDG-PET provides new or additional information in the pelvis and the rest of the body, where whole-body PET studies may reveal distant metastases. Therapy moni-
is another diagnostic approach that holds promise for detection of recurrent ovarian cancer, with a diagnostic accuracy as high as 84%. And finally, PET is also used for ovarian cancer.

**FDG-PET**

PET with FDG, the most common radioisotope in oncology, is a unique imaging tracer in oncology, is a unique imaging tracer in oncology, and is becoming a widely accepted diagnostic tool in most cancerous tissues because of increased glucose metabolism in, for instance, the brain, muscles, and tumors. Most PET studies in oncology are done with and without SUV information. However, metabolic activity can be applied for semiquantitative analyses that depend on software, or the use of hybrid PET/CT fusion technology, add a new level of sophistication to PET in oncology and should improve sensitivity and specificity.

**FDG-PET in Ovarian Cancer**

FDG-PET is a noninvasive radiotracer; its uptake by a particular tissue simply corresponds to the amount of glucose used to sustain metabolic activity. FDG-PET is commonly used in oncology and should improve sensitivity and specificity. It can be applied for semiquantitative analyses that depend on software, or the use of hybrid PET/CT fusion technology, add a new level of sophistication to PET in oncology and should improve sensitivity and specificity.

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PET/CT Various dedicated positron imaging devices as well as gamma cameras for positron imaging in coincidence mode are commercially available. In addition, advanced hybrid PET/CT imaging systems introduced in 2000 permit fusion of emission and transmission images. First results obtained with PET/CT in ovarian cancer are promising and suggest that this new approach could have a significant impact on patient management, reducing morbidity and the expenses of surgical exploration. Most PET studies in oncology are done as whole-body scans and are evaluated by visual interpretation. Various relative uptake scales or activity concentration ratios can be applied for semiquantitative analyses, however. FDG accumulation can be expressed by the standardized uptake value (SUV), calculated by using a calibration factor and correcting ‘PET counts’ for body weight as well as injected dose. Plotting time activity curves or graphical data analyses introduced by Patlak is also possible, but the latter option is generally reserved for research applications and is rarely used in routine clinical PET examinations.

**FDG UPTAKE PATTERNS**

Ovarian cancer typically tends to spread early by direct extension and later by intraperitoneal seeding, lymphatic invasion, and hematogenous routes. FDG-PET in ovarian cancer is insensitive to many patients with elevated CA-125 and a negative CT scan. However, earlier results by Zimny et al., Römer et al., Fenchel et al., Kubih-Huch et al., and Grab et al. suggested a range of 50% to 86% in specificity. A low negative predictive value for PET raises some concern, but this was expressed by Römer et al. who studied 24 patients prospectively for the presence of ovarian cancer and found a specificity of only 54%. Cho et al. concluded that PET was not more effective in detecting recurrent ovarian cancer than CT scans in small lesions. Hany and Kubih-Huch, in a discussion of PET/CT applications, recommended exercising caution regarding the clinical use of PET-FDG in gynecological cancer. In contrast, Picchio et al demonstrated a lesion-based sensitivity and specificity of 83% and 92% when using PET information in combination with CT. Nakamoto et al combined PET findings using SUV with and without SUV information in combination with CT. PET was not more effective in detecting recurrent ovarian cancer than CT. However, PET/CT can provide new or additional information in the pelvis and the rest of the body, where whole-body PET studies may reveal distant metastases. Therapy moni-

**SHORTCOMINGS AND CAVITIES**

FDG-PET in detecting recurrent ovarian cancer has increased during the last 10 years. The results obtained in more than 1000 patients are encouraging, especially when FDG-PET is used in conjunction with other imaging modalities. Numerous contributions on the subject have been published. Overall, the sensitivity for FDG-PET in primary and recurrent ovarian cancer ranged from 83% to 100%.

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in ovario maligno. El nuevo PET/TC combinado o con obtenido con la tecnología FDG-PET, además de hacerse para el diagnóstico, es válida para el tratamiento y para el sufrimiento de la misma.

La información de PET/TC y las conductas obtenidas con la nueva tecnología PET/TC combinada debería resultar en un mejoramiento del diagnóstico y el tratamiento de la enfermedad.

CONCLUSIÓN

En el marco de la “necesidad de la FDG” y los límites de la resolución espacial de la FDG-PET, que pueden combinarse con otros métodos de imagen, se necesita más investigación para mejorar los resultados y la precisión del diagnóstico.

El uso de FDG-PET para el diagnóstico y tratamiento de la enfermedad ovarian maligna es un campo de investigación en constante evolución.

Referencias