

Role of Integrated 18-F FDG PET/CT in Recurrent Ovarian Cancer

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Abstract: Carcinoma of the ovary is the third most common cancer of the female genital tract but it accounts for over half of all deaths related to gynecologic neoplasms. This is primarily because, unlike patients with other common malignant gynecologic tumors, most patients with ovarian cancer have advanced stage of disease at the time of initial diagnosis. After completion of initial surgery, patients with ovarian cancer receive systemic chemotherapy for disease control. Despite the fact that ovarian cancer is very sensitive to platinum-based chemotherapy, 5-year survival for patients with advanced disease is only 17%, due to the high rate of recurrent disease. Although its limited accuracy, serial determination of the tumor marker CA 125 is the most frequently used method for monitoring the disease. Morphologic imaging modalities have played a major role to accurately delineate disease status. Computed tomography (CT) proved to be useful for evaluating response to treatment in these patients. Fluorodeoxyglucose (FDG) positron emission tomography (PET), which provides metabolic information useful in the identification of cancer tissue, also proved to be of value for the assessment of recurrent ovarian cancer. Recently, a new imaging technique combining state of the art PET and CT equipments (integrated PET/CT) has been introduced in clinical use. PET/CT device acquires PET and CT images, that are contemporaneous and coregistered, to localize elevated FDG uptake with improved anatomic specificity. Potential advantages of PET/CT include increased lesion conspicuity, anatomic localization of lesions, and differentiation of neoplastic disease process from posttreatment fibrosis. In this article we illustrate the role of PET/CT relative to CT and MR imaging in the field of recurrent ovarian cancer.

Keywords: Ovary, neoplasms, recurrent ovarian cancer, computed tomography (CT), comparative studies, FDG positron-emission tomography, dual-modality imaging, PET/CT.

RECURRENT OVARIAN CANCER: SECOND-LOOK PROCEDURES AND CLINICAL FOLLOW-UP

In patients with advanced ovarian cancer, following primary debulking surgery and usually three to six cycles of platinum-based chemotherapy, a second-look surgical procedure will be performed in most institutions, as this is currently considered the most accurate method of assessing disease status in patients who have completed first-line treatment. For patients in whom recurrence is diagnosed, secondary cytoreductive surgery is beneficial if the largest tumor deposit is less than 5 cm. In the other cases a second-line chemotherapeutic treatment is usually performed. However, the justification for routine use of second-look procedure has been questioned, and its role as a part of the standard treatment in the management of ovarian cancer is still discussed [1-12]. Recently, Sijmons and Heintz [9] reported that about 35% of patients with macroscopic or microscopic negative findings at second-look laparotomy will develop recurrent disease within one year of the procedure. In fact, determining disease status accurately is difficult when no gross tumor is seen in the abdominal cavity, and small viable neoplastic foci may be missed especially in those patients in whom adhesions due to prior surgery occurred.

At present, serial measurements of tumor-related antigen CA 125 is the most common method used for monitoring clinical response after first-line treatment. Its limited reliability, however, is well known as CA 125 elevation may indicate tumor persistence or recurrence but a negative value does not provide absolute assurance of absence of disease [13-16].

RECURRENT OVARIAN CANCER: ROLE OF MORPHOLOGIC IMAGING – CT AND MR IMAGING

The traditional imaging modalities for evaluating patients for possible recurrence of ovarian cancer are CT and MR imaging. Two recent reports of the Radiology Diagnostic Oncology Group [17-18] stated that CT and MR imaging are equally accurate, and either modality can be used for staging patients with ovarian cancer. However, correctly assessing persistent or recurrent disease, using only these conventional imaging modalities, can be difficult. MR imaging was found to be a useful adjunct to the clinical examination to identify patients with recurrent disease but is limited in depicting small calcified peritoneal implants. In previous works [19-20], where findings at MR imaging and surgery were correlated, MR imaging showed an accuracy for lesions less than 2 cm of only 35% which increased to 82% when lesion diameter was greater than 2 cm, resulting in a poor overall accuracy rate of 59% for evaluating recurrent disease. Due to its wide availability and lower cost as compared to MR imaging, CT presently is the most common non invasive

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imaging modality used to monitor patients with ovarian cancer after first-line treatment. Nevertheless, the effectiveness of CT scanning even with the use of state of the art dynamic techniques still remains unclear, and a wide range in CT accuracy (38% up to 88%) is found in the current literature. This is mainly because CT proved to have low sensitivity for small lesions, and hardly allows reliable differentiation between persistent disease and postoperative changes. Although morphologic imaging is the mainstay for evaluating patients for possible recurrence of ovarian cancer, it is well known that small lesions may not be appreciated due to partial volume averaging, or lack of significant differences in attenuation value at CT or signal intensity at MR imaging between tumor tissue and normal structures.

RECURRENT OVARIAN CANCER: ROLE OF FUNCTIONAL IMAGING – FDG PET

Differently from CT and MR imaging, diagnoses with FDG PET are made on functional rather than morphological criteria. In fact, PET with the radiolabeled glucose analogue fluorodeoxyglucose (FDG) is a method based on the increased glucose metabolism of malignant tumor tissues [21-23]. FDG PET has been shown effective in staging and restaging different tumor types. It can reveal the biochemical differences between normal and malignant tissues, and it has been used as a functional method of determining tumor viability in several cancers. A potential advantage of PET is that lesions are more conspicuous relative to minimal background activity due to increased radiotracer uptake in tumor lesions. This phenomenon may help detect metastatic tumor on visceral surfaces and in normal-sized nodes. On the other hand, as ovarian cancer metastases manifest as scattered focal implants, distinguishing between physiologic and pathologic activity at PET due to tumor lesions may be troublesome. In addition, for lesions that are considered to be pathologic, accurate localization for surgical resection is difficult, because of the lack of precise anatomic landmarks. At present, there are several studies available reporting on the role of FDG PET in the evaluation of ovarian cancer response after primary surgery and chemotherapy [24-34]. Torizuka *et al.* [31] recently assessed the value of FDG PET for the diagnosis of recurrent tumor in a series of 25 patients, who had previously undergone surgery for ovarian cancer. FDG PET showed a sensitivity of 80%, and an accuracy of 84%. In the same series, conventional imaging studies, comprising CT, showed lower sensitivity and accuracy rates as these were 55%, and 64%, respectively. Findings in that study confirmed that viable lesions in patients with treated ovarian cancer may become detectable due to metabolic changes before any morphological correlate. Nakamoto *et al.* [28] looked at the clinical value of FDG PET in 24 patients with a suspicion of ovarian tumor recurrence. In their work, FDG PET alone had a fairly good rate (79%) of diagnostic accuracy. Interestingly, by adding information of conventional imaging modalities comprising CT, FDG PET accuracy rate improved to 94%. Similar results were also obtained by Picchio *et al.* [34] in their series, where FDG PET and CT images were coregistered with software. These investigators also showed that, due to the limited spatial resolution of PET ranging from 0.4 to 0.6 cm, persistent microscopic disease can be found at histologic analysis in patients with negative PET findings. These observations are

in line with the results of Rose *et al.* [27] who recently reported a limited sensitivity of PET imaging for small-volume disease.

RECURRENT OVARIAN CANCER. INTEGRATED PET/CT: TECHNIQUE AND PRELIMINARY RESULTS

Recently, a new imaging technique, combining a full-ring-detector clinical PET scanner and a multi-detector row helical CT scanner in one machine, has been introduced in clinical practice [35-39]. Both scanners are aligned so that patients can undergo imaging in either of two gantries by moving the one system table. In this way, coverage of anatomically coregistered images from the head to pelvic floor is obtained by means of hardware, rather than by means of postacquisition software. One of the advantages of integrated PET-CT over PET alone is the capability to localize foci of elevated tracer uptake with improved anatomic specificity.

Imaging Technique

All imaging and data acquisition are performed with a combined PET-CT in-line system that was able to acquire CT images and PET data for the same patient in one session. At present there are 3 most common PET/CT commercialised systems, whose technology has been described elsewhere. A PET scanner, and a multi-detector row helical CT scanner are integrated in this dedicated system. The axes of both systems are mechanically aligned so that shifting the examination table by 60 cm moved the patient from the CT into the PET gantry. The resulting PET and CT images are coregistered on hardware. Forty-five minutes after the injection of 370Mq of FDG, the combined examination starts. CT data are acquired first; an unenhanced CT image is generally obtained from the patient's head to the pelvic floor with use of a standardized protocol. Several CT protocols are available, one of the most used is the following: 140 kV, 80 mA (but adjusted for body thickness), a tube rotation time of 0.5 second per revolution, a pitch of 6, a section thickness of 5 mm to match the section thickness of PET images, and an acquisition time of 22 seconds. CT scans are acquired during shallow breathing. Oral contrast agent can be administered for small bowel opacification. Routinely, no intravenous contrast agent is administered although intravenous injection of iodinated contrast media is feasible, and can be useful for specific clinical question especially in cancer patients. Immediately after CT scanning, PET is performed covering the identical axial field of view. The mean acquisition time for PET is 4 minutes per table position; as six incremental table positions are acquired, PET study has a mean duration of 24 minute; PET images are acquired during quiet breathing. The PET component of the scanner has an in-plane spatial resolution which may range between 0.4 and 0.6 cm. Attenuation correction is performed by using CT images: the CT pixel values in Hounsfield units are transformed into linear attenuation coefficients for the 511 KeV energy radiation. For fusion with the PET data, images are reconstructed with a 128 X 128 matrix, an ordered subset expectation maximum iterative reconstruction algorithm, an 8-mm gaussian filter, and a 50-cm field of view. Attenuation correction on the PET scans is needed for

fusion with the CT scans; in fact, attenuation correction compensates for differing activity in deep versus superficial lesions.

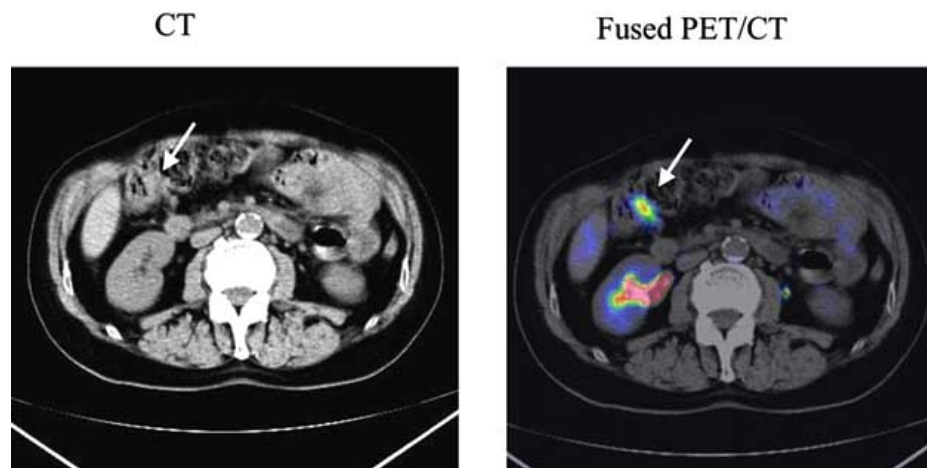
Image Analysis

Image analysis for integrated PET/CT is performed as follows: attenuation-corrected PET images, CT images, and coregistered PET-CT images are displayed together on the monitor and the PET-CT examination analysed as a single study. At PET/CT, regions of increased activity seen at PET can be localized on the CT scans, and lesions seen at CT can be evaluated for pathologic activity on the PET scans. For peritoneal and pelvic recurrent lesions, the PET/CT results are reported as whether or not abnormal FDG uptake is present in any abdominal region, and if present, its exact anatomic site is indicated on the basis of CT findings. Lymph node sites also have to be evaluated. The diagnosis of pathologic lymph node on PET-CT images is based on the presence of focal increased FDG uptake on PET images, whose location corresponded to lymph nodal chains on CT images. All data sets are analyzed at a workstation capable of providing interactively multiplanar reformations and any appropriate window and level settings: the images are reviewed in axial, coronal, and sagittal planes with a varying gray scale and rotating views. Few pitfalls are associated with PET/CT. Misregistration can result from physiologic patient activity that occurs during the acquisition time. Although the external anatomy is aligned within a few millimetres on the fused scan, respiratory motion and bowel peristalsis can result in a mismatch between the location of a lesion at PET and its location at CT. A relatively common pitfall involves the gastrointestinal tract, where normal activity may be misinterpreted as pathologic or vice versa, especially if the activity is focal. Moreover, size of lesions with intense radiotracer uptake can be overestimated on a PET scan relative to the lesion size at CT scan, due to the "blooming" of intense activity that occurs at PET.

Quantitative evaluation of areas of increased activity can be performed on attenuation-corrected scans. The standardized uptake value (SUV) of a lesion is calculated to determine metabolic changes occurring during therapy and is defined as follows: $SUV = [\text{dose in tissue}/\text{injected dose}] \times \text{patient weight or body surface}$. The SUV is dependent on many variables, including body mass and the region of interest. In ovarian cancer, SUVs can range up to 5.5 or more, being those over 3.0 of great concern.

Preliminary Results

The value of PET/CT in detecting ovarian cancer recurrence has not yet definitively established because relatively few scanners are currently available. In a recent study of eight patients, the sensitivity of PET/CT for recurrent disease was 62% (32). Results in a recent investigation (40), in which PET/CT findings have been compared with histopathologic findings, indicate that integrated PET-CT may be an effective means of detecting persistent or recurrent ovarian carcinoma, showing an overall accuracy of 77%. Results in that study (40) also indicate that integrated PET-CT has low (57%) negative predictive value (NPV), and high (89%) positive predictive value (PPV) in detecting residual neoplastic lesions after first-line treatment. Interestingly, this is in agreement with previous results obtained with PET alone [29, 31]. Low NPV seems to depend on the limited capability of PET/CT in depicting microscopic or small-volume lesions: such limitation of PET-CT may make it difficult to identify patients with minimal tumor deposits in whom, therefore, assessment of disease may still require surgical second-look. On the other hand, integrated PET-CT in that study (40) showed high PPV in revealing persistent disease: this could allow to reliably identify those patients with macroscopic disease who are candidates for salvage treatment (Fig. 1).



Re-staging of ovarian carcinoma: peritoneal lesion

Fig. (1).

CONCLUSIONS

PET/CT study has a potential role in evaluating patients for recurrent ovarian cancer, particularly those with negative CT or MR imaging findings and rising tumor marker levels.

PET-CT may be a valuable diagnostic investigation for the follow-up of ovarian cancer patients after first-line treatment, mainly because of its ability to depict macroscopic residual disease. Furthermore, integrated PET-CT could have a clear clinical impact on the therapeutic management of patients with ovarian cancer: In fact, following primary cytoreductive surgery and chemotherapy, a patient could be evaluated for persistence of disease by this imaging modality, and then proceed to the most appropriate second-line treatment. Additional investigation with accurate histopathologic correlation is necessary to determine the benefits of lesion conspicuity at PET and anatomic localization at CT, on combined PET/CT scans.

REFERENCES

- [1] Cannistra SA. Cancer of the ovary. *N Engl J Med* 1993; 329: 1550-1559.
- [2] American Cancer Society. Cancer facts and figures: 1998. Atlanta, Ga: American Cancer Society, 1998.
- [3] Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics. *CA Cancer J Clin* 1999; 49: 8-31.
- [4] Hoskins WJ. Surgical staging and cytoreductive surgery of epithelial ovarian cancer. *Cancer* 1993; 71: 1534-1540.
- [5] Hoskins WJ. Epithelial ovarian carcinoma: principles of primary surgery. *Gynecol Oncol* 1994; 55: 91-96.
- [6] McGuire WP, Hoskins WJ, Brady MF, *et al.* Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996; 334: 1-6.
- [7] Friedman JB, and Weiss NS. Second thoughts about second-look laparotomy in advanced ovarian cancer. *N Engl J Med* 1991; 322: 1079-1081.
- [8] Creasman WT. Second-look laparotomy in ovarian cancer. *Gynecol Oncol* 1994; 55: 122-127.
- [9] Sijmons EA, and Heintz AP. Second-look and second surgery: second chance or second best? *Semin Surg Oncol* 2000; 19: 54-61.
- [10] Omura GA, Brady MF, Homesley HD, *et al.* Long-term follow-up and prognostic factor analysis in advanced ovarian carcinoma: the Gynecologic Oncology Group experience. *J Clin Oncol* 1991; 9:1138-1150.
- [11] NIH Consensus Development Panel on Ovarian Cancer. Ovarian cancer. Screening, treatment and follow-up. *JAMA* 1995, 273: 491-496.
- [12] Rose PG. Surgery for recurrent ovarian cancer. *Semin Oncol* 2000; 27: 17-23.
- [13] Thigpen JT, Vance RB, Khansur T. Second-line chemotherapy for recurrent carcinoma of the ovary. *Cancer* 1993; 71: 1559-1564.
- [14] Rubin SC, Hoskins WJ, Hakes TB, *et al.* Serum CA 125 levels and surgical findings in patients undergoing secondary operations for epithelial ovarian cancer. *Am J Obstet Gynecol* 1989; 160: 667-671.
- [15] Pastner B, Orr JW, Mann WJ, Taylor PT, Patridge E, Allmen T. Does serum CA 125 level prior to second-look laparotomy for invasive ovarian carcinoma predict size of residual disease? *Gynecol Oncol* 1990; 38: 373-376.
- [16] Folk JJ, Botsford M, Musa AG, *et al.* Monitoring cancer antigen 125 levels in induction chemotherapy for epithelial ovarian carcinoma and predicting outcome of second-look procedure. *Gynecol Oncol* 1995; 57: 178-182.
- [17] Kurtz AB, Tsimikas JV, Tempany CM, *et al.* Diagnosis and staging of ovarian cancer: comparative values of Doppler and conventional US, CT, and MR imaging correlated with surgery and histopathologic analysis. Report of the Radiology Diagnostic Oncology Group. *Radiology* 1999; 212: 19-27.
- [18] Tempany CM, Zou KH, Silverman SG, *et al.* Staging of advanced ovarian cancer: comparison of imaging modalities. Report from the Radiological Diagnostic Oncology Group. *Radiology*; 2000; 215: 761-767.
- [19] Kubik-Huch RA, Dorfler W, von Schulthess GK, *et al.* Value of FDG positron emission tomography, computed tomography, and magnetic resonance imaging in diagnosing primary and recurrent ovarian carcinoma. *Eur Radiol* 2000; 10: 761-767.
- [20] Forstner R, Hricak H, Powell CB, Azizi L, Frankel SB, Stern JL. Ovarian cancer recurrence: value of MR imaging. *Radiology* 1995; 196: 715-720.
- [21] Ak I, Stokkel MP, Pauwels EK. Positron emission tomography with FDG in oncology. The clinical value in detecting and staging primary tumors. *J Cancer Res Clin Oncol* 2000; 126: 560-574.
- [22] Flamen P, Stroobants S, Cutsem EV, *et al.* Additional value of whole-body positron emission tomography with FDG in recurrent colorectal cancer. *J Clin Oncol* 1999; 17:894-901.
- [23] Schelling M, Avril N, Nahrig J, *et al.* Positron emission tomography using FDG for monitoring primary chemotherapy in breast cancer. *J Clin Oncol* 2000; 18: 1689-1695.
- [24] Hubner KF, McDonald TW, Niethammer JG, Smith GT, Gould HR, Buonocore E. Assessment of primary and metastatic ovarian cancer by positron emission tomography (PET) using FDG. *Gynecol Oncol* 1993; 51: 197-204.
- [25] Karlan BY, Howkins R, Hoh C, *et al.* Whole-body positron emission tomography with FDG can detect recurrent ovarian carcinoma. *Gynecol Oncol* 1993; 51: 175-181.
- [26] Casey MJ, Gupta NC, Muths CK. Experience with positron emission tomography (PET) scans in patients with ovarian cancer. *Gynecol Oncol* 1994, 53: 331-338.
- [27] Rose PG, Faulhaber P, Miraldi F, Abdul-Karim FW. 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.
- [28] Nakamoto Y, Saga T, Ishimori T, *et al.* Clinical value of positron emission tomography with FDG for recurrent ovarian cancer. *AJ R* 2001; 176: 1449-1454.
- [29] Zimny M, Siggelkow W, Schroder W, *et al.* FDG positron emission tomography in the diagnosis of recurrent ovarian cancer. *Gynecol Oncol* 2001; 83: 310-315.
- [30] Cho SM, Ha HK, Byun JY, *et al.* Usefulness of FDG PET for assessment of early recurrent epithelial ovarian cancer. *AJ R* 2002; 179: 391-395.
- [31] Torizuka T, Nobezawa S, Kanno T, *et al.* Ovarian cancer recurrence : role of whole-body positron emission tomography using FDG. *Eur J Nucl Med* 2002; 29: 797-803.
- [32] Makhija S, Howden N, Edwards R, Kelley J, Townsend DW, Meltzer CC. Positron emission tomography-computed tomography imaging for the detection of recurrent ovarian and fallopian tube carcinoma: a retrospective review. *Gynecol Oncol* 2002; 85: 53-58.
- [33] Bristow ER, Simpkins F, Pannu HK, Fishman EK, Montz FJ. Positron emission tomography for detecting clinically occult surgically respectable metastatic ovarian cancer. *Gynecol Oncol* 2002; 85: 196-200.
- [34] Picchio M, Sironi S, Messa C, *et al.* Advanced ovarian carcinoma: usefulness of FDG PET in combination with CT for lesion detection after primary treatment. *Q J Nucl Med* 2003; 47: 77-84.
- [35] Beyer T, Townsend DW, Brun T, *et al.* A combined PET-CT scanner for clinical oncology. *J Nucl Med* 2000; 41: 1369-1379.
- [36] Kluetz PG, Meltzer CC, Villemagne VL, *et al.* Combined PET-CT imaging in oncology: impact on patient management. *Clin Positron Imaging* 2000; 3: 223-230.
- [37] Townsend DW. A combined PET-CT scanner: the choices. *J Nucl Med* 2001; 42: 533-534.
- [38] Hany FT, Steinert HC, Goerres GW, Buck A, von Schulthess GK. PET diagnostic accuracy: improvement with in-line PET-CT system: initial results. *Radiology* 2002; 225: 575-581.
- [39] Lardinois D, Weder W, Hany TF, *et al.* Staging of non-small-cell lung cancer with integrated positron emission tomography and computed tomography. *N Engl J Med* 2003; 348: 2500-2507.
- [40] S. Sironi, C. Messa, G. Mangili, *et al.* Value of integrated FDG PET/CT for persistent ovarian cancer: correlation with histopathologic findings. *Radiology* 2004 (in press).