

## RECURRENCE OF BORDERLINE OVARIAN TUMORS

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**Aim:** To increase the efficiency of diagnosis and treatment of patients with recurrences of borderline ovarian tumors (BOT). **Materials and Methods:** 106 patients with BOT of stage I have been treated and clinically observed: the I group (82 patients, mean age —  $38.9 \pm 5.5$  years), who were treated with standard surgical operation (panhysterectomy); the II group (24 patients, mean age —  $30.3 \pm 5.5$  years), who underwent preserving surgery. **Results:** The main method of treatment of patients with BOT is surgical. For patients of older age effective extension is panhysterectomy with the greater omentum resection. Further chemotherapy can be applied as the second stage of complex treatment in case of confounding factor of prognosis. Preserving treatment does not aggravate the indices of the survival rate among patients with BOT, which is confirmed by results of 5- and 10-years survival rate among patients after the preserving (I group) and standard surgery (II group): 87.4 and 79.2% in the I group respectively, and 80.1 and 72.3% in the II group respectively. The frequency of recurrence is higher in cases of bilateral affection of ovaries (IB stage), collapse of a capsule prior to the surgery. Sonography is a highly informative method of diagnostics of BOT relapse with its sensitivity 83.5%, specificity — 64%, favorable prognostic possibility — 56%, unfavorable prognostic possibility — 66.4%. **Conclusion:** Additional criterion to evaluate correctness of sonographic investigation is the CA-125 level in the blood serum. In majority of cases (85%) it coincided with the sonographic results after some time. Sonography in combination with determination of CA-125 level in the blood serum is a reliable method of diagnostics of BOT. Radical cytoreductive surgery with adjuvant polychemotherapy is important for the treatment of BOT recurrence.

**Key Words:** borderline ovarian tumors, sonography, recurrence.

Borderline ovarian tumours (BOT), i.e., tumors with a potentially low level of malignancy, belong to a single category of epithelial new formations in the International Hystological Classification of WHO and make up to 8–16% in the structure of all ovarian neoplasias [1–3]. BOT during favourable course have a malignant potential — can relapse and metastasize, and the threat of tumorous process remains during 10 and more years [4, 5].

First described by Taylor in 1929, BOT are characterized by cellular stratification, architectural atypia, papillary excrescences, have not histological evidence of stromal invasion, but can be associated with peritoneal implants [6]. They account for 10–15% of ovarian epithelial tumors and frequently occur in younger women who want to preserve their reproductive function. The most common histologic type is serous, the others are mucinous, endometrial, clear cell and transitional cell tumors. The last three types are very uncommon. Approximately 65–70% of all serous and 90% of all mucinous borderline tumors are stage I by TNM classification, with extra ovarian spreading, in the form of peritoneal implants, occurring in the rest [7].

Serous borderline tumors are bilateral in about 50% of cases and in about 20% of cases with mucinous borderline tumors. Endometrioid, clear-cell and transitional cell tumors are almost always stage I, and almost exclusively unilateral. The peritoneal implants are classified as non-invasive or invasive depending on their histological structures, and in any individual patient may be purely non-invasive, invasive or a combination of both [8, 9]. Mucinous BOT are further classified into intestinal or endocervical types, according to the nature of the cell types. Microinvasion of BOT, although described, however is a controversial

subject, and it is said to be occurred in about 10% of cases, and especially in pregnant women. It is defined as a focus less than 3 mm in diameter with infiltration into the stroma by single cells, nests cells or papillae [10–13]. Although the data are derived from only small studies, it appears that microinvasion does not change the patient overall prognosis, although if it is combined with extra ovarian spreading, it may be an adverse prognostic factor [14–16].

There are no pathognomonic ultrasonographic features associated with borderline tumors. Nevertheless, ultrasonography is a priority in the diagnostic work-up, not uncommonly confirming the presence of a complex ovarian mass in one of the adnexum. CA125 is elevated by 40–50% of stage I, and >90% in patients with advanced stage serous tumour and in about 50% of patients with stage I mucinous tumors [17–18].

### MATERIALS AND METHODS

106 adult patients with BOT were included in this study. Patients were staged in the accordance with TNM classification (the 6<sup>th</sup> edition) as T1N0M0. 106 patients with BOT of stage I have received treatment and been clinically observed: 1<sup>st</sup> group (82 patients, mean age  $38.9 \pm 5.5$ ), who received standard surgical treatment (panhysterectomy), and the 2<sup>nd</sup> group (24 patients, mean age  $30.3 \pm 5.5$ ), who underwent preserving surgery. The study protocol was approved by Ethical Committee permission of National Cancer Institute (Kyiv, Ukraine).

The selection of patients with BOT for the preserving surgery was conducted by the following way: affection of one ovary (IA stage); tumor capsule was not damaged with breakage; tumor spreading on the ovarian surface was absent; tumorous cells were absent in the ascite liquid or in swabs of the abdominal cavity, pelvis, diaphragm, liver, retroperitoneal lymph nodes during urgent cytological investigation; the size of a tumor did not exceed 10 cm.

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**Abbreviations used:** BOT – borderline ovarian tumors; NMI – nuclear magnetic imaging; PET – positron emission tomography.

The method of preserving surgery is represented by the following way: after the peritoneal cavity was cut with mid-line laparotomy the organs and tissues were carefully studied, after which the surgical staging was performed, which is described above. In case the spread of the process did not find its place in parietal and visceral peritoneum as well as tumorous cells in swabs of the peritoneum were absent (diagnosed by urgent cytological investigation), we considered the stage of the disease to equal T1aN0M0. In case of only one ovary being affected, we performed unilateral removal of the uterine annexes on the affected side and biopsy of the contralateral ovary, omentum resection with urgent intrasurgical morphological investigation.

To be able to detect a relapse after the primary treatment was completed, patients were under dynamic surveillance as out-patients. Complex check-up apart from clinical examination, included sonography of the pelvic organs applying vaginal and abdominal sensors, colour Doppler mapping, determination of CA-125 tumor marker's concentration in the blood serum, and additional methods of investigation (X-Ray of the thoracic organs, CT) when they were requested.

**Statistics.** Statistical processing was performed using the parametric criteria of Student's t-test. Differences were considered statistically significant at  $p < 0.05$  (95% accuracy).

**RESULTS AND DISCUSSION**

3 patients out of 82 of the 1<sup>st</sup> group were excluded from the observation, and 79 patients have been observed during 1–16 years after the primary treatment. Out of 79 patients 16 (20.2%) had tumor progress, 10 (12.6%) patients out of whom underwent a full surgery, 6 patients (7.5%) — after the preserving surgery.

Monitoring of CA-125 after the treatment of 82 patients with BOT was conducted to 73 (89.0%), 13 (17.8%) out of whom had increased level of CA-125 and diagnosed disease relapse. Increase of marker's concentration was registered within 2–8 months before the clinical signs of the disease progress among 25.0% of cases (3 patients out of 13). Average index of CA-125 among patients with BOT relapse was high and constituted  $354.0 \pm 22.7$  unit/ml.

Relapse occurred among 16 patients at different times after the surgery: more often late — 12–14 years of observation — 7 (43.8%) patients: 1–6 years — 6 (37.6%) patients. Thus, relapse among patients with BOT during the observation occurred within the period of 1–12 years (Table).

**Table.** Frequency and term of relapse among patients with BOT (I group after the surgery)

Diagnosis	Term of relapse occurrence, years	Number of patients	
		n	%
BOT	< 1	1	6.3
	1–3	3	18.8
	3–5	3	18.8
	5–12	7	43.8
	> 12	2	12.3
Total		16	100.0

In the II group of 24 patients, who were performed preserving surgery, distant metastases occurred in 23 (95.7%). Tumor relapse after preserving surgery became known among 3 (13.0%) patients in the term

of 5–11 years. Metastases into the greater omentum were diagnosed in 1 (4.3%) patient.

Disease progress among patients of group I and II had manifestations of severe dissemination in the peritoneum. It has to be noted the aggressiveness of the disease among patients with serous BOT, more greater number of relapse within 5 years after the primary treatment, and more often among patients with bilateral ovarian affection, rather than among patients with mucinous BOT. Progression of the main process by local regional recurrence was determined in 4 (25%) patients, dissemination on the abdomen complicated by polyserositis — in 6 (37.5%) of 16 patients of group I. At mucinous BOT the most frequent sign of tumor progression was the development of pseudomyxoma.

Loco-regional relapse in the greater omentum was diagnosed in 2 out of 6 patients, who did not undergo omentectomy during the primary treatment. 1 patient after the conventional surgery with omentectomy had metastases in the residual limb of the greater omentum.

Local relapse of BOT after standard surgery (bilateral adnexectomy with the uterus removal and the greater omentum resection) appear in the region of the pelvis affecting adjacent organs. After the preserving surgery (unilateral adnexectomy, ovary resection) a tumor has grown primarily in the remaining tissue of the operated ovary with its further spread to the uterus and adjacent tissues.

To identify sonographic criteria of treatment's efficiency among patients with BOT there was conducted a retrospective analysis of sonographic data of the peritoneal space and pelvis among the women, who have been treated or consulted for BOT in National Cancer Institute from 2000 to 2012.

It was detected that the increase of CA-125 level in the blood serum was correlated with sonographic results and each of mentioned indices separately confirmed disease recurrence in 77% of patients with BOT. In 11.1% of patients CA-125 level primarily increase from 36 to 100 units/ml without any sonographic signs of the relapse was observed. Moreover, in 7.6% of patients CA-125 level was below to be detected and did not increase within the normal range, but the sonography detected signs of BOT recurrence 2–4 months before the CA-125 increase (more than 33 units/ml). At primary treatment CA-125 level among these patients was higher.

Sonographic signs of BOT recurrence were tumor nodes from 0.5 to 1.5 cm in diameter with fine-grained or "spongy" solid structure, round or irregular shape which were localized in vesicouterine fold or above the cervical stump or in lateral canals.

Tumors of more than 2 cm had solid or cystic-solid structure. It must be mentioned that tumor recurrence had distinct borders in most cases (81.6%) and lumpy, uneven (8.4%). Tumors of more than 1.5 cm had solid or cystic-solid structure (Fig. 1 a–c).

Clinic-ultrasound correlation has identified that tumour size evaluated by laparotomy, in general coincided with the sonographic reports (83.5%). The difference ranged within millimeters. During some observations the size of tumors was mistakenly announced bigger with the sonography (1–6 cm). The ground of sonographic and gyn-

aecological checkup mistakes were mostly caused by the frank adhesive process — intestinal loops grown together with the tumor — which were identified as a single node.

Sonographic evaluation of the state of anatomical structures and functional changes due to the characteristic reactions to the tumorous process lead to improvement of the diagnostics of topographic relations between the tumour and adjacent tissues and organs.

Deformation of the urinary bladder's wall and pyelectasis were considered as a signs of uterine-bladder ligament tumors infiltration and probable invasive growth into the urinary bladder, which was confirmed in 3 patients while the secondary cytoreductive intervention. Pyelectasia was the first indirect sign of metastatic affection of ileac lymph nodes.

Having collated the sonographic reports with intra-surgical and morphological ones the following signs were proclaimed for the operability of patients with BOT recurrence: one or more tumorous nodes mostly of solid structure with distinct borders, regular shape, signs of partial or complete mobility, located in the pelvis or in the retroperitoneum; the absence of distant metastasis of BTO in liver, spleen, retroperitoneal lymph nodes.

The signs of visual multiple metastases along the parietal and visceral space and the diaphragm, spread tumorous affection on the pelvic region, deformation of urinary bladder's walls, frank adhesive process, referred to impossibility of surgical intervention to be conducted.

Received data proved that sonography is a highly informative method of diagnostics for BOT relapse with its sensitivity of 83.5%, specificity of 64%, favourable prognostic accuracy 56%, unfavourable prognostic possibility 66.4%.

Summarizing the results of clinicosonographic correlation, it is important to emphasize that such an investigation expands our insight about sonography for the diagnostics of BOT recurrence. The acquired parallel data explains to a full extent variability of the sonographic picture, which hinges on histological structure of an ovarian tumor, allows analyzing a possibility of tumor invasion in other organs.

On the grounds of the correlated reports of the ultrasound investigation with intrasurgical and morphological results it is possible to distinguish main signs of operability of patients with BOT relapse: recidive tumor of solid or cystic-solid structure, mobile with vivid lumpy border; no multiple distant metastases.

An additional evaluation criterion of correct sonographic conclusion for tumors with positive markers

is CA-125 in the blood serum. In the most observations (85%) after some time it coincided with sonographic reports.

Thus, sonography in combination of CA-125 level in the blood serum is a reliable method of diagnostics for patients with BOT. Also, it must be emphasized that sonography is remained the only generally available method, that allows to control the efficiency of therapy and to correct the treatment in the group of patients with tumors and negative markers.

Among all BOT patients with recurrence after a conventional surgery, 8 patients have been undergone to surgical treatment. The terms of the surgery are from 7 months to 3 years. The following surgical interventions were conducted: removal of the recidivating tumor located in the pelvis (5), eliminating of obstruction which arose due to general tumor growth (1), mucinous liquid evacuation from the peritoneum at pseudomyxoma of the peritoneum (2), in addition 1 patient was operated twice (Fig. 2 a–c).

Among all patients who underwent the preserving surgery on the first stage of treatment 3 patients with the disease relapse had secondary laparotomy and panhysterectomy with the resection of greater omentum. In all patients who underwent cytoreductive operations BOT were confirmed histologically. All the patients after the detected BOT progression had 3–6 cycles of polychemotherapy after the surgery according to the PC system (cysplatin 75 mg/m<sup>2</sup> + cyclophosphan 600 mg/m<sup>2</sup> intravenously/intracutaneously within 3 weeks). Therefore organ preserving treatment doesn't affect the long-term results in patients with BTO of stage I. It was confirmed by the results of 5- and 10-years survival rate: in group of patients who underwent standard operation it equaled to 92.7 and 83.2% and in case of organ preserving treatment — 98.2 and 91.4%, respectively.

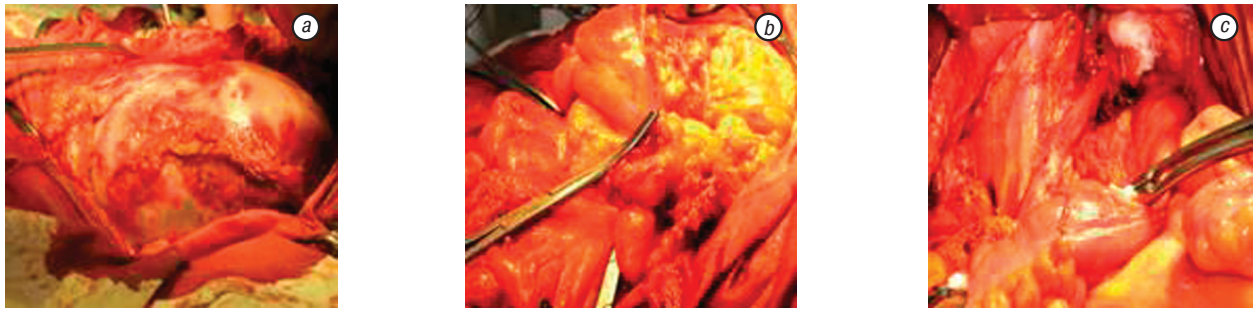
Therefore, the main method of treatments for BOT patients is surgical one. For patients of older age group effective expansion is panhysterectomy with the greater omentum resection. Further chemotherapy will be applied as the second stage of combined treatment in case of confounding factor of prognosis. High survival rate among young patients at early stages of BOT (47.6% patients of the reproductive period) confirms the necessity of active implementation of preserving surgery.

According to the results of investigation one of the most important factor of BOT recurrence is insufficient



**Fig. 1.** Sonography of the BOT relapse: *a* — seedy cystic structure of the round shape; *b* — multi-chamber cystic structure of irregular shape; *c* — “sponge” solid structure of irregular shape





**Fig. 2.** Secondary surgical treatment of a patient with recurrence of BOT: *a* — before the tumor removal; *b* — after the tumor removal; *c* — surgical intervention is completed

expansion of the surgical treatment. In the treatment of BOT recurrence main importance is given to surgical intervention for radical cytoreductive surgery, which further will be complemented with adjuvant polychemotherapy.

During the dynamic observation of patients with BOT after the surgery the determination of CA-125 level in the blood serum demonstrates a great clinical relevance for the control of disease progression.

It was studied the dynamics of tumor marker CA-125 and sonography for conservative treatment of patients with BOT relapse. As for the information content these methods are not inferior to others and are available for a great group of patients. Sonography being in demand is caused by the fact that palpatory data for the evaluation of conducted treatment's efficiency is subjective, but the endoscopic or X-ray investigation is linked to radioactive burden and certain risk for complications, which prohibits the application of this method often. Such high-tech methods as magnetic resonance tomography and positron emission tomography have high informational content but characterized by high cost.

An additional criterion to assess the correctness of sonographic conclusion at marker positive tumors is CA-125 level in the blood serum. In majority of cases (85%) it coincides with the sonography investigation. Therefore, sonography in combination with determination of tumour marker CA-125 in the blood serum is a reliable method of diagnostics for patients with recurrence of BOT.

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