

PET-CT in Recurrent Ovarian Cancer: Impact on Treatment Planning

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Abstract. *Background: Positron emission tomography-computed tomography (PET-CT) is currently not established in the management of recurrent ovarian cancer. Here, its value in diagnosis and therapy planning was evaluated. Patients and Methods: Seventy patients received PET-CT for suspicion of recurrent ovarian cancer. PET-CT and surgery were reviewed to analyze the accuracy in the diagnosis of recurrence and prediction of full resectability. Results: PET-CT showed disease relapse in 63 of 70 patients, with full sensitivity and specificity. Thirty cases were operated on. PET-CT indicated full resectability in 24, but in fact only incomplete resection was possible in three cases. Thus sensitivity and specificity for the identification of full resectability were 100% and 66%, respectively. Seven negative results in PET-CT were confirmed by a relapse-free follow-up of 1 year. Conclusion: PET-CT offers reliable detection of recurrent ovarian cancer. Although diagnostic accuracy in the prediction of full resectability is limited, surgical planning is improved by identifying sites of intraperitoneal involvement.*

Being the third most common cancer of the female genital tract, ovarian cancer is the leading cause of death related to gynecological malignancies (1). Due to a lack of early clinical symptoms, ovarian cancer is often diagnosed at an advanced stage (1). Primary treatment includes operative cytoreduction and a subsequent platinum-based combined chemotherapy. Response rates to this standard primary

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treatment range at around 80%, but even with this high sensitivity, survival rates are low and 60-70% of patients with ovarian cancer relapse or die within 5 years of diagnosis (2). The importance of debulking in recurrent ovarian cancer was demonstrated in a retrospective data analysis (3-5). In a retrospective study, Harter and colleagues found that only those patients in whom a macroscopic tumor-free resection could be achieved benefited from surgery in terms of overall survival (6). Regarding these aspects of patient management, it is necessary to find a diagnostic tool to select patients who benefit from surgery and to identify those who are better off with primary systemic therapy, preferentially as an interdisciplinary approach involving radiologists, nuclear medicine physicians and gynecological or oncological surgeons.

A continuous rise of the CA-125 level is frequently a first sign of recurrence in ovarian cancer that precedes clinical symptoms or evidence in imaging by about 6 months (7). As a differentiation between localized and diffuse tumor spread is not possible based on tumor markers, sufficient diagnostic imaging is necessary in suspicion of relapse. The purpose of diagnostic imaging is to assist treatment planning, e.g. in the indication of operative and or systemic therapy. Computed tomography (CT) offers the possibility to cover the whole abdomen and to detect lymph node abnormalities, but the assessment is generally based on morphological criteria and the size of lesions rather than the actual detection of malignant tissue (8). Therefore, it has limited value in detecting microscopic and small macroscopic disease, especially small peritoneal lesions. Moreover, it is difficult to distinguish benign postoperative changes from tumor relapse in CT (9).

Therefore, whole-body positron emission tomography computed tomography (PET-CT) using ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) may be a useful diagnostic tool in recurrent ovarian cancer. It was described to be effective in distinguishing between benign and malignant disease in lung, colorectal and head and neck cancer (10), and its applicability has also been shown for ovarian cancer (11). A prospective

study by Sironi *et al.* based on the use of ^{18}F -FDG with a combined PET-CT system has demonstrated good results in the follow-up of patients with ovarian cancer after first-line treatment (12).

The aim of this study was to evaluate the use of PET-CT in recurrent ovarian cancer focusing on sensitivity, specificity and accuracy of ^{18}F -FDG PET-CT for detecting ovarian cancer relapse in patients with clinical signs of recurrent disease or elevated CA-125 levels in the clinical follow-up. A further aim of this study is to assess whether PET-CT can assist treatment planning by predicting resectability and by localizing tumor tissue for surgical planning.

Patients and Methods

Patients. All women undergoing PET-CT for investigation of possible recurrent epithelial ovarian cancer at our institution between November 2003 and January 2008 were included in a retrospective analysis. Clinical data of the patients' disease were available from patient charts, aftercare files and follow-up surveys. Serum tumor markers (at primary diagnosis, after chemotherapy and in follow-up), recent imaging results and indication for PET-CT were also included in the assessment. The standard follow-up consists of physical examination and evaluation of serum CA-125 and CA-72-4 levels (automated enzyme immunoassay; Elecsys, Roche Diagnostics, Penzberg, Germany) at 3-month intervals for the first 2 years after completion of primary therapy and every 6 months afterwards.

Indication for PET-CT was based on clinical symptoms, suspicion of relapse at physical examination, or a rise of blood tumor markers. Suspicion of relapse was defined as an elevation of serum CA-125 above the normal range (>35 U/ml) after achieving normal levels, or a doubling of the lowest level after primary therapy. Contraindications to PET scanning were a blood glucose level higher than 140 mg/dl, a history of diabetes and intolerance of PET-CT due to claustrophobia.

Integrated PET-CT. PET-CT was performed using a Philips Gemini System (Philips, Eindhoven, Netherlands). After a fasting period of at least 6 hours, 250 MBq ^{18}F FDG were administered at normal blood glucose levels and the patient was then instructed to rest in the supine position for 45 minutes to avoid non-specific muscular uptake. Twenty milligrams of furosemide were additionally injected intravenously to limit the radiation exposure of the urinary bladder and to increase the diagnostic accuracy for the urinary tract (13). In addition, 20 mg of butylscopolamine were administered to reduce non-specific intestinal uptake due to bowel peristalsis (14). Iso-osmotic mannitol was applied as negative oral contrast material to improve bowel assessment without interfering with the attenuation correction. A low-dose CT scan was acquired for attenuation correction at 120 kVp tube potential with 30 mAs current at a pitch of 1.5 and 2x5 mm collimation, covering a range from the skull base to the thighs. Positron emission scans were acquired with a 144x144 matrix and 10 cm field of view during 3 minutes per table position, so that 12 table positions were required on average to cover the range. The subsequent diagnostic CT scan was acquired during a single breath-hold, 70 seconds after administration of 120 ml of non-ionic contrast material (Ultravist, 623 mg/ml Iopromide; Bayer

Schering, Berlin/Germany) at a higher tube current of 160 mAs and otherwise identical parameters as the previous low-dose scan. PET data were reconstructed with three-dimensional maximum-likelihood algorithm (Ramla) with attenuation correction. Both CT and PET data were reconstructed in 5-mm slices. With specific software (Syntegra, Philips), CT and PET datasets were reviewed on a post-processing workstation in axial, coronal and sagittal orientation (Figure 1a) and fused with color-coded superimposition of the PET (Figure 1b) on the CT image (Figure 1c).

Image analysis. The images were reviewed by a radiologist experienced with CT and a nuclear medicine physician experienced with PET. The readers were unaware of the patients' serum CA-125 levels and of results of other imaging modalities.

For review, attenuation-corrected PET images, CT scans and co-registered PET-CT images were displayed simultaneously. The presence of abnormally increased FDG uptake was noted and its exact anatomical location was indicated on the CT. In the report, the readers indicated the presence or absence of elevated specific uptake values which raised suspicion of distant metastases. Moreover, they differentiated abdominal lesions, classifying them by location in the lower pelvis, pelvic lymph nodes, para-aortal lymph nodes or in the peritoneum, the latter including diffuse peritoneal carcinosis. All examinations were interpreted by both physicians individually and in consensus.

Surgical procedure. A secondary laparotomy for cytoreductive surgery was considered for patients if PET-CT raised suspicion of a relapse and a possibly resectable tumor spread. Surgery was conducted with palliative indication in two patients to reduce their clinical symptoms from bowel obstruction. All operative procedures were performed by an experienced oncological gynecological surgeon. Intra-abdominal tumor spread was classified by location according to the sites assessed in the PET-CT evaluation. In addition, the surgeon reported whether a macroscopically tumor-free resection was achieved.

Data analysis. Calculations of sensitivity, specificity, accuracy and positive and negative predictive values for tumor detection with PET-CT were performed on a per-patient basis, regarding intra-operative findings and results at histological analysis after surgery as standards of reference. Additionally, the respective values were calculated for the prediction of complete resectability in patients with intra-abdominal findings and without distant metastases. To account for the limited sample size of negative findings, 95% confidence intervals were also included. To quantify the agreement between imaging and operative findings, diagnostic accuracy was also calculated for the individual sites of intra-abdominal involvement. All statistical tests were performed with MedCalc software (MedCalc, Mariakerke, Belgium).

Results

Histological findings and patient characteristics. Altogether, 70 patients who had received a PET-CT for suspicion of recurrent ovarian cancer were included in the analysis (Table I). The patients' age at primary diagnosis ranged from 20 to 83 years (mean age 56) and averaged 59 years at relapse. All patients underwent primary cytoreductive surgery at initial diagnosis and subsequently received a platinum-based

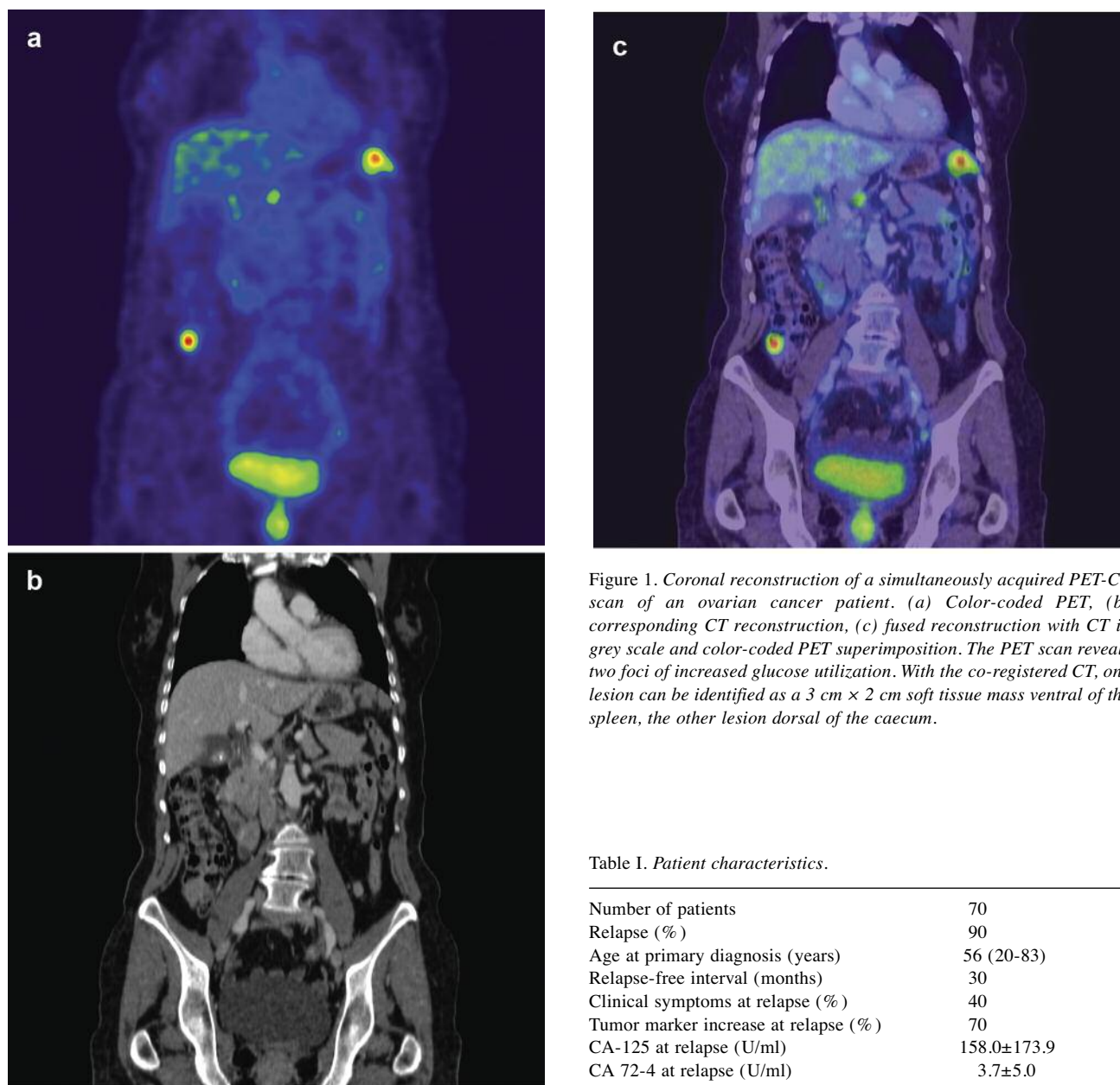


Figure 1. Coronal reconstruction of a simultaneously acquired PET-CT scan of an ovarian cancer patient. (a) Color-coded PET, (b) corresponding CT reconstruction, (c) fused reconstruction with CT in grey scale and color-coded PET superimposition. The PET scan reveals two foci of increased glucose utilization. With the co-registered CT, one lesion can be identified as a 3 cm \times 2 cm soft tissue mass ventral of the spleen, the other lesion dorsal of the caecum.

Table I. Patient characteristics.

Number of patients	70
Relapse (%)	90
Age at primary diagnosis (years)	56 (20-83)
Relapse-free interval (months)	30
Clinical symptoms at relapse (%)	40
Tumor marker increase at relapse (%)	70
CA-125 at relapse (U/ml)	158.0 \pm 173.9
CA 72-4 at relapse (U/ml)	3.7 \pm 5.0

chemotherapy. Suspicion of relapse was based on an increase of serum tumor markers in 49 cases (CA-125: 158.0 \pm 173.9 U/ml and CA 72-4: 3.7 \pm 5.0 U/ml). In 28 patients, there were clinical symptoms such as ascites, intestinal symptoms, abdominal pain or deteriorated general condition. The median relapse-free interval was 30.4 \pm 22.4 months. Of all patients, 80% had an advanced ovarian cancer at initial diagnosis (FIGO I (5/70), FIGO II (9/70), FIGO III (49/70), FIGO IV (7/70)). The most common histological tumor type was a serous-papillary ovarian cancer with 69% incidence (48/70), followed by adenocarcinomas at 11% (8/70).

PET-CT imaging findings. In PET-CT, a relapse was found in 63 of 70 patients. Seven patients were not found to have a relapse, and a tumor-free follow-up of at least 1 year confirms these negative results. Of the 63 positive cases, there was an indication for laparotomy in 30: in 28 patients the aim was full resection and in two patients there was a palliative indication to resolve bowel obstruction. Tumor tissue was removed and confirmed histologically in all operated patients, confirming the positive result of PET-CT. In the remaining 33 patients with relapse suspected in PET-CT, there was no indication for surgery because in 22 there

Table II. Diagnostic accuracy of PET-CT with reference to surgery.

		95% Confidence interval
Detection of relapse		
Sensitivity (%)	100	94-100
Specificity (%)	100	63-100
Diagnosis of full resectability		
Sensitivity (%)	100	84-100
Specificity (%)	66	30-92

was evidence of distant metastases and irresectable diffuse peritoneal spread was present in 23; in 12 there were both distant and peritoneal metastases. Thus, a histological confirmation was not available in these patients, except for three in whom biopsies were taken from mediastinal lymph nodes to confirm relapse. However, systemic chemotherapy was initiated and the positive finding in PET-CT was then confirmed by response to systemic therapy in all patients, evident either by a drop of tumor markers or regression of soft tissue masses in follow-up imaging, except for two patients in whom there was progressive disease. Thus, regarding the diagnostic accuracy of PET-CT per patient in the diagnosis of recurrence, there were no false-positive and no false-negative results, yielding full sensitivity and specificity, with 95% confidence intervals of 94-100% and 63-100%, respectively (Table II).

In the 30 patients with an indication for surgery, full resectability was expected at PET-CT imaging in 24. In 21 patients, the tumor was removed without macroscopic remnants, while only an incomplete resection was possible in 9 cases, two of those with primary palliative indication. Thus, sensitivity and specificity of PET-CT in the identification of fully resectable patients were 100% and 66%, with 95% confidence intervals of 84-100% and 30-92%, respectively.

Altogether, PET-CT described 113 lesions with suspicion of recurrence (17 lesions in the lesser pelvis, 9 lesions in the region of pelvic lymph nodes, 17 lesions in the region of para-aortic lymph nodes, 38 peritoneal and 32 distant lesions). Regarding the site of involvement in the abdomen, there was an excellent correlation between PET-CT and operative findings, with full sensitivity and specificity for all sites except for para-aortic lymph nodes, in which histological analysis revealed one metastasis that had not been detected in PET-CT, resulting in a sensitivity of 83% (9/9 lesions in the lesser pelvis, 5/5 lesions in the region of pelvic lymph nodes, 10/11 lesions in the region of para-aortic lymph nodes, 11/11 distant intraperitoneal lesions) (Table III). In contrast, diffuse peritoneal carcinosis was only detected in 15 out of 19 cases, corresponding to a sensitivity of only 79%, which was the limiting factor for macroscopic tumor-free resection in those four patients.

Table III. Sensitivity of localization.

	Sensitivity (%)
Lesser pelvis	100
Pelvic lymph nodes	100
Para-aortic lymph nodes	91
Distant lesions	100
Peritoneal carcinosis	79

Serum tumor markers. An increase of a tumor marker according to defined criteria, *i.e.* elevation of a serum marker above the normal range after achieving normal levels or a doubling of the lowest level achieved after primary therapy, was the most frequent indication for PET-CT imaging in our patient group. Of the patients with suspected tumor recurrence, 70% had elevated tumor markers, while clinical symptoms occurred in only 40% of the patients. Suspicion of recurrence was based on an increase of serum tumor markers CA-125 in 49 and CA 72-4 in 7 cases. All patients with elevated levels of CA 72-4 also had a high CA-125. Median levels at the time of PET-CT imaging were 158.0 ± 173.9 U/ml for CA-125 and 3.7 ± 5.0 U/ml for CA 72-4. Of seven patients in whom there was no evidence of recurrence in PET-CT, only two had elevated tumor marker levels. However, there was no statistically significant relationship between serum tumor markers and the extent or site of recurrence as observed in PET-CT imaging or at surgery, neither for CA-125 nor CA 72-4. Moreover, there were no differences in tumor marker levels for the histological tumor types.

Discussion

The oncological follow-up of ovarian cancer patients consists of physical and gynecological examination, clinical history and imaging. Even though tumor markers such as CA-125 are not part of routine follow-up according to guidelines, they are widely used. They have been described to occur as the first evidence of recurrent ovarian cancer, typically 6 months prior to clinical signs. A rise of tumor markers often triggers a cascade of further diagnostic procedures, especially imaging. With the combination of functional and anatomical information, PET-CT offers a powerful tool in oncological imaging. According to our results, early recurrent ovarian cancer can be detected by this imaging modality independently of the absolute value of CA-125. In our population, there were ten patients with a serum CA-125 of 35 U/ml or less. All of them showed a positive PET-CT scan. This is in agreement with data by Simcock *et al.* which

showed positive PET-CTs for patients with normal CA-125 (15). We found no evidence of a relation between anatomical site of tumor tissue and serum CA-125 or CA 72-4. Further analysis did not show any relationship between tumor markers and histological tumor type as there were no significant differences between serous-papillary tumors, adenocarcinomas and others. Thus, serum tumor markers do not seem to reveal any information on the type of tumor tissue, the extent or the localization of the recurrence. These findings are in agreement with other studies which showed a limited correlation between tumor marker levels and extent of disease and no association between histological type and the pattern of recurrence in PET-CT (16, 17).

Apart from the suspicion of recurrent disease mostly based on the PET information, the CT scan was able to identify the exact site of recurrence (Figure 1a-c). Surgical planning can be improved by the exact knowledge of sites and the extent of the tumor, including the involvement of intestinal or urinary tract and abdominal wall, with the possibility of consulting surgical or urological colleagues. Importantly, PET-CT can also help to identify patients in whom a complete surgical resection is possible and thus preoperatively differentiates between a curative and a palliative approach with respect to radicality. Bristow *et al.* have described PET-CT to be a sensitive tool to assist the early identification of disease suitable for surgical resection (18). Our data are in agreement with this finding in that 21 of our patients were correctly identified for radical surgery. In another four, a macroscopically tumor-free resection was not possible due to diffuse peritoneal spread which had not been identified in PET-CT. This supports the finding of other studies which reported diffuse peritoneal carcinosis to be difficult to detect with PET-CT (19). Although PET-CT may fail to detect peritoneal carcinosis of recurrent ovarian cancer (20), positive findings do help to optimize the therapeutic strategy in these patients. Yet, there are no better imaging modalities available for the detection of diffuse peritoneal carcinosis. CT, which is used most frequently for suspected relapse of ovarian cancer, has a sensitivity of only 47% and a specificity of 87% with reference to second-look operation (21). Moreover, CT has been shown to have quite a low negative predictive value for this indication as Makhija *et al.* reported that PET-CT could identify recurrent disease in 62% of patients with negative CT scans (22). PET scans alone have been described to be a reliable tool to detect recurrent or residual ovarian cancer (17), although its diagnostic value is limited with respect to the anatomic localization of tumor and small tumors. Thus, PET-CT can aid surgical planning by combining metabolic and anatomical information. In the patients with recurrence in whom there was no indication for surgery, PET-CT was a useful tool to avoid unnecessary surgery or laparoscopy.

Conclusion

PET-CT represents a useful diagnostic means in the workup of clinically or serologically suspected relapse of ovarian cancer. The modality offers a reliable detection of recurrent ovarian cancer and can assist surgical planning by identifying sites of intraperitoneal involvement. Additionally, the exclusion or detection of distant metastases can support general therapy planning.

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