

# DISCUSSIONS IN

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# I M A G I N G

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## LEARNING OBJECTIVES

Upon completion of this activity,  
participants should be able to:

- Recognize the typical clinical aspects of ovarian cancer.
- Discuss the value of FDG-PET and other tests in the management of ovarian cancer, especially recurrent cases.
- Describe FDG uptake patterns in ovarian cancer.
- List the indications for whole-body FDG-PET for ovarian cancer.

## 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,<sup>1</sup> 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. “Misleading” 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.<sup>1</sup> The high probability of advanced disease demands accurate staging for appropriate treatment decisions.

Most ovarian cancers are serous 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 that would help reduce mortality and morbidity is not available. The immunoassay for CA-125 might be considered as a screening test in conjunction with state-of-the-art color and Doppler pelvic ultrasonography.<sup>2</sup> Ultrasound can identify abnormal morphology and blood flow as well as enlargement of the ovaries with a sensitivity of 92% and a specificity of 59%, but such findings should be confirmed by MR imaging.<sup>2</sup> CA-125, although useful for surveillance of symptomatic and high-risk women and for follow-up of patients with ovarian cancer, is not considered a general screening test.

The diagnostic modalities for initial diagnosis, staging, and evaluation of recurrent disease are

rectovaginal examination, CT, MR, laparoscopy, and exploratory laparotomy. CT is 70% to 90% accurate for initial preoperative staging; CT and MR detect 40% to 50%, and ultrasound 60% to 90%, of recurrent disease.

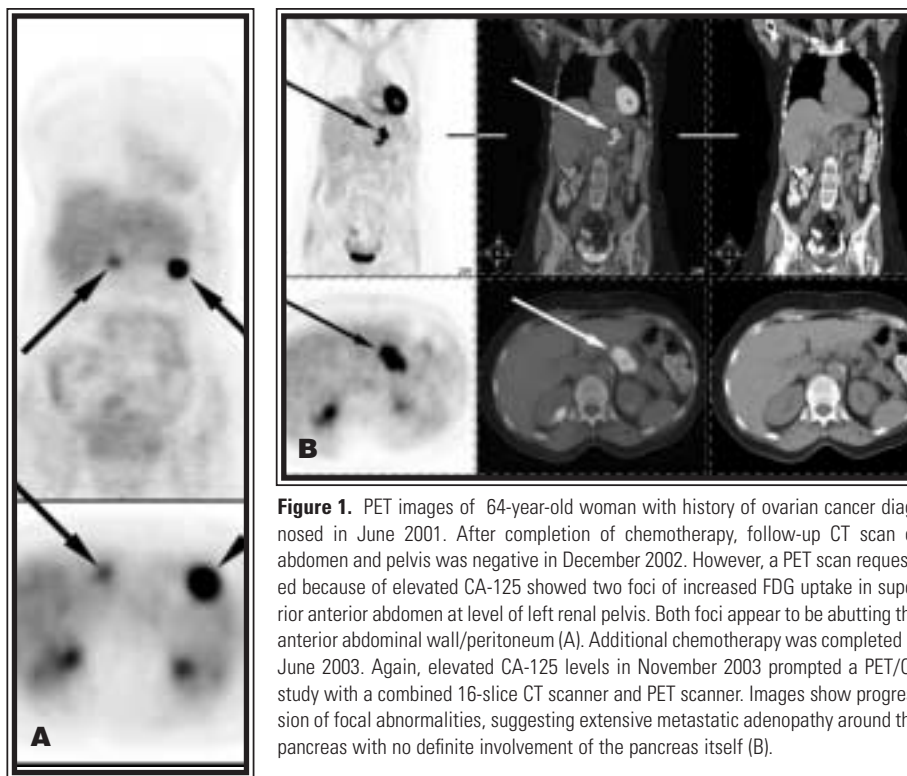
Hysterectomy, salpingo-oophorectomy, and pelvic and aortic lymph node resection are used for treating early-stage ovarian cancer. “Second-look” surgical exploration that used to be the standard procedure for detecting recurrent ovarian cancer does not appear to have a beneficial effect on survival.<sup>3</sup> Among patients with initial stage III and IV disease, 40% to 65% will have recurrent disease, and only 15% to 20% survive five years. Subclinical residual microscopic disease is present in as many as 30% of patients but is not detected by laparotomy.

### FOLLOW-UP TESTS

Diagnostic tests for follow-up of patients with ovarian cancer may include CT, MR, ultrasound, CA-125 assay, and monoclonal antibody (MoAb) scintigraphy. CT, MR, and ultrasound have reasonably high sensitivity and specificity for peritoneal implants (CT, 92% and 82%; MR, 95% and 80%; ultrasound 69% and 93%).<sup>4</sup> CA-125 is elevated (>35U/mL) in more than 80% of patients with advanced epithelial ovarian cancer, but its specificity is poor, particularly in premenopausal women. Thirty-five percent of patients with residual disease have normal CA-125 levels.<sup>5</sup> Radioimmunoscintigraphy

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**Figure 1.** PET images of 64-year-old woman with history of ovarian cancer diagnosed in June 2001. After completion of chemotherapy, follow-up CT scan of abdomen and pelvis was negative in December 2002. However, a PET scan requested because of elevated CA-125 showed two foci of increased FDG uptake in superior anterior abdomen at level of left renal pelvis. Both foci appear to be abutting the anterior abdominal wall/peritoneum (A). Additional chemotherapy was completed in June 2003. Again, elevated CA-125 levels in November 2003 prompted a PET/CT study with a combined 16-slice CT scanner and PET scanner. Images show progression of focal abnormalities, suggesting extensive metastatic adenopathy around the pancreas with no definite involvement of the pancreas itself (B).

is another diagnostic approach that holds promise for detection of recurrent ovarian cancer,<sup>6</sup> 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 radiotracer 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 nonspecific radiotracer; its uptake by a particular tissue simply corresponds to the amount of glucose used to sustain metabolism in, for instance, the brain, muscles, myocardium, or in macrophages. Since most cancerous tissues use relatively more FDG than normal tissue, FDG-PET has become a widely accepted diagnostic tool in oncology.

First results with FDG-PET in ovarian cancer reported by Hubner et al,<sup>7</sup> Wahl,<sup>8</sup> and Casey et al<sup>9</sup> were promising. Schröder et al found a sensitivity and specificity of 90%, positive and negative predictive values of 90% and 75%, respectively, and 90% accuracy for FDG-PET, especially in patients with recurrent ovarian cancer.<sup>10</sup> Other investigators have subsequently

used FDG-PET in clinical investigations for detecting, staging, and monitoring ovarian cancer.

### PET/CT

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,<sup>11</sup> 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.<sup>3,4</sup> Omental and peritoneal implants, seeding in the right paracolic gutter and subdiaphragmatic space, the surface of the liver, and the mesentery, and involvement of spleen and bowel are common. Metastases in the thorax are seen less frequently, and liver metastases occur late in the disease.

FDG-PET and CT readily identify pelvic and abdominal lymph node metastases. Hydronephrosis, a complication of lymph node metastases causing ureteral obstruction, is easily seen on FDG-PET scans. Hematogenous spread can result in metastases in the liver, lung, spleen, pancreas, and kidney, all of which are identifiable on PET images. Renal metastases, however, may be missed because of sometimes intense renal, ureteral, and bladder FDG activity.

Nonspecific bowel uptake reduces the specificity of FDG-PET for cancerous processes in the abdomen and pelvis. Hydration, forced diuresis, and bowel preparation are sometimes used in an attempt to improve results, but they are not always successful. Another shortcoming of PET is its limited spatial resolution. Current state-of-the-art PET scanners have an axial resolution of 4 or 5 mm FWHM (full width at half maximum) and a transaxial resolution of 8 mm FWHM or slightly better.

### CLINICAL UTILITY

Investigations into the potential utility of FDG-PET in ovarian cancer have 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.<sup>7-9,12-17</sup> Overall, the sensitivity for FDG-PET in primary and recurrent ovarian cancer ranged from 83% to 100%.

In a study involving 54 patients, Zimny et al demonstrated a 96% sensitivity for FDG-PET in detecting recurrent ovarian cancer when rising CA-125 levels prompted the PET studies. They also found that negative PET scan results predicted longer relapse-free survival intervals than positive

PET results.<sup>18</sup> More recently, Chang et al applied FDG-PET and detected tumor with a sensitivity of 95% and a specificity of 86% in 28 asymptomatic patients with elevated CA-125 indicating possible recurrence.<sup>19</sup> An example of such a case is presented in Figure 1, showing a positive PET scan in a patient with elevated CA-125 and a negative CT scan.

However, earlier results by Zimny et al,<sup>20</sup> Römer et al,<sup>21</sup> Fenchel et al,<sup>22</sup> Kubik-Huch et al,<sup>23</sup> and Grab et al<sup>24</sup> 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,<sup>21</sup> who studied 24 patients prospectively for the presence of ovarian cancer and found a specificity of only 54%. Cho et al concluded that FDG-PET was not more effective in detecting recurrent ovarian cancer than CT, especially in small lesions.<sup>25</sup> Hany and Kubik-Huch, in a discussion of PET/CT applications, recommended exercising caution regarding the clinical use of FDG-PET in genitourinary cancer.<sup>26</sup> In contrast, Picchio et al demonstrated a lesion-based sensitivity and specificity of 83% and 92% when using PET information in combination with CT.<sup>27</sup> Nakamoto et al combined PET findings with results from conventional imaging modalities and obtained similar results.<sup>28</sup>

### SHORTCOMINGS AND CAVEATS

Discordant results regarding the specificity of FDG-PET for ovarian cancer are of some concern but may be due to dif-

ferences in patient selection (inhomogeneity), tumor size, effectiveness of surgery or chemotherapy, and/or definitions 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 nonspecific FDG uptake in normal tissues, and good technical quality of FDG-PET studies should improve the specificity for ovarian cancer. Image coregistration 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.<sup>29</sup>

Several investigators have reported false-positive and false-negative findings on FDG-PET in ovarian cancer.<sup>10,30</sup> Benign mucinous cystadenomas, endometrial and follicular cysts, corpus luteum cysts, fibromas, cystadenofibromas, misinterpreted gastrointestinal tract activity, salpingo-oophoritis and coexisting peritonitis, teratomas, dermoid cysts, tubo-ovarial abscesses, benign thecoma, and schwannoma are included in the rubric of “false positives.” False-negative results include well-differentiated serous/mucinous cystadenocarcinoma, borderline tumors, disseminated carcinomatosis, and pT1a adenocarcinomas.<sup>21</sup>

False-negative results with FDG-PET are not only related to low metabolic activity of some neoplastic or benign,

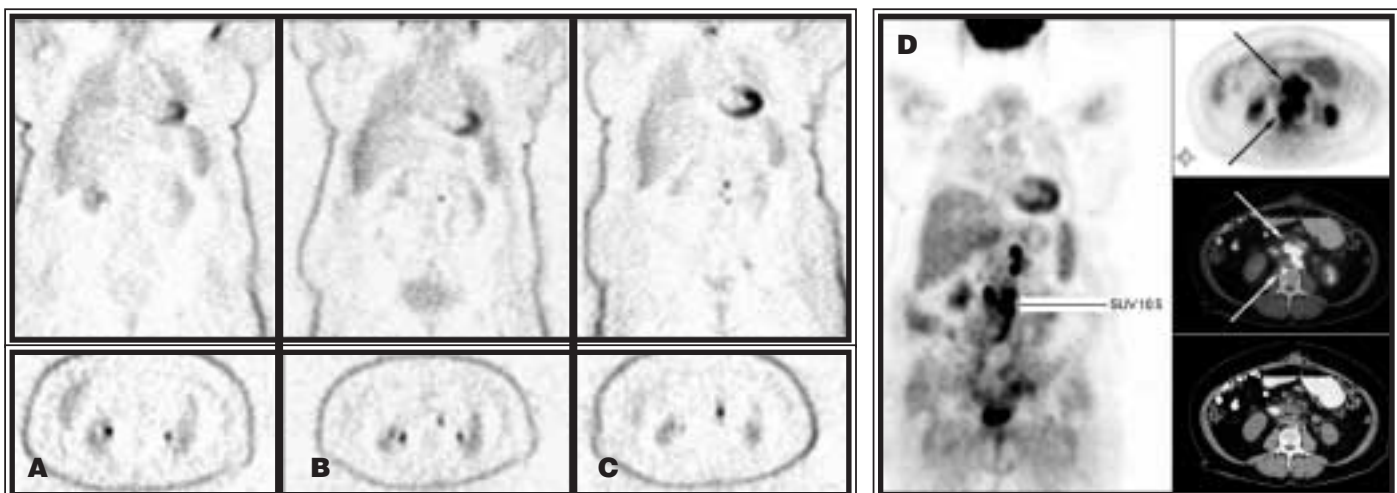
especially inflammatory, processes, but are also due to the limitations of the spatial resolution obtainable with PET. The modality is unlikely to detect metastases smaller than 5 mm and can also miss small retroperitoneal lymph nodes and sheets of tumor in carcinomatosis peritonei.

Hubner et al<sup>7</sup> suggested that 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,<sup>21</sup> 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, SUVs did improve specificity. Koyama et al used SUV calculations successfully for distinguishing malignant from benign uterine and ovarian tumors.<sup>31</sup>

### DISCUSSION

PET using F-18 FDG is probably not needed for the initial diagnosis of ovarian cancer, but it 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-



**Figure 2.** Sequential FDG-PET scans of 60-year-old woman with history of ovarian cancer. Patient had initial surgery in 1994, subsequent additional surgeries, chemotherapy, radiation therapy, and several negative PET scans. A: Last negative PET scan, obtained in May 1996. B: Seven months later there was evidence of FDG uptake in a paraaortic lymph node. C: Despite additional chemotherapy there was pro-

gression and eventually definite evidence of recurrent disease (1998), also seen in D. Most recent PET/CT scan (November 2003) demonstrated persistent metastatic disease in axilla soft tissue, and peripancreatic, celiac axis, retroperitoneal, and mesenteric lymph nodes. Representative PET, fused PET/CT, and CT images show the extent of the neoplastic process.

toring in ovarian cancer is another important application of FDG-PET that could play a role in optimizing neoadjuvant therapy protocols and might help avoid ineffective treatment of nonresponders, as has been suggested by Baum and Przetak.<sup>32</sup>

Figure 2 demonstrates how FDG-PET imaging can help in the medical management of ovarian cancer. FDG-PET results can modify the surgical approach and help identify patients who should receive chemotherapy and those who might benefit from surgery. Suspicious lesions smaller than 2 cm by CT criteria but positive on FDG-PET probably do not have to be debulked and are best treated with chemotherapy alone. The information from FDG-PET and CT combined or obtained with the new hybrid PET/CT technology should

result in improved accuracy of the diagnosis and the exclusion of ovarian cancer.

## CONCLUSION

In spite of the "nonspecificity" of FDG and the limitations of the spatial resolution of the various PET imaging devices, the positive-predictive value (PPV) of PET, especially when combined with other imaging techniques, is adequate for clinical use. PET/CT imaging, which displays metabolic information from PET and exquisite anatomic pictures from CT in a single stack of tomographic images, will lead to even better results and facilitate localization of lesions for biopsies and planning surgical approach or radiation 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 PPV 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 C-11-labeled choline in gynecologic tumors are promising.

At the present time, FDG-PET might be considered in patients with ovarian cancer for the following indications: rising CA-125 and negative CT; preoperative assessment for recurrent ovarian cancer, especially when CT findings are equivocal; and monitoring response to chemotherapy.

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