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The value of [^{18}F]FDG PET/CT examination in the detection and differentiation of recurrent ovarian cancer

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Abstract

Background: The exact role of positron emission tomography with fluorine-18-deoxyglucose ([^{18}F]FDG PET/CT) in an early diagnosis of relapsed ovarian cancer is not clearly defined. The aim of the study was to assess the value of [^{18}F]FDG PET/CT in the detection and differentiation of recurrent ovarian cancer.

Material and methods: Eighty-four patients with suspected recurrent ovarian cancer underwent [^{18}F]FDG PET/CT examination. Results of PET/CT were analyzed taking into account clinical data of the patients, histological diagnosis, and 6-month follow-up.

Results: The [^{18}F]FDG PET/CT examinations showed abnormal findings in 67 patients (79.76%). There were 63 true positive results (75.00%), 14 true negative (16.67%), 4 false positive (4.76%), and 3 false negative (3.57%) results. Sensitivity, specificity, positive and negative predictive values of [^{18}F]FDG PET/CT were 95%, 78%, 94%, and 82%, respectively. In patients with elevated serum Ca 125 concentration (n = 43), sensitivity and specificity of [^{18}F]FDG PET/CT was 95.00% and 66.67%, respectively. Recurrence was confirmed in 22 (88.00%) of 25 patients referred for [^{18}F]FDG PET/CT due to suspected relapse in imaging tests.

Conclusions: A high frequency of recurrent ovarian cancer detected in the [^{18}F]FDG PET/CT examinations due to increased Ca 125 concentration in patients without clinical symptoms and without changes in other imaging tests confirmed the usefulness of [^{18}F]FDG PET/CT in such cases. In patients with suspected recurrent ovarian cancer implied in radiological findings, [^{18}F]FDG PET/CT results in most cases differed from the original results of imaging examination. Our results showed high accuracy of [^{18}F]FDG PET/CT in the evaluation of recurrent ovarian cancer and presented this diagnostic method as a useful tool in detecting and differentiating suspected lesions in this group of patients.

KEY words: ovarian cancer; relapse; diagnostics; [^{18}F]FDG PET/CT

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Introduction

Ovarian cancer is usually diagnosed at an advanced stage. It is characterized by the highest mortality rate of all types of gynecological cancers [1]. Despite successful initial treatment, relapse occurs within 2 years in 20–30% of patients at an early stage of the disease (FIGO IA–IIA), and up to 80% of patients at an advanced stage (FIGO IIB–IV) [2]. Early detection of recurrent ovarian cancer allows for optimal treatment, which can improve the prognosis for patients [3].

The Ca 125 glycoprotein (Ca 125), produced by epithelial cells, is used in the diagnosis and monitoring of non-mucinous ovarian cancer. Generally, Ca 125 has relatively high specificity and 80% accuracy in the detection of non-mucinous recurrent ovarian cancer [2, 4, 5]. However, the sensitivity of the marker remains insufficient, especially for a small-volume disease [6–8]. Moreover, raised Ca 125 levels provide no information about the size and site of recurrence, which all are considered limitations of the method [3, 9, 10]. Imaging methods focused on detecting abnormalities in the morphological structure of the organs,

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such as ultrasonography (US) and computed tomography (CT), lack the accuracy to detect asymptomatic peritoneal dissemination with small volume lesions, metastases to lymph nodes without changes in their structure and size, or with postoperatively changed anatomical conditions [4, 11].

When the diagnosis of recurrent ovarian cancer based on another diagnostic tool is unclear, positron emission tomography/computed tomography with fluorine-18-deoxyglucose ([^{18}F]FDG PET/CT) may play an important role [12, 13]. The [^{18}F]FDG PET/CT is a non-invasive, highly sensitive imaging method widely used in staging and monitoring of treatment in many cancers. Being a diagnostic method that identifies both structural and metabolic abnormalities of tissue, it can diagnose relapse up to 6 months earlier than compared CT [14]. The non-specific nature of the [^{18}F]FDG tracer uptake, which accumulates at any site with increased glucose metabolism, e.g. areas of inflammation and infection or in muscles on contraction, is however a limitation of the method [15, 16]. The normal physiological uptake in loops of bowel or urinary bladder activity is considered pitfalls of [^{18}F]FDG PET/CT and may be difficult to interpret [17]. The resolution of the method is currently 4–5 mm; thus even small lesions can be detected. For lesions < 5 mm in diameter, the PET/CT false negative result rate increases by 5–10% [15]. The aim of the study was to evaluate the value of [^{18}F]FDG PET/CT in the detection and differentiation of recurrent ovarian cancer.

Material and methods

The prospective study included 84 patients, aged 39–78 (60.00 ± 10.01) years old, who were referred to the Nuclear Medicine Unit of the the Copernicus Memorial Provincial Multidisciplinary Center of Oncology and Traumatology of Lodz between 2017–2021 with suspected recurrent ovarian cancer. In the treatment of primary cancer, 78 patients (92.86%) underwent complete or optimal (residual disease < 1 cm in greatest diameter) tumor cytoreduction and the remaining 6 patients (7.14%) underwent non-optimal cytoreductive surgery. Chemotherapy was administered in all cases, including neoadjuvant chemotherapy in 7 cases (83.33%). The treatment was completed 1–132 months before qualification for the [^{18}F]FDG PET/CT examination.

A research questionnaire containing clinical data and the treatment history of the patients was designed. It was filled in by patients during a medical consultation preceding the PET/CT examination. The data collected from the questionnaires, [^{18}F]FDG PET/CT results, histological diagnosis, and clinical follow-up findings were analyzed. The follow-up period after [^{18}F]FDG PET/CT was at least 6 months.

[^{18}F]FDG PET/CT procedure

All patients fasted for at least 6 hours and their fasting blood sugar levels were lower than 180 mg/dL. Oral contrast was given to all the patients. Intravenous injection of 240–380 MBq of [^{18}F]FDG was performed and followed by a 60-minute interval, during which patients rested in a quiet room. After this period, a PET/CT examination was performed. Scanning, from the patient's skull base to the mid-thigh level was done using Biograph mCT 128 scanner. Unenhanced low-dose CT was used for anatomical localization and attenuation correction.

Image interpretation

In all cases, [^{18}F]FDG PET/CT results were evaluated by a medical team consisting of a specialist in nuclear medicine and a specialist in radiology. For semi-quantitative evaluation, the maximum standardized uptake value (SUV_{max}) was used, which was determined within the detected pathological lesions. Locations of suspected lesions were classified on the base of CT results into 5 groups: lymph nodes above the diaphragm, lymph nodes below the diaphragm, local recurrence, peritoneal recurrence (including malignant ascites), and distant metastases. The $SUV_{max} > 2.5$ was adopted as the malignancy criterion.

Data analysis

Results of the [^{18}F]FDG PET/CT examination were classified into four groups: true positive (TP), false positive (FP), true negative (TN), and false negative (FN). In cases with diagnosed relapse in [^{18}F]FDG PET/CT, results were verified on the basis of histological diagnosis after biopsy taken from detected lesions (relapse: confirmed n = 30; not confirmed n = 5).

If the lesions were not histologically confirmed, cases were qualified to the TP group when:

— the lesions were observed in other imaging tests — including progression in control [^{18}F]FDG PET/CT examinations,
— disease regression in control [^{18}F]FDG PET/CT after initiation of systemic treatment was observed,
— plasma increased Ca 125 concentration decreased due to the applied treatment, disease progression despite treatment was observed.

When the [^{18}F]FDG PET/CT result was negative and relapse was not detected within 6 months of the follow-up, the case was classified into the TN group. When the [^{18}F]FDG PET/CT result was negative but the relapse was detected within 3 months of the follow-up, the result was considered FN. Metabolically active lesions ($SUV_{max} > 2.5$) observed in the [^{18}F]FDG PET/CT exam, which within a 6-month diagnostic period turned out to be benign lesions, were classified as FP.

Statistical analysis

The data were statistically analyzed using the Statistica 10.0 PL program (StatSoft Inc., Tulsa, OK, USA). In order to compare the parametric data, the Student's t-test was used. For the analysis of non-parametric data, the χ^2 test and Fisher's exact test were used. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PET/CT in diagnostics of relapsed ovarian cancer were calculated. The "p" value below 0.05 was considered statistically significant.

The study was approved by the Bioethics Commission of the Medical University of Lodz No. RNN/64/16/KE.

Results

The most frequently diagnosed histological types of ovarian cancer were: serous (n = 63; 75.00%), less frequent endometroid (n = 15; 17.86%), clear cell (n = 4; 4,76%) and mucinous (n = 2; 2.38%). In 15 patients (17.86%), ovarian cancer was initially diagnosed at stage I; in 19 patients (22.62%), at stage II; in 47 patients (56.63%), at stage III and in 3 patients (3.57%), at stage IV in

Table 1. Characteristics of the study group

Selected clinical and pathological data		n	%
Age [years]	≤ 50	17	20.24
	51–70	52	61.9
	> 70	15	17.86
Initial FIGO staging	Ia	3	3.57
	Ib	7	8.33
	Ic	5	5.95
	IIa	6	7.14
	IIb	10	11.9
	IIc	3	3.57
	IIIa	9	10.71
	IIIb	10	11.9
	IIIc	28	33.33
	IV	3	3.57
WHO grading	G1	2	2.38
	G2	17	20.24
	G3	65	77.38
Histopathology of ovarian cancer	Serous	63	75
	Mucinous	2	2.38
	Endometrioid	15	17.86
	Clear cell	4	4.76
	Complete cytoreduction	66	78.57
Primary treatment	Optimal cytoreduction	12	14.29
	Suboptimal cytoreduction	6	7.14
Total		84	100.0

FIGO — Federation of Gynecology and Obstetrics; WHO —World Health Organization

Table 2. The results of [^{18}F]FDG PET/CT in the diagnosis of relapsed ovarian cancer

[^{18}F]FDG PET/CT	Value	95% CI
Sensitivity	95.45%	87.29% to 99.05%
Specificity	77.78%	52.36% to 93.59%
Disease prevalence	78.57%	68.26% to 86.78%
Positive predictive value	94.03%	86.89% to 97.40%
Negative predictive value	82.35%	60.05% to 93.54%

[^{18}F]FDG PET/CT — fluorine-18-deoxyglucose positron emission tomography/computed tomography; CI — confidence interval

the FIGO 2009 Classification. Detailed clinical data on the studied population are presented in Table 1.

Patients were referred to [^{18}F]FDG PET/CT due to an isolated increase in serum Ca 125 level with no data of abnormal findings in imaging tests (n = 41; 48.81%), suspected relapse in a clinical examination and/or in imaging tests (n = 29; 34.52%) and for other reasons (n = 12; 14.29%). In 2 cases (2.38%), both the elevated serum Ca 125 level and suspected lesions in the imaging tests were observed. Among other indications for the [^{18}F]FDG PET/CT, clinical symptoms (n = 6), follow-up (n = 4), and poor mental condition of the patient (fear of cancer) (n = 2) were reported.

Recurrent ovarian cancer was present in 66 patients (78.57%). The sensitivity, specificity, and positive and negative predictive value of the [^{18}F]FDG PET/CT in the diagnosis of recurrent ovarian cancer are presented in Table 2. TP (Fig. 1–2), TN (Fig. 3), FP (Fig. 4), and FN [^{18}F]FDG PET/CT results were observed in 63 (75%), 14 (16.67%), 4 (4.76%) and 3 (3.57%) patients, respectively. The sensitivity and specificity of the [^{18}F]FDG PET/CT in the diagnosis of recurrent serous ovarian cancer were 95.65% and 76.47%, respectively. In endometrioid ovarian cancer, it was 93.33% and 100%. The distribution of TP, TN, FP, and FN results according to histopathology of the ovarian cancer is presented in Table 3.

Locations of the relapsed ovarian cancer, revealed in the [^{18}F]FDG PET/CT exam, are presented in Table 4. With regards to TP results, three cases of malignant ascites appeared to be the only manifestation of relapse (Fig. 1). In the FP group, the lesions were located in: the parotid gland (n = 1; Fig. 4), peritoneum (n = 1), left external iliac lymph node (n = 1) and mediastinal lymph nodes (n = 1). In 3 FP patients, relapse was excluded after biopsy; in 1, patient serum Ca 125 concentration decreased without treatment and no recurrence was detected during the follow-up. In the FN group, the [^{18}F]FDG PET/CT examination showed no abnormal findings, but relapsed ovarian cancer was detected within 1–3 months of the follow-up.

In 5 patients, [^{18}F]FDG PET/CT enabled to detection of abnormalities unrelated to ovarian cancer. Of this number, there were 2 cases of colorectal cancer (Fig. 2), and 1 case of benign thyroid lesion, sarcoidosis, and benign neoplasm of the parotid gland. They were detected as the only lesions in these patients; therefore, they were qualified to the FP group.

Serum Ca 125 levels ranged between 4.3 — 1820 IU/mL. [^{18}F]FDG PET/CT detected recurrence in 26 patients with Ca 125 < 35 IU/mL (63.41%) and in 37 patients with Ca 125 ≥ 35 IU/mL (86.05%) (p = 0.036). The patients were divided into 3 groups depending on the serum Ca 125 concentration: < 35 IU/mL, ≥ 35 < 100 IU/mL, and ≥ 100 IU/mL. In patients with elevated serum Ca 125 concentration (n = 43), the sensitivity of [^{18}F]FDG PET/CT was 95.00% and specificity — 66.67%. The exact data are presented in Table 5. In TP patients with Ca 125 < 35 IU/mL, multifocal and unifocal recurrences were detected in 9 cases (34.62%) and in 17 cases (65.38%), respectively (p < 0.001). Among TP patients with 125 ≥ 35 IU/mL, multifocal and unifocal recurrences were detected in 34 cases (91.89%) and in 3 cases (8.11%), respectively (p < 0.001).

Of 25 patients referred to the [^{18}F]FDG PET/CT exam due to suspected relapse of ovarian cancer in imaging tests, 18 showed symptoms of metabolic malignancy in the lesions. In 8 of them, relapse was detected in some other locations. In the remaining 7 patients the [^{18}F]FDG PET/CT exam did not confirm lesions suspected in radiological examinations, but in 4 cases, the relapse was present in a different location. In 3 patients, the [^{18}F]FDG PET/CT examination excluded relapse (Fig. 3).

Discussion

Although the role of [^{18}F]FDG PET/CT in the diagnosis of recurrent ovarian cancer was discussed in the literature, our study was valuable because it was prospective. All PET/CTs were performed at the same department by the same medical team and the patients were observed within 6 months following the implementation of diagnostic procedures. Unfortunately, the relapse was histologically confirmed only in 30 patients, while in the other 36 patients, it was only a clinical evaluation.

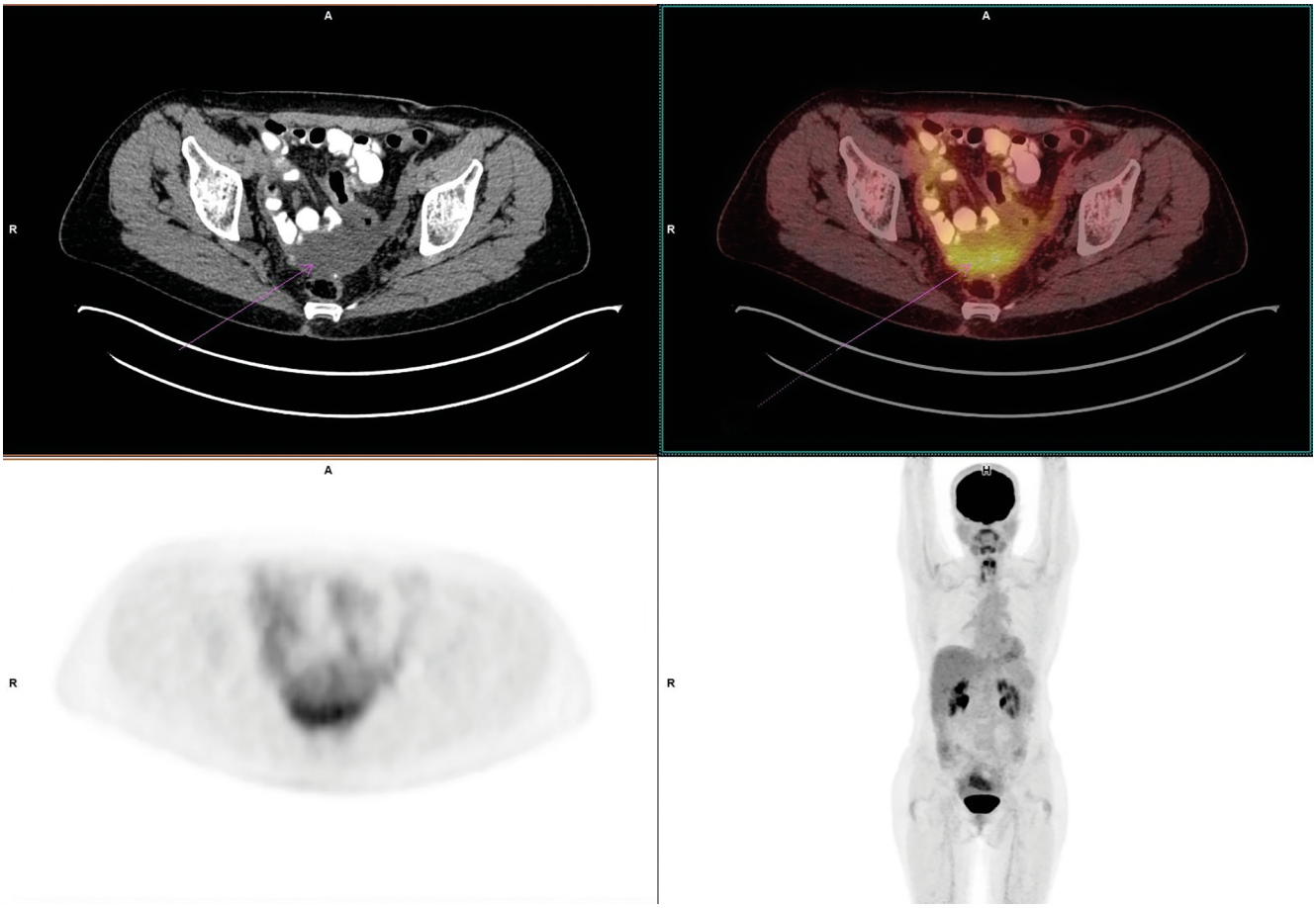

Figure 1. Axial CT and axial fused [^{18}F]FDG PET/CT images (upper row), [^{18}F]FDG PET/CT axial and coronal whole-body maximum intensity projection images (lower row). Malignant ascites (arrow) as the only site of recurrence detected in [^{18}F]FDG PET/CT. The [^{18}F]FDG PET/CT was performed due to an elevated Ca 125 level (467 mL/IU)

The advantage of [^{18}F]FDG PET/CT over conventional imaging methods, like US, CT and MRI, was demonstrated in the literature [18, 19]. Among 84 patients in the study group, sensitivity and specificity of [^{18}F]FDG PET/CT in diagnosing relapse of ovarian cancer were 95.45% and 77.78%, respectively. The sensitivity of [^{18}F]FDG PET/CT was very high in serous and endometrioid ovarian cancers. In our material specificity calculated for clear cell and mucinous ovarian cancers could not be taken into account due to the very small number of cases. According to the literature, mucinous and clear-cell ovarian cancers represent a potential source of [^{18}F]FDG PET-negative findings [20]. The high sensitivity of the method is similar to studies conducted by other authors [4, 8, 9,14, 18, 19, 21–24]. Risum et al. [21] reported that sensitivity and specificity in the detection of relapse of ovarian cancer are 66% and 90% for the US and 81% and 90% for CT [21]. In other published studies, the sensitivity and specificity of the above methods in the diagnosis of recurrent ovarian cancer ranged from 40 to 93% and from 50 to 98% for CT, from 62 to 91%, and from 40 to 100% for MRI [22]. In patients with ovarian cancer, the sensitivity of CT drops to 25–50%, for metastatic peritoneal lesions smaller than 1 cm [25–27]. The presence of postoperative anatomical alterations in the abdominal cavity reduces the specificity of the MRI in detecting recurrence [4, 28]. In PET/CT, these anatomical conditions are not such important for the diagnosis. In our study, carried out on 25 patients being qualified to [^{18}F]FDG PET/CT due to suspicion of relapsed ovarian cancer in other imaging techniques, we confirmed the relapse in 22 cases and excluded it in 3 cases.

Literature data show that relapsed ovarian cancer is in most cases multifocal and in almost 75%, it is found in the peritoneal cavity and retroperitoneal space [22, 29, 30]. In our study, multifocal relapse was found in 77.61% of cases. In 84.13%, the cancer was localized in the peritoneal cavity and/or in retroperitoneal space. Only 15.87% of cases, metastatic foci were located in supradiaphragmatic lymph nodes and in distant organs. All patients with a single-site recurrence were qualified for surgery.

According to literature data, the sensitivity and specificity of [^{18}F]FDG PET/CT in detecting peritoneal implants of recurrent ovarian cancer are very high [3, 8, 19, 23]. Rubini et al. [9] described an advantage of [^{18}F]FDG PET/CT over other imaging methods (85% sensitivity and 92.31% specificity). Furthermore, [^{18}F]FDG PET/CT is a useful method for differentiation between malignant ascites and benign ascites [31]. This observation was also confirmed in our study. Three cases of ascites with $SUV_{max} > 2.5$ were diagnosed correctly as the only site of relapse. Unfortunately, the sensitivity of [^{18}F]FDG PET/CT decreases in diffuse or small-volume (implants < 0.5 cm in diameter) peritoneal

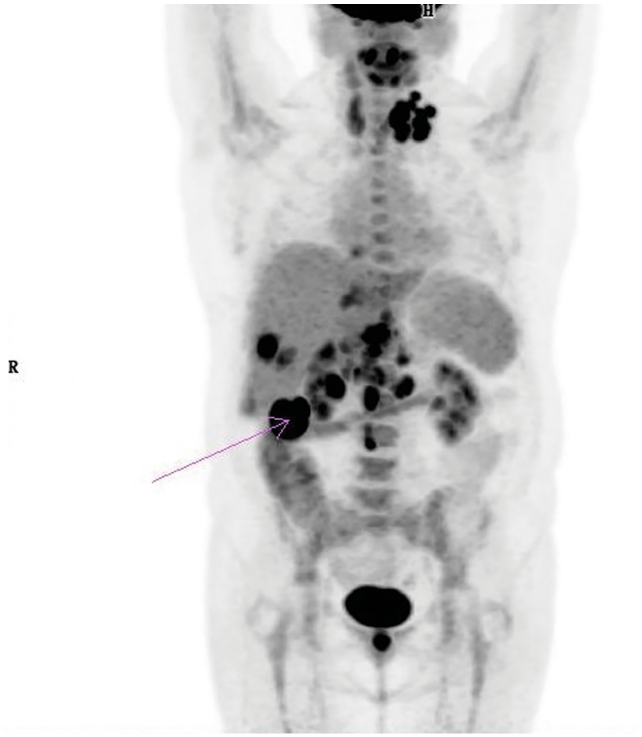

Figure 2. [18F]FDG PET/CT coronal whole-body maximum intensity projection image. Synchronous colorectal cancer detected in [18F]FDG PET/CT (hepatic flexure tumor) (arrow), metastases in the liver, supra- and infra-diaphragmatic lymph nodes. The [18F]FDG PET/CT was performed due to suspicion of a liver metastatic lesion in the CT

involvement [32]. Such an observation was made for 3 patients in our FN group.

Lymph nodes, especially those located retroperitoneally, are a common site of relapse in ovarian cancer [30, 33] and this was confirmed in our study. [18F]FDG PET/CT enables detection of metastases even in non-enlarged lymph nodes. A meta-analysis conducted on patients from 18 centers, to assess the diagnostic value of various imaging methods in detecting relapse in lymph nodes, revealed that the sensitivity and specificity of [18F]FDG PET/CT were 73.2% and 96.7%, respectively. These values were higher when compared to those obtained for CT (sensitivity 42.6%, specificity 95%) and MRI (sensitivity 54.7%, specificity 88.3%) [34]. On the other hand, small and necrotic lymph nodes may not be detected on [18F]FDG PET/CT scans, hereby generating false negative results [35].

[18F]FDG PET/CT appears to have the highest sensitivity in ovarian cancer patients with elevated serum Ca 125 levels and negative CT results [4, 12, 36]. Our results confirmed this observation among patients with Ca 125 ≥ 100 IU/mL (100% sensitivity), but also showed very high sensitivity (96.30%) in detection relapse in patients with normal ranged Ca 125. In patients with elevated Ca 125 levels, multifocal recurrence was detected in 91.89%, while 65.38% of unifocal relapses occurred in patients with normal Ca 125 values. In general, in our study [18F]FDG PET/CT detected recurrence less often in patients with normal Ca 125 values (63.41%) than compared to patients with abnormal Ca 125 levels (86.05%). Literature data correspond to this observation [24, 34]. [18F]FDG PET/CT also allowed us to exclude relapse in cases of postoperative

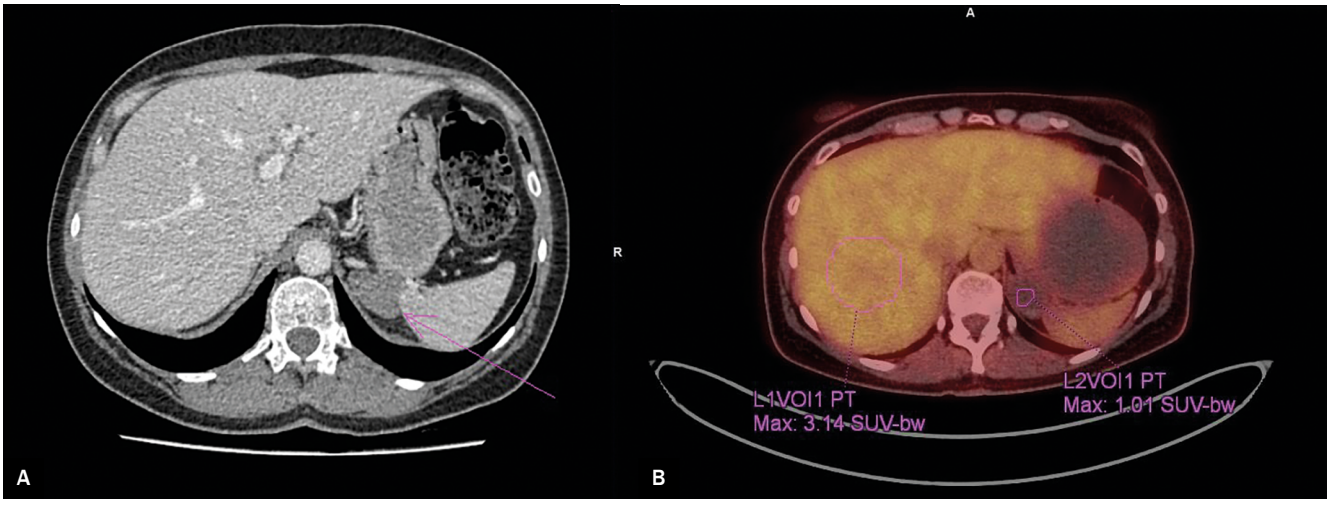

Figure 3. Axial CT (with contrast enhancement) and fused [18F]FDG PET/CT images. Soft tissue lesion located between the stomach, spleen and the left crus of the diaphragm (arrow) which was suspected of recurrence on a CT scan (**A**). The [18F]FDG PET/CT was performed due to an abnormal CT result. [18F]FDG PET/CT showed no metabolic activity within the lesion (**B**)

Table 3. Relapses of ovarian cancer in [18F]FDG PET/CT and histopathology

Histopathology			[18F]FDG PET/CT results and relapse of ovarian cancer					
	n	%	TP (n)	TN (n)	FP (n)	FN (n)	Sensitivity [%]	Specificity [%]
Serous ovarian cancer	63	75.00	44	13	4	2	95.65	76.47
Mucinous ovarian cancer	2	2.38	1	0	0	1	50.00	–
Endometrioid ovarian cancer	15	17.86	14	1	0	0	93.33	100.00
Clear-cell ovarian cancer	4	4.76	4	0	0	0	100.00	–

FN — false negative; FP — false positive; TN — true negative; TP — true positive

Table 4. Frequency of abnormal [^{18}F]FDG PET/CT findings by the site of involvement in TP patients

Location of the recurrence	No.	%
Lymph nodes	32	50.79
Above diaphragm	2	3.17
Below diaphragm	19	30.16
Above and below the diaphragm	11	17.46
Peritoneum (including malignant ascites as the only finding)	39	61.9
Local recurrence	11	17.46
Distant metastasis	17 (24 locations)	26.98
Liver	11	17.46
Lung	5	7.93
Spleen	2	3.17
Bones	2	3.17
Rectus abdominis muscle	1	1.59
Brain	1	1.59
Pleura	1	1.59
Adipose tissue near the iliac muscle	1	1.59
Total number of locations	106	

fibrosis in patients with abnormal CT results, and this observation is similar to the one made in previous reports [11, 18].

When describing the role of [^{18}F]FDG PET/CT imaging in the diagnosis of patients suspected of relapse it should be mentioned that this whole-body examination enables to detect not only distant metastases but also other synchronous conditions [37–41]. It was confirmed in our study.

A lack of histological verification of relapses in many cases and a relatively small number of patients were limitations of our study. For this reason, the results cannot be generalized to the whole population. In our opinion, further prospective studies in larger populations are required to better characterize the group of patients who benefit from an [^{18}F]FDG PET/CT examination the most. Identification of these patients will facilitate optimal individualization of diagnosis and treatment for each patient.

In conclusion: a high incidence of recurrent ovarian cancer, detected in [^{18}F]FDG PET/CT due to increased Ca 125 concentration in patients without clinical symptoms and without changes in other imaging tests, confirmed the usefulness of [^{18}F]FDG PET/CT. In patients with suspected recurrent ovarian cancer implied in radiological findings, [^{18}F]FDG PET/CT results in most cases differed from the original results of imaging examination. Our results showed

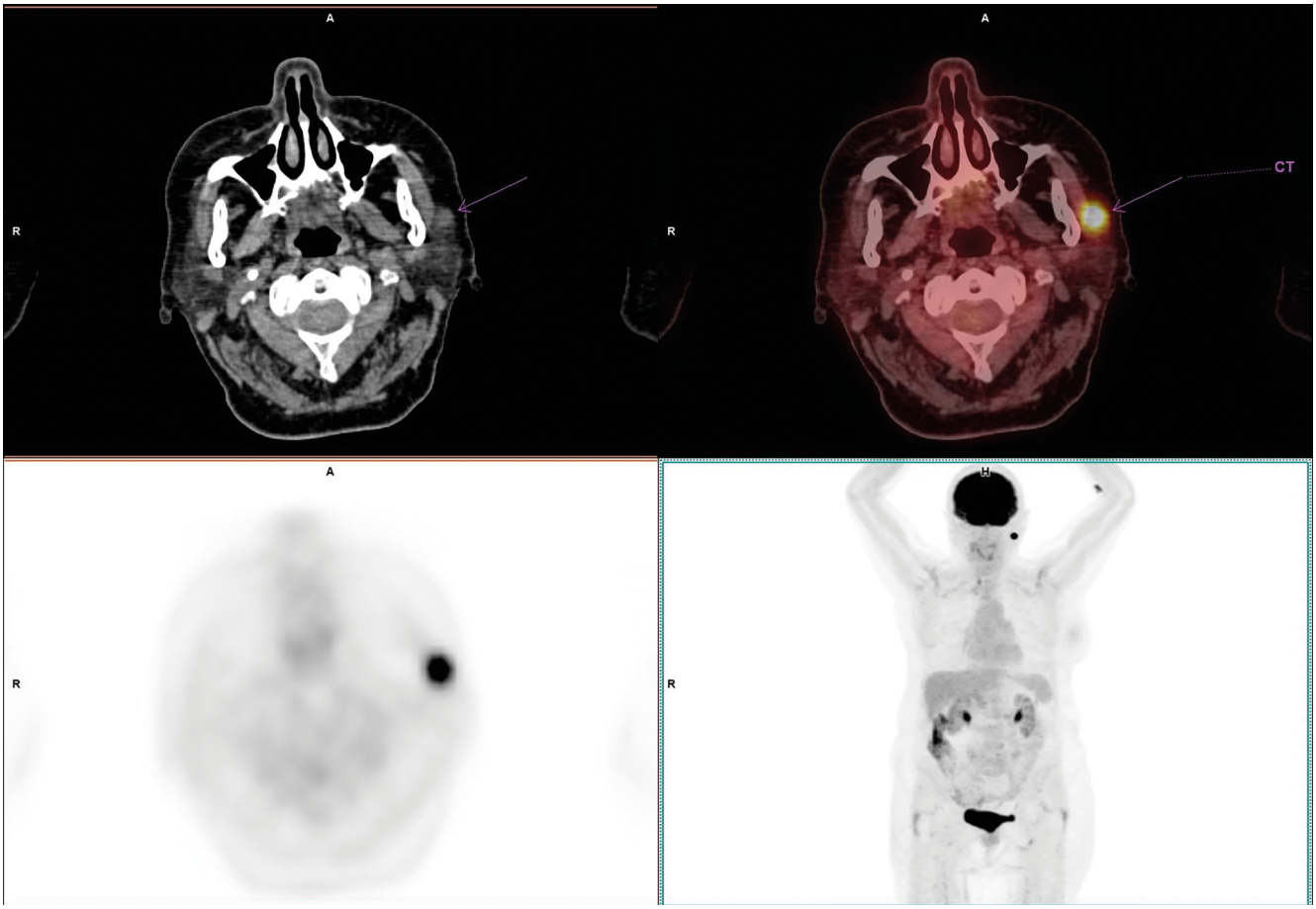

Figure 4. Axial CT and fused [^{18}F]FDG PET/CT images (upper row), axial and coronal [^{18}F]FDG PET/CT whole-body maximum intensity projection images (lower row). The metabolically active lesion in the left parotid gland was detected in [^{18}F]FDG PET/CT. Further biopsy of the parotid gland showed a benign neoplastic process; hence, the [^{18}F]FDG PET/CT result was qualified as false positive. The [^{18}F]FDG PET/CT examination was performed due to clinical symptoms

Table 5. Relapses of ovarian cancer in [^{18}F]FDG PET/CT and Ca 125 levels

Ca 125 (IU/mL)	n	%	[^{18}F]FDG PET/CT results and relapse of ovarian cancer					
			TP (n)	TN (n)	FP (n)	FN (n)	Sensitivity [%]	Specificity [%]
< 35	41	48.81	26	11	3	1	96.30	78.57
≥ 35 < 100	17	20.23	12	3	0	2	85.71	100.00
≥ 100	26	30.96	25	0	1	0	100.00	—

FN — false negative; FP — false positive; PET/CT — positron emission tomography/computed tomography; TN — true negative; TP — true positive

high accuracy of [^{18}F]FDG PET/CT in the evaluation of recurrent ovarian cancer and confirmed that this diagnostic method is a useful tool in detecting and differentiating suspected lesions.

Conflict of interests

None declared.

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