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The role of PET/CT with fluorine-18-deoxyglucose in the detection of relapsed serous ovarian cancer in patients with normal serum CA125 levels

Malgorzata Kosinska[1], Jacek Fijuth[2, 3], Piotr Misiewicz[1], Katarzyna Kalita[1], Maciej Foks[4], Lukasz Kuncman[2, 3], Leszek Gottwald[2, 3]

[1]*Positron Emission Tomography Unit, Department of Nuclear Medicine, Copernicus Memorial Hospital of Lodz, Poland*
[2]*Department of Radiotherapy, Medical University of Lodz, Poland*
[3]*Department of Teleradiotherapy, Regional Cancer Centre, Copernicus Memorial Hospital of Lodz, Poland*
[4]*Health Care Institution Diagnostics Consilio, Lodz, Poland*

ABSTRACT

Objectives: To assess the role of the positron emission tomography with fluorine-18-deoxyglucose (PET/CT) in the detection of recurrent serous ovarian cancer in patients with normal serum CA125 level.

Material and methods: Thirty-one patients with suspected recurrent serous ovarian cancer with normal (< 35 IU/mL) serum CA125 level and no prior recurrence underwent PET/CT imaging. The results of the PET/CT were analyzed considering clinical data of the patients, histological diagnosis and 6 months follow-up.

Results: The patients were referred to the PET/CT due to suspected relapse in imaging tests (CT — 11 cases, US — 3 cases, MRI — 2 cases; n = 16; 51.6%), clinical examination (n = 4; 12.9%) and clinical symptoms (n = 11; 35.5%). The recurrent serous ovarian cancer was present in 16 patients (51.6%). In 9 these cases (56.3%) the recurrences were diagnosed in patients aged 51–70 years. In 15 cases (93.8%) the recurrences were diagnosed within 24 months after treatment. There were 15 true positive (48.4%), 12 true negative (38.7%), 3 false positive (9.7%) and 1 false negative (3.2%) PET/CT results. Sensitivity, specificity, positive and negative predictive value of the PET/CT were calculated as 93.8% (95% CI, 86.1–97.4%), 80.0% (95% CI, 69.7–88.9%), 83.3% (95% CI, 74.3–90.4%) and 92.3% (95% CI, 84.2–98.3%), respectively.

Conclusions: In patients with a diagnosis of complete remission after treatment for serous ovarian cancer, even a multifocal recurrence may occur during follow up despite normal serum CA125 levels. Our results showed a usefulness of the PET/CT in detecting and differentiating malignant from benign lesions in patients with normal serum CA125 levels but inconclusive results in other imaging tests. We observed false results of the PET/CT for lesions in parotid gland, mesorectal adipose tissue and mediastinal lymph nodes.

Keywords: [^{18}F]FDG PET/CT; ovarian cancer; relapse; normal CA125 level

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INTRODUCTION

Ovarian cancer is characterized by the highest mortality rate of all gynecologic malignant tumors. Serous ovarian cancer is its most frequent histological subtype [1]. Despite successful initial treatment, relapse occurs in most patients with a median time of 18–24 months [2, 3]. For this reason, it is important to accurately assess ovarian cancer patients during follow-up to determine whether a relapse has occurred.

Imaging methods focused on detecting abnormalities in morphological structure of the organs, 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]. When the diagnosis of recurrent ovarian cancer is unclear, positron emission tomography with fluorine-18-deoxyglucose (PET/CT) may play an important role. The PET/CT identifies both structural and metabolic abnormalities of the tissue and it can diagnose relapse up to 6 months earlier than compared to the

Corresponding author:
Leszek Gottwald
Department of Radiotherapy, Chair of Oncology, Medical University of Lodz, 4 Paderewskiego St., 93–509 Lodz, Poland
phone: +48 42 689 55 51; fax: +48 42 689 55 52; e-mail: leszek.gottwald@umed.lodz.pl

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CT [5]. The resolution of the method is currently 4–5 mm, therefore even small lesions can be detected. In cases of lesions < 5 mm in diameter, the PET/CT false negative result rate increases by 5–10% [6].

In 1983, a cancer antigen 125 (CA125) radioimmunoassay was introduced, with the specific aim to monitor treatment of non-mucinous ovarian cancer patients. CA125 is a glycoprotein produced by epithelial cells and the test could reliably, and at an early stage, detect recurrences after initial successful treatment of ovarian cancer. It is known, that CA125 has relatively high specificity and 80% accuracy in detection recurrence of the ovarian cancer [2, 4, 7]. However, sensitivity of the marker remains insufficient, especially for small-volume disease. As the effect, normal serum CA125 concentration can coexist with relapsed cancer [8, 9]. The optimal cutting point for the CA125 level (17.6–18 U/mL) was established that helps determine for which patients the PET/CT scan is the most justified [5].

The appearance of disturbing symptoms and inconclusive results in imaging tests, despite normal serum CA125 level, can be an indication to perform the PET/CT. The questions about the sensitivity and specificity of the PET/CT in this group of patients and about the anatomical location of false positive and negative results are still valid.

Objective

The aim of the study was to assess the role of the PET/CT in the detection of recurrent serous ovarian cancer in patients with normal CA125 levels.

MATERIAL AND METHODS

The prospective study included 31 consecutive patients aged > 18 years with normal (< 35 IU/mL) serous CA125 concentration, who were referred with suspected recurrent ovarian cancer of the serous type to the Nuclear Medicine Unit of the Copernicus Memorial Provincial Multidisciplinary Center of Oncology and Traumatology of Lodz between 2017–2021. The suspicion of the relapse was based on results of imaging tests (CT — 11 cases, US — 3 cases, MRI — 2 cases), clinical examination (n = 4) and clinical symptoms (n = 11). The patients with the follow-up period < 6 months were excluded from the study.

In the treatment of primary cancer, 29 patients (93.6%) underwent complete or optimal tumor cytoreduction (residual less than 1 cm) and the remaining 2 patients (6.4%) — suboptimal cytoreductive surgery. Chemotherapy was given in all cases, including neoadjuvant chemotherapy in 3 cases. In all patients a clinical complete remission was diagnosed. nTreatment was completed 2–44 months before the PET/CT. Characteristics of the study group are presented in Table 1.

A research survey containing clinical data and treatment history of the patients was designed. It was filled by patients on medical consultation preceding the PET/CT. The data collected from the questionnaires, results of the PET/CT, histological diagnosis and clinical follow-up findings were analyzed. The follow-up period was at least 6 months.

Table 1. Characteristics of the study group

Selected clinical and pathological data	n	[%]
Age of patients [years]		
≤ 50	6	19.3
51–70	18 5	8.1
> 70	7	22.6
FIGO staging of the cancer		
I	4	12.9
II	7	22.6
III	18	58.1
IV	2	6.4
WHO grading of the cancer		
G1	1	3.2
G2	3	9.7
G3	27	87.1
Time from completion of treatment to the [^{18}F] FDG PET/CT [months]		
2–12	12	38.7
13–24	14	45.2
25–36	3	9.7
> 36	2	6.4
Total	31	100.0

FIGO — International Federation of Gynecology and Obstetrics; WHO — World Health Organization; FDG PET/CT — positron emission tomography with fluorine-18-deoxyglucose

PET/CT procedure

All patients had at least six hours fasting, and their fasting blood sugar levels were less than 180 mg/dL. Oral contrast was given to all the patients. Intravenous injection of 240–380 MBq of the [18F]FDG was performed and followed by a 60 min interval, during which patients rested in quiet room. After this period 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 the PET/CT 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. The SUV_{max} > 2.5 was accepted as a criterium of malignancy.

Data analysis

Results of the PET/CT were qualified to four groups: true positive (TP), false positive (FP), true negative (TN) and false negative (FN). In cases diagnosed with relapse in the PET/CT, the results were verified based on histological diagnosis after biopsy taken from detected lesions (relapse: confirmed n = 6; not confirmed n = 3). If the lesions were not histologically examined, cases were qualified to the TP group when:

- the lesions were observed in other imaging tests — including progression in control PET/CT,
- disease regression in control PET/CT after applied systemic treatment was observed,
- disease progression despite treatment was observed.

When the PET/CT result was negative and relapse was not detected during 6 months of the follow-up, the case was classified to the TN group. When the PET/CT result was negative, but the relapse was detected during 3 months of the follow-up, the result was considered as FN. Metabolically active lesions (SUVmax > 2.5) in the PET/CT, which during further diagnostics within 6 months turned out to be benign lesions, were classified as the FP.

Statistical analysis

The data were statistically elaborated using the Statistica 10.0 PL program (Statsoft Inc., Tulsa, OK, USA). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in the diagnosis of relapsed serous 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 patients were referred to the PET/CT due to suspected relapse in imaging tests (51.6%), clinical examination (2.9%) and clinical symptoms (35.5%). The recurrent serous ovarian cancer was finally confirmed in 16 patients (51.6%). In 15 cases (93.8%) the recurrences were diagnosed within 24 months after treatment and only in 1 patient (6.2%) later ($p < 0.001$).

The median age of patients in the study group was 60.6 ± 10.0 years. The median age of patients diagnosed with relapsed ovarian cancer was 61.8 ± 10.5 years. In patients with no relapse, it was 57.3 ± 9.5 years ($p = 0.222$). The recurrences were diagnosed in 4 of 6 patients ≤ 50 years (25%), in 8 of 18 patients aged 51–70 years (50%) and 4 of 7 patients aged ≥ 71 years (25%). Characteristics of the group with recurrent serous ovarian cancer is presented in Figure 1.

There were 15 TP (48.4%), 12 TN (38.7%), 3 FP (9.7%) and 1 FN (3.2%) PET/CT results. Sensitivity, specificity, positive and negative predictive value of the PET/CT were calculated as 93.8% (95% CI, 86.1–97.4%), 80.0% (95% CI, 69.7–88.9%), 83.3% (95% CI, 74.3–90.4%) and 92.3% (95% CI, 84.2–98.3%), respectively.

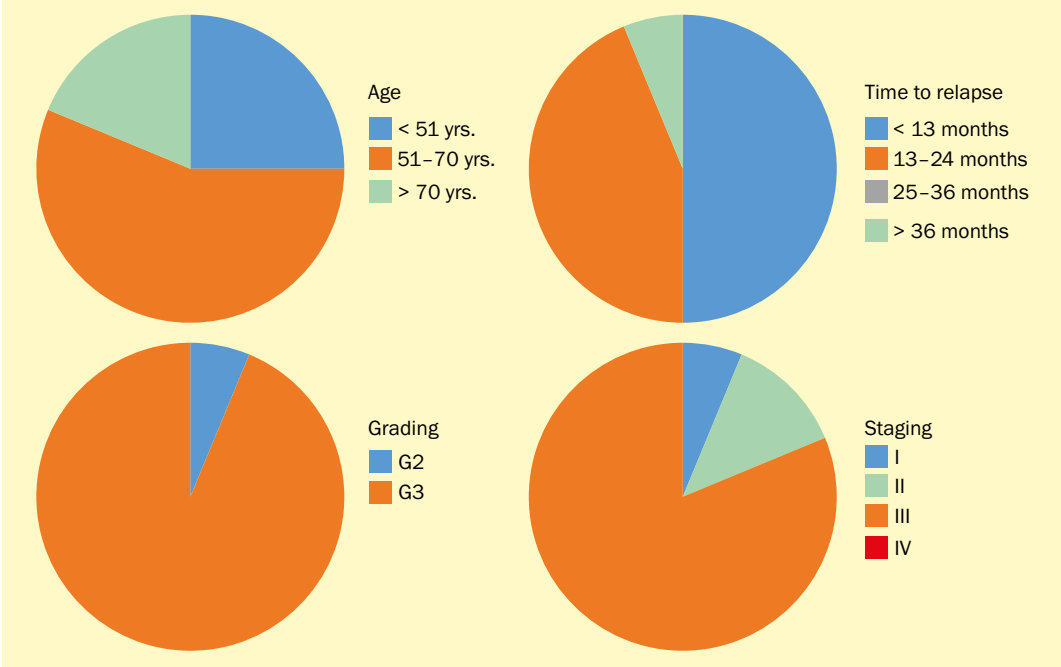

Figure 1. Characteristics of the group with recurrent serous ovarian cancer

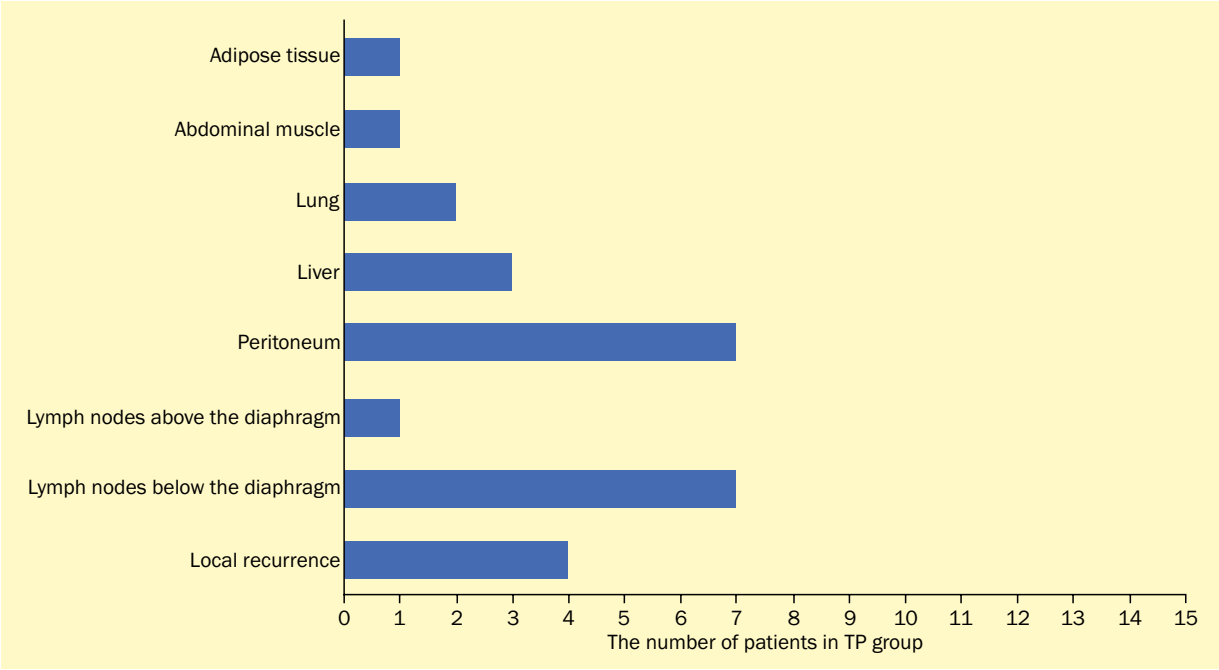

Figure 2. Frequency of abnormal FDG PET findings by the site of involvement in true positive (TP) patients

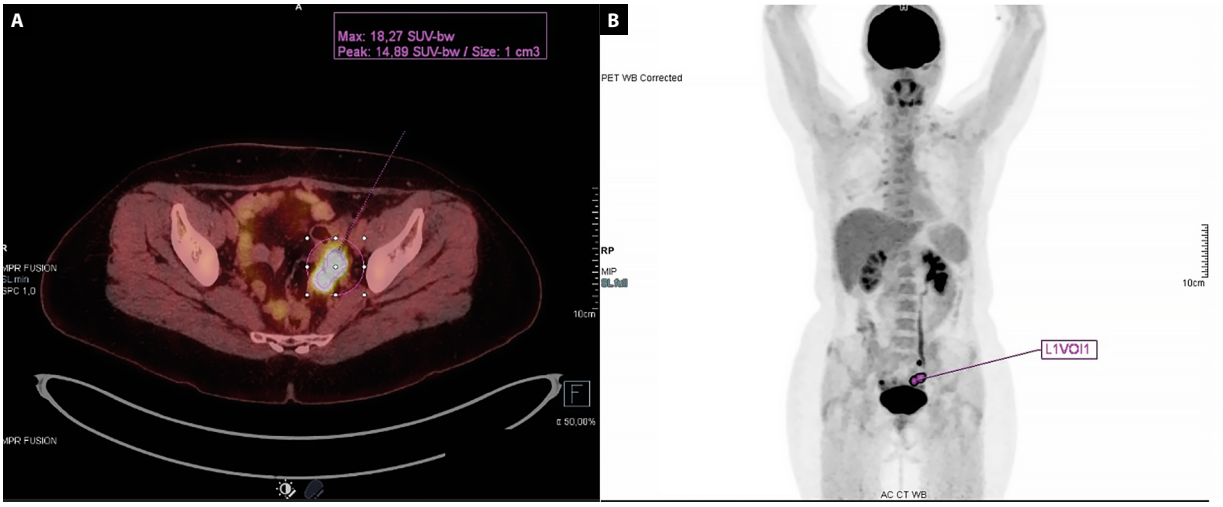

Figure 3. Example of TP findings of positron emission tomography (PET/CT) scan; **A.** Transaxial slice; **B.** 3D maximum intensity projection (MIP)

The locations of the relapsed serous ovarian cancer in the TP group are presented in Figure 2. In the TP group 3 unifocal and 12 multifocal recurrences were diagnosed ($p = 0.043$) (Fig. 3). In the FP group metabolically, active lesions were located in the parotid gland (n = 1), mesorectal adipose tissue (n = 1) (Fig. 4) and mediastinal lymph nodes (n = 1), but in these cases relapse was excluded after biopsy. In one FN case, the PET/CT showed no abnormal findings, but lung metastases were detected 2 months after the PET/CT.

DISCUSSION

In about 70% of patients with ovarian cancer, an increase in the level of the CA125 is the first sign of recurrence, that anticipates clinical recurrence by about 3–4.5 months [7, 10]. Our study confirmed the observation of Bhosale et al. [9], that normal CA125 levels can coexist with even a multifocal recurrence. In our study, patients with relapsed disease had multifocal lesions and the recurrence appeared within 24 months after end of treatment. According to the literature,

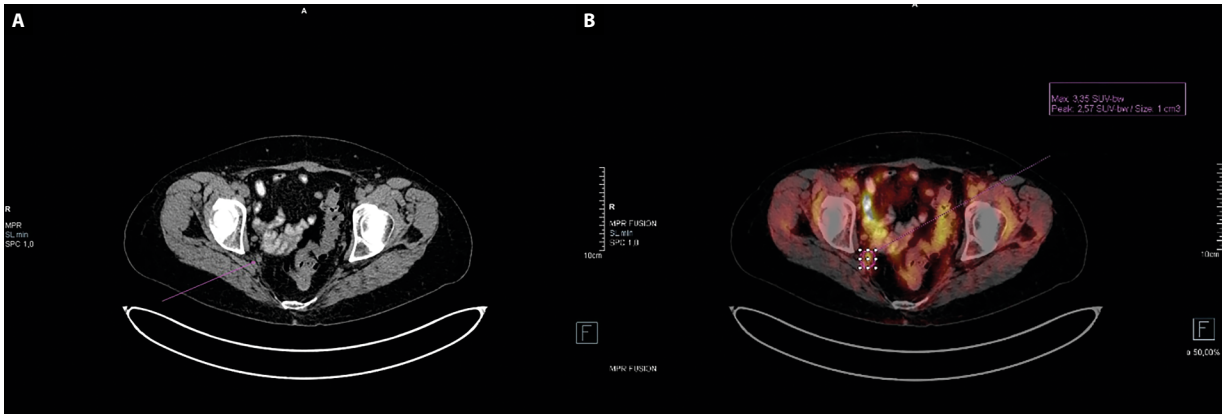

Figure 4. Hypermetabolic lesion suspected of recurrence located in mesorectal adipose tissue; **A.** Computed tomography (CT) presentation; **B.** Positron emission tomography (PET/CT) presentation

the median interval to first recurrence in ovarian cancer is 18 to 24 months [3]. The data from the literature show that relapsed ovarian cancer in most cases is multifocal [11–13]. In our patients only in 3 cases (20.00%) the relapses detected in the PET/CT were unifocal. These patients were qualified for surgery.

Among 31 patients in our study group, we achieved 93.75% sensitivity and 80.00% specificity in diagnosing the recurrence of ovarian cancer. The high sensitivity of the method is similar to studies [4, 5, 8, 11, 14–19]. Superiority of the PET/CT over conventional imaging methods, like US, CT and MRI was demonstrated in the literature [9, 18–20]. Risum et al. [17], reported sensitivity and specificity of US and CT to detect recurrence in ovarian cancer patients as 66% and 90% for US and 81% and 90% for CT [17]. In another studies, sensitivity and specificity of these methods in the diagnosis of recurrent ovarian cancer ranged between 40–93% and 50–98% for CT, 62–91% and 40–100% for MRI [21]. The sensitivity of the CT drops to 25–50%, when metastatic lesions in the peritoneum are smaller than 1 cm [22, 23]. The presence of postoperative anatomical alterations in the abdominal cavity reduces specificity of the MRI in detecting recurrence [4, 24]. In the PET/CT these anatomical conditions are less important for the diagnosis [11, 15, 16], but non-specific nature of the [18F]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 and like in our study can cause false positive results [6, 25]. The normal physiological uptake in loops of bowel or urinary bladder activity are considered pitfalls of PET/CT and may be difficult to interpret [26].

Relapsed ovarian cancer in near 75% is diagnosed in peritoneal cavity and retroperitoneal space [11–13]. The high incidence of both peritoneal implants and retroperitoneal lymph nodes involvement in recurrent serous ovarian cancer was confirmed in our study. According to the data from the literature, the sensitivity and the specificity of the PET/CT in detecting peritoneal implants in recurrent ovarian cancer are very high [8, 15, 16, 27]. Rubini et al. [14] described an advantage of the PET/CT over another imaging methods in this indication (85% sensitivity and 92.3% specificity) [14, 18].

The lymph nodes, especially of retroperitoneal location, are common site of relapse in ovarian cancer [13, 28]. The PET/CT can detect metastases even in non-enlarged lymph bnodes. In a meta-analysis of patients from 18 centers, which examined the diagnostic value of various imaging methods in detecting recurrence in lymph nodes, the sensitivity and specificity of the PET/CT were 73.2% and 96.7%, respectively.

These values were higher when compared to CT (sensitivity 42.6%, specificity 95%) and MRI (sensitivity 54.7%, specificity 88.3%) [29]. On the other hand, small and necrotic lymph nodes may not be detected on the PET/CT scans, leading to false negative results [30].

The limitations of our study were lack of histological verification of the relapses in most cases and a small number of patients. For this reason, the results cannot be generalized to whole population. In our opinion, further prospective studies in larger populations of patients with serous ovarian cancer are required to better characterize the group of patients, who get the most benefit from PET/CT examination. Identification of these patients will facilitate optimal individualization of diagnosis and treatment for each patient.

Although the role of PET/CT in the diagnosis of recurrent ovarian cancer was discussed in the literature, our study was valuable because it was prospective, the study group was homogeneous composed only from patients with serous ovarian cancer with no prior recurrence and normal CA125 levels. Additionally, the patients were observed within 6 months following the PET/CT, that increased reliability of bthe results.

CONCLUSIONS

In patients with a diagnosis of complete remission after treatment for serous ovarian cancer, even a multifocal recurrence may occur during follow up despite normal serum CA125 levels. Our results showed the usefulness of the PET/CT in detecting and differentiating malignant from benign lesions in patients with normal serum CA125 levels but inconclusive results in other imaging tests. We observed false positive results of the PET/CT in parotid gland, mesorectal adipose tissue and mediastinal lymph nodes.

Article information and declarations

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None

Ethics approval statement

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

Conflict of interest

All authors declare no conflict of interest.

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Supplementary material

None.

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