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**BORDERLINE OVARIAN TUMORS, OPTIMIZATION OF  
DIAGNOSTIC AND TREATMENT METHODS**

**321.20 – ONCOLOGY AND RADIOTHERAPY**

**Summary of PhD thesis in medical sciences**

**Chişinău, 2025**

The thesis was developed within the Department of Oncology of the State University of Medicine and Pharmacy "Nicolae Testemițanu" and IMSP Oncological Institute.

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The defense will take place on 04.06.2025 at 15.00 in the premises of the "Nicolae Testemițanu" USMF, 165 Ștefan cel Mare și Sfânt blvd., office 205 in the meeting of the Committee for the public defense of the doctoral thesis, approved by the decision of the Scientific Council of the Consortium of 10.04.2025 (minutes no. 57).

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## CONCEPTUAL MARKINGS OF THE RESEARCH

**Actuality and importance of the problem addressed.** Borderline ovarian tumors (BTOs) represent a distinct group of heterogeneous lesions, characterized by atypical epithelial proliferation, nuclear atypia and multilayered epithelium, without an infiltrative pattern or stromal invasion [1].

These diseases are a less frequent but not rare clinical entity, constituting about 10-20% of ovarian epithelial tumors, with an incidence of about 1.8-4.8 cases per 100,000 women annually. TOBs are lesions intermediate between benign ovarian cystadenomas and invasive carcinomas, usually diagnosed in young women of reproductive age (in about 34% of cases under the age of 40). They have a generally better prognosis than malignant ovarian tumors and most are curable with surgery. The average age of onset of BOD is approximately 10 years younger than that of women with ovarian cancer [2].

About 70-80% of TOBs are in stage I at the time of diagnosis. A diagnosis of TOB in stages II and III is rare (30%) and exceptional in stage IV. The condition has a good long-term prognosis with 5-year survival rates of 95-100%. For stage II, III and IV the 5-year survival is respectively 66-96%, 68-86% and 50% [3].

From a histological point of view, TOBs are divided into the following subtypes: serous, mucinous, endometrioid, clear cell or transitional cell (Brenner) [10]. For a good differentiation of the histological subtype and for the assessment of tumor aggressiveness, it is necessary to perform immunohistochemical tests, which monitor the expression of markers of proliferation and aggressiveness (p53, Ki67, ER, PR) [1]. Cancer antigen 125 (CA-125) is the most useful tumor marker available in the diagnosis of advanced stage TOB cases [12].

Despite the fact that therapeutic behavior is adopted depending on the staging of the disease and the need to preserve ovarian function and reproductive potential, the management and optimal surgical staging of TOB are controversial [1, 3]. Different surgical approaches are applied in different institutions for the treatment of these diseases. Some surgeons prefer full surgical staging for early detection of subclinical extraovarian implants: cytology after peritoneal lavage, infracolic omentectomy, omental biopsies, random peritoneal biopsies, appendectomy, palpation of pelvic and para-aortic lymph nodes. Other surgeons do not perform a staging procedure for TOB or exclude the lymph nodes from this procedure. Surgical staging is a crucial point to determine the exact stage of the disease and the standard criterion for the selection of surgical treatment of TOB, but also to estimate the risk of recurrence and survival [3, 9].

Although complete surgical resection of the tumor is the best curative method for TOB, there are no clear answers regarding the volume of surgery, the surgical approach, the need to preserve fertility in the treatment of a young woman, the use of laparoscopic surgery, the use of postoperative chemotherapy and infertility treatments [7].

Several scholars have suggested that patients with ODB can be safely treated with conservative surgery—a well-established and available strategy for young ODB patients who wish to preserve fertility, with excellent reproductive outcomes and long-term survival [4, 8]. Advanced (II-III) serous TOB can also be safely selected for fertility preservation management. Despite the high recurrence rate, fertility preservation offers a high chance of reproductive success without a negative impact on overall survival [6].

Based on the literature review, the use of chemotherapy as adjuvant treatment for TOB remains controversial [13]. Postoperative adjuvant chemotherapy or radiotherapy does not reduce the recurrence rate or improve survival in both early and advanced stages of the disease with

residual tumor masses or lymph node involvement. Thus, the adverse effects of postoperative chemotherapy, radiotherapy and hormonal therapy outweigh the benefits and are not recommended for patients with TOB [13,14]. The authors of a systematic literature review and meta-analysis also found no evidence to support adjuvant platinum-based chemotherapy for TOB, including TOB with invasive implants [11].

Therefore, TOBs are a heterogeneous group of tumors commonly seen in younger women and diagnosed after primary surgery for a presumed benign lesion. Careful inspection of the abdominal and pelvic cavities should be performed for proper and complete staging for removal of the lesion. Complete surgical staging is the cornerstone of management, but conservative surgery is an acceptable alternative for those patients who wish to preserve fertility. However, the role of long-term surveillance is controversial [15].

Thus, according to the scientists' opinion, the main opportunities for future research in the clinical management of TOB are: improving preoperative and intraoperative diagnostic methods, determining the risks associated with conservative treatment, the role of laparoscopic surgery in the removal of complex cysts, the effectiveness of postoperative adjuvant treatment, the development of optimal, standardized algorithms of diagnosis, treatment and surveillance, determination of more accurate reproducible criteria to distinguish benign cystadenomas, borderline tumors and malignant carcinomas [4].

**The aim** of the scientific study: Analysis of diagnostic and treatment methods (surgical and chemotherapeutic) applied to patients with borderline ovarian tumors, depending on age and clinical-morphological factors, in order to optimize the diagnosis and increase therapeutic efficiency.

To achieve the goal, the following research objectives were stipulated:

1. Clinical, paraclinical study and intraoperative macroscopic assessment of patients with borderline ovarian tumors.
2. Study of morphological, immunohistochemical criteria in differentiating borderline ovarian tumors from benign ovarian tumors and ovarian cancer.
3. Assessment of indications for radical and conservative surgical treatment according to the patient's age and stage of the tumor process.
4. Evaluation of indications for chemotherapeutic treatment according to the stage of the tumor process.
5. Development of the diagnostic and treatment algorithm for borderline ovarian tumors.

**Scientific research methodology.** Clinical cohort study, retrospective, prospective and controlled, carried out in the departments of Gynecology and Medical Oncology no. 1, 2 and 3 of IMSP IO from Moldova, between January 2010 and August 2024. The study was approved by the Ethics Committee of USMF "Nicolae Testemițanu" (no. 12/14.11.2016). The study was based on the evaluation of clinical, anamnestic, morphopathological, immunohistochemical and imaging characteristics in patients with TOB depending on the treatment administered (surgical treatment with or without chemotherapy). Patient data were coded in specially developed data sheets (questionnaires) for statistical processing.

**The scientific novelty of the work.** Based on a complex study, for the first time, there were:

- establish the risk factors in patients with TOB in different periods of life, the reproductive period or menopause;

- determined the particularities of clinical evolution, preoperative and intraoperative diagnostic methods;
- determined the morphopathological and immunohistochemical characteristics;
- appreciated the indications and contraindications, the advantages and disadvantages of the volume of radical or conservative surgical interventions (with preservation of the reproductive function);
- determined the risks associated with conservative treatment in young patients;
- evaluated chemotherapeutic treatment depending on the morphopathological result and tumor stage;
- estimated survival of TOB patients depending on the histological type (serous or mucinous), tumor stage, type of surgical treatment (conservative or radical) or combined (surgical or chemotherapy).

**The important scientific problem** solved in the paper consists in the optimization of diagnostic and treatment methods (surgical and chemotherapeutic) in patients with borderline ovarian tumors.

**The theoretical significance of the work** consists in the assessment of risk factors, contemporary methods in diagnosis, surgical treatment, chemotherapeutic and complex treatment (surgical and chemotherapeutic) in patients with serous and mucinous TOB in the reproductive and menopausal period.

**The applicative value of the work.** The results of the work aim at: the assessment of clinical features, preoperative and intraoperative diagnostic methods; assessment of radical or conservative surgical treatment (with preservation of reproductive function) depending on the patient's age, tumor stage and histological form; the need to administer chemotherapy depending on the stage of the tumor process, the morphopathological result and the presence of invasive implants.

**Implementation of scientific results.** Based on the results of the study, a management algorithm for patients with TOB was developed, which will determine the application of conservative and radical surgical treatment depending on the reproductive age, the administration of chemotherapy treatment depending on the tumor stage and the histological type of the disease.

**Approval of thesis results.** The results of the study were presented and discussed in the following national or international scientific forums,

The study was approved by the Ethics Committee of the USMF "Nicolae Testemițanu" (no. 12/14.11.2016).

The results of the thesis were approved in the Meeting of the Oncology Department of the IP USMF Nicolae Testemițanu of 22.09.2024 (minutes no. 5) and in the Meeting of the Scientific Seminar of the profile: 321. General Medicine / Specialty: 321.10. Hematology and hemotransfusion, 321.20 Oncology and radiotherapy of 23.12.2024 (minutes no. 19).

**Publications on the topic of the thesis.** Author and co-author of more than 32 scientific papers. In the base thesis, 22 scientific papers were published, including 3 single-author articles, 15 articles and 7 national and international theses abroad, 1 national clinical protocol, 1 innovation certificate and an innovator certificate.

**Summary of the sections of the thesis.** The work is presented on 129 pages of text, consists of annotations in Romanian, Russian and English, introduction, 4 chapters, general conclusions, practical recommendations, bibliographic index with 180 references, statement

regarding the assumption of responsibility and the author's CV. The illustrative material includes 33 figures, 2 tables, 1 statistical formula and 4 annexes.

**Key words:** borderline ovarian tumor, radical surgical treatment, conservative surgical treatment, chemotherapy treatment, invasive implants, non-invasive implants, prognosis, recurrence, survival. Sumarul compartimentelor tezei.

## **THESIS CONTENT**

**INTRODUCTION** the topicality and scientific-practical importance of the addressed problem are argued, the aim and objectives of the study are formulated, the scientific innovation of the results obtained, the theoretical significance and applied value of the work and the approval of the results.

According to the opinion of the scientists, the main opportunities for future research in the clinical management of TOB are: improving preoperative and intraoperative diagnostic methods, determining the risks associated with conservative treatment, the role of laparoscopic surgery in the removal of complex cysts, the effectiveness of postoperative adjuvant treatment, the development of optimal diagnostic algorithms, treatment and standardized surveillance, determination of more accurate reproducible criteria to distinguish benign cystadenomas, borderline tumors and malignant carcinomas.

The important scientific problem solved in the paper consists in the optimization of diagnostic and treatment methods (surgical and chemotherapeutic) in patients with borderline ovarian tumors.

### **CHAPTER I**

#### **CONTEMPORARY ASPECTS OF DIAGNOSIS AND TREATMENT OF PATIENTS WITH BORDERLINE OVARIAN TUMORS**

This chapter reports the contemporary information from the specialized literature with reference to borderline ovarian tumors. The epidemiological peculiarities, risk factors, classification, diagnosis, treatment methods, prognosis and prophylaxis of borderline ovarian tumors are elucidated.

TOBs are a heterogeneous group of tumors commonly seen in younger women and diagnosed after primary surgery for a presumed benign lesion. Careful inspection of the abdominal and pelvic cavities should be performed for proper and complete staging for removal of the lesion. Complete surgical staging is the cornerstone of management, but conservative surgery is an acceptable alternative for those patients who wish to preserve fertility. OBTs have a generally better prognosis than malignant ovarian tumors and most are curable with surgery. However, the role of long-term surveillance is controversial.

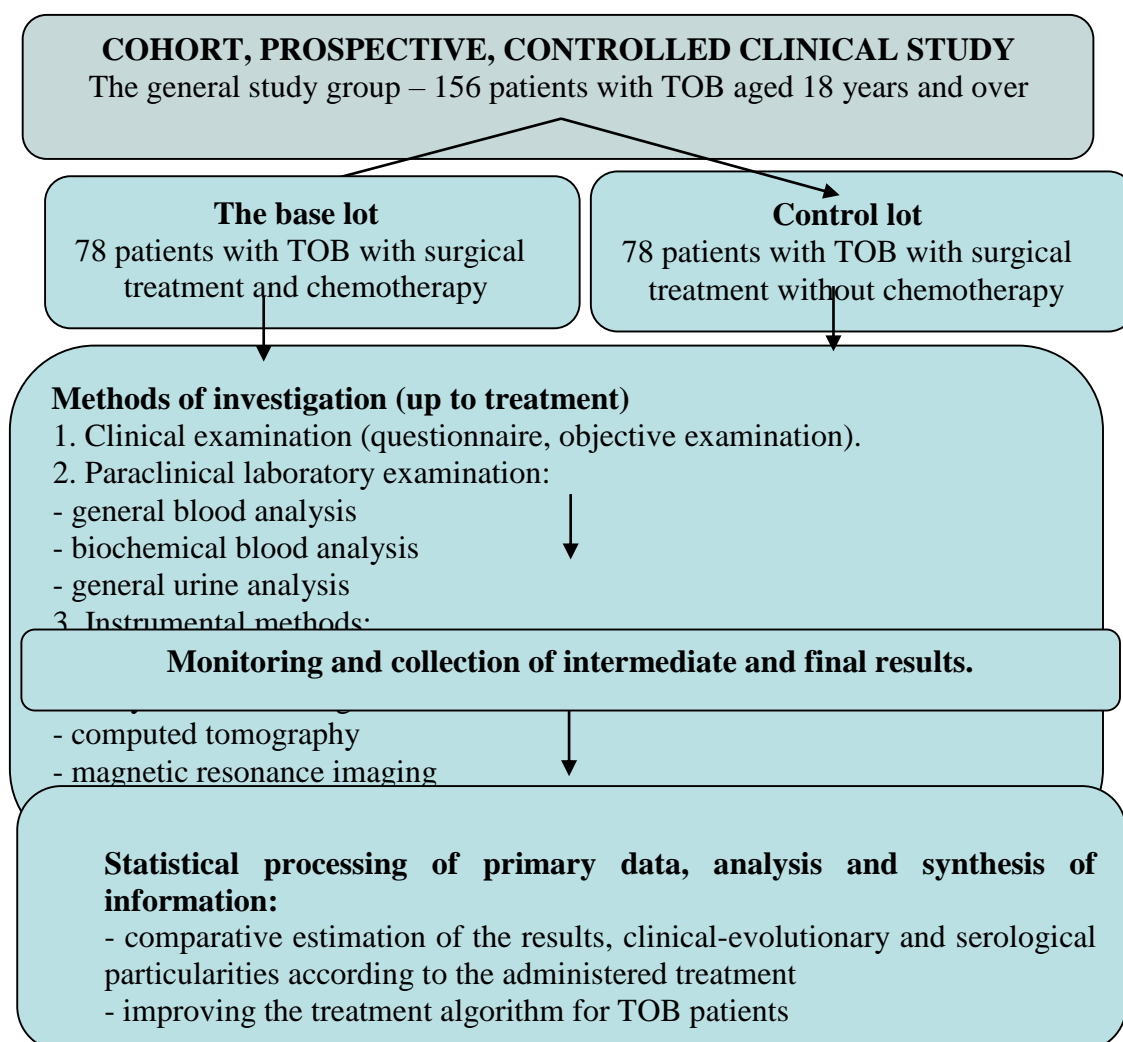
### **CHAPTER II**

#### **MATERIALS AND RESEARCH METHODS**

In this chapter, the general research methodology, the general characteristic and the methods of examining the study groups, the methods of statistical processing of the obtained data are described. The stages of research, the investigation methods used, the diagnostic criteria and the principles of application of paraclinical methods (ultrasonography, computed tomography, laparoscopy, histological examination of the tumor), the characteristics of the applied surgical and

chemotherapy methods are presented. The statistical processing methods of the obtained data are described in detail.

156 patients with TOB were included in the study. The overall study sample was divided into 2 groups: 78 patients with TOB with surgical treatment and chemotherapy (base group – LB) and 78 patients with TOB with surgical treatment without chemotherapy (control group – LM).



The primary study materials were entered into an electronic database and processed on a personal computer using the functions and modules of the Statistical Package for the Social Science (SPSS) software, version 16.0 for Windows (SPSS Inc., Belmont, CA, USA, 2008) and Microsoft Excel 2019 through descriptive and inferential statistical procedures. We used the  $\chi^2$  method after Pearson,  $\chi^2$  with Yates' correction or Fisher's exact method for comparing discrete variables; independent samples "t" test (for interval-scaled variables with normal distribution of values) or non-parametric statistical tests (for ordinal-scaled or interval-scaled variables with nonnormal distribution of values) to determine the statistical difference of values means between groups; univariate analysis of variance with application of post hoc analysis tests for testing multiple differences between mean values in study groups; correlation analysis to determine the relationship between variables, its strength and direction.

### CHAPTER III



## OPTIMIZING THE TREATMENT METHODS OF BORDERLINE OVARIAN TUMORS

This chapter found that the management of borderline ovarian tumor, primarily primary surgery (conservative or radical), is personalized and depends on the age of the woman, the size of the ovarian mass, the type and stage of the disease, reproductive desires, the extent and nature of the peritoneal implants (invasive or non-invasive). The researches were carried out in the Department of Oncology of IP USMF Nicolae Testemițanu and in the sections of Gynecology and Medical Oncology of IMSP IO.

### 3.1. Clinical-paraclinical peculiarities of patients with borderline ovarian tumors treated with surgery and chemotherapy

**Socio-demographic and anamnestic data.** 78 patients with TOB, hospitalized in IMSP IO between January 2015 and August 2024, treated surgically and with chemotherapy, with an average age of  $44.44 \pm 13.1$  years (from 18 years to at 73 years old).

Depending on the age group, 16 (20.5%) patients were between 18-30 years old, 37 (47.4%) - between 31-50 years old and 25 (32.1%) were >50 years (figure 2). More than  $\frac{1}{2}$  (41 - 52.6%) of the patients were from the urban environment and 37 (47.4%) - from the rural environment.

More than  $\frac{3}{4}$  of the patients with TOB (59 - 75.6%) from LB did not mention exposure to harmful factors, 7 (9.0%) indicated smoking, 4 (5.1%) - alcohol consumption, 3 (3.8%) - administration of combined oral contraceptives, 5 (6.4%) – alcohol consumption and smoking.

In 24 (30.8%) patients with TOB from LB, concurrent comorbidities were absent. 25 (32.1%) women recorded cardiovascular diseases in the antecedents, endocrine diseases – 36 (46.2%), benign uterine tumors – 22 (28.2%) and sexually transmitted diseases – 2 (2.6%) patients. It is important to note that 21 (26.9%) patients with TOB have 2 and 5 (6.4%) – 3 concurrent comorbidities. Heredocollateral antecedents of oncological diseases were mentioned by 27 (34.6%) patients.

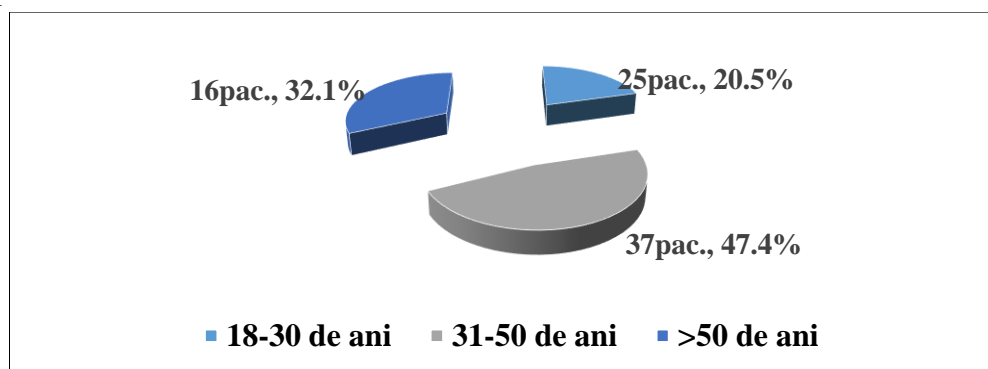


Figure 2. Distribution of patients with TOB from the base group depending on the age group.

**Previous obstetric status.** Regular menstrual cycle indicated 26 (33.3%), irregular menstrual cycle – 26 (33.3%) and menopause – 26 (33.4%) patients with TOB from LB.

Previous births were indicated by 51 (65.4%) women, 15 (19.4%) patients with 1 birth each, 25 (49.0%) patients with 2 births each, 6 (11.8%) patients with 3 births each, 4 (7.8%) 4 births each and 1 (2.0%) patient 5 births. The mean number of births was  $2.04 \pm 1.0$  births (from 1 birth to 5 births).

30 (38.5%) women mentioned previous abortions, 11 (36.7%) patients had 1 abortion, 14 (46.7%) patients had 2 abortions, 2 (6.7%) patients had 3 abortions and 3 (10.0%) patients with 4 abortions each. The mean value of abortions was  $1.90 \pm 0.9$  abortions (from 1 abortion to 4 abortions).

**Subjective and objective clinical data.** Patients with TOB from LB accused the impairment of the general condition in 65 (83.3%) cases, pain syndrome of the small pelvis in 69 (88.5%) cases, palpable tumor mass in the small pelvis in 62 (79.5%) of cases, chronic constipation in 30 (38.5%) cases, dyspeptic disorders (nausea, vomiting) in 21 (26.9%) cases, irregularities of the menstrual cycle in 27 (34.6%) cases.

During the objective examination, the following were found: enlarged abdomen in 60 (76.9%) patients, abnormally developed external genital organs in 6 (7.7%) patients, uterus removed in history in 4 (5.1%) patients, enlarged uterus on palpation in 29 (37.2%) patients, normal uterus on palpation in 45 (57.7%) patients. The enlarged uterus on palpation had an average size of  $9.55 \pm 2.0$  weeks of gestation (from 6 to 12 weeks of gestation).

Depending on the location, on palpation the ovarian tumor was on the right in 18 (23.1%) patients, on the left – in 16 (20.5%) patients, bilaterally – in 39 (50.0%) patients and not could be assessed in 5 (6.4%) patients. On palpation, the ovarian tumor was mobile in 61 (78.2%) cases, immobile in 17 (21.8%) cases, tender in 71 (91.0%) cases, hard in 53 (67.9 %) cases and of hard-elastic consistency in 25 (32.1%) cases.

**Immunological and immunohistochemical data.** Cancer antigen CA-125 had a mean value of  $181.227 \pm 212.4$  U/mL, was within normal limits in 23 (29.5%) patients and increased in 55 (70.5%) patients. CA19-9 carbohydrate antigen had a mean value of  $55.98 \pm 73.7$  U/mL, was within normal limits in 49 (62.8%) patients and increased in 29 (37.2%) patients. The CEA carcino-embryonic antigen had a mean value of  $6.09 \pm 18.23$  U/mL, was within normal limits in 63 (80.8%) patients and increased in 15 (19.2%) patients.

Immunohistochemical investigations were performed in 7 (9.0%) patients. Including, estrogen receptors were positive in 6 (85.7%) cases, progesterone receptors – in 7 (100.0%) cases, tumor suppressor p53 – in 5 (71.4%) cases and proliferation index Ki -67 – in all 7 (100.0%) cases with an average value of  $12.9 \pm 8.3\%$  (from 1% to 25%).

Therefore, 78 patients with TOB aged 18-73 years (mean age  $44.44 \pm 13.1$  years) were included in LB, including 20.5% patients aged between 18-30 years, 47.4% - aged between 31-50 years and 32.1% - over 50 years old. Cancer antigen CA-125

it was elevated in 70.5% of patients, the carbohydrate antigen CA19-9 – in 37.2% of patients and the carcino-embryonic antigen CEA – in 19.2% of patients. Immunohistochemical investigations were performed in 9.0% of patients. Estrogen receptors were positive in 85.7% of cases, progesterone receptors – in 100.0% of cases, tumor suppressor p53 – in 71.4% of cases and proliferation index Ki-67 – in 100.0% of cases.

**The intraoperative appearance of the tumor.** Depending on the location, in LB patients, TOB was located on the right ovary in 21 (26.9%) patients, on the left ovary – in 16 (20.5%) patients and bilaterally – in 41 (52.6%) of patients. The size of the ovarian formation was  $\leq 4$  cm in 3 (3.8%) cases, within 5-10 cm – in 45 (57.7%) cases and  $\geq 11$  cm in 30 (38.5%). The mean value of TOB size was  $13.67 \pm 10.1$  cm (from 4.0 cm to 50.0 cm).

Intraoperative rupture of the tumor was found in 25 (32.1%) patients, damage to the omentum – in 20 (25.6%) patients and damage to the lymph nodes – in 3 (3.8%) patients.

The appearance of the cyst content was serous in 38 (48.7%) patients, mucinous - in 21 (26.9%) patients, endometriotic - in 7 (9.0%) patients, serous-mucinous - in 4 (5, 1%) patients, serous-endometriosis – in 7 (9.0%) patients and mucinous-endometriosis – in 1 (1.3%) patient.

Vegetation on the surface of the tumor was missing in 3 (3.8%) patients, was identified on the external surface of the tumor in 3 (3.8%) patients, on the internal surface of the tumor in 48 (61.5%) patients, on the surface external and internal tumor in 24 (30.8%) patients.

The involvement of the peritoneum was absent in 50 (64.1%) patients and was affected in 28 (35.9%) patients, including parietal lesions were identified in 14 (17.9%) cases, visceral lesions in 3 (3, 8%) cases, parietal and visceral lesions in 11 (14.1%) cases.

Abdominal free fluid was absent in 48 (61.5%) patients, it was revealed in a volume below 500 ml in 14 (17.9%) cases, within the limits of 500-5000 ml in 11 (14.1%) cases and >5000 ml in 5 (6.4%) cases. The appearance of the free abdominal fluid was serous in 23 (76.7%) patients and mucinous – in 7 (23.3%) patients.

In our study we diagnosed the following histological forms of TOB: serous in 51 (65.4%) cases, mucinous in 24 (30.8%) cases and mixed (sero-mucinous) in 3 (3.8%) cases (figure 3.).

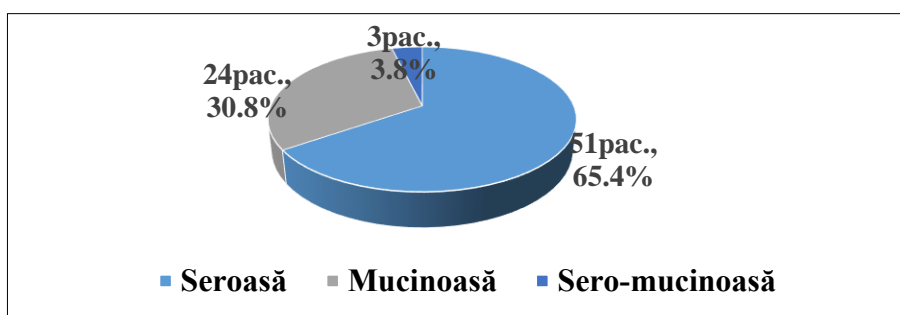


Figure 3. Distribution of patients from the base group by function of the histological form of TOB

According to tumor stage and TNM, patients with TOB in our study were classified as follows: stage IA T1aNoMo 4 (5.1%) cases, stage IB T1bNoMo 27 (34.6%) cases, stage IC T1cNoMo 3 (3.8%) cases, stage IIA T2aNoMo 9 (11.5%) cases, stage IIB T2bNoMo 10 (12.8%) cases, stage IIIA T3aNoMo 9 (11.5%) cases, stage IIIB T3bNoMo 1 (1.3%) cases and stage IIIC T3cNoMo 15 (19.2%) cases (figure 4).

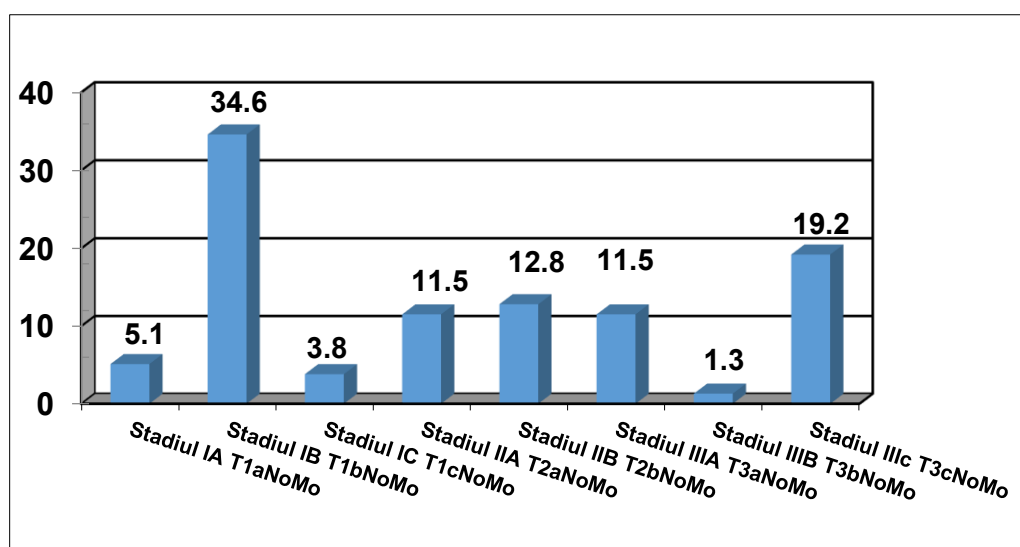


Figure 4. Distribution of patients from the base group according to function

### **by tumor stage and TNM (%).**

So, in our study we diagnosed the following histological forms of TOB: serous in 65.4% cases, mucinous in 30.8% cases and mixed (sero-mucinous) in 3.8% cases. The tumor was located on the right ovary in 26.9% of patients, on the left ovary - in 20.5% of patients and bilaterally - in 52.6% of patients. The average value of the TOB size was  $13.67 \pm 10.1$  cm (from 4.0 cm to 50.0 cm), including  $\leq 4$  cm in 3.8% of cases, within the limits of 5-10 cm – in 57.7% cases and  $\geq 11$  cm in 38.5%. Vegetation on the surface of the tumor was found in 96.2% of patients, damage to the peritoneum - in 35.9% of patients, free abdominal fluid - in 38.5% of patients.

**Treatment.** In the vast majority of cases (75 – 96.2%) the surgical intervention was performed through a laparotomy approach and only in 3 (3.8%) cases the laparoscopic approach was used. Conservative surgical treatment was applied to 16 (20.5%) patients with TOB and radical surgical treatment to 62 (79.5%) patients.

Among all cases of conservative surgical treatment, unilateral ovarian cystectomy was performed in 3 (3.8%) women, bilateral ovarian cystectomy in 1 (1.3%) women, ovarian cystectomy with omentectomy in 4 (5.1%) women, in 1 (1.3%) women ovarian cystectomy with omentectomy and appendectomy, in 3 (3.8%) women unilateral adnexectomy with omentectomy and in 3 (3.8%) women unilateral adnexectomy with omentectomy and appendectomy.

Among all cases of radical surgical treatment, 2 (2.6%) patients – total hysterectomy with bilateral adnexectomy, 45 (57.7%) patients – total hysterectomy with bilateral adnexectomy and omentectomy and 14 (17.9%) patients – total hysterectomy with bilateral adnexectomy, omentectomy and appendectomy. Among 4 patients with TOB who underwent a history of total hysterectomy, 3 (3.8%) women underwent bilateral adnexectomy with omentectomy and 1 (1.3%) woman underwent bilateral adnexectomy with omentectomy and appendectomy.

Peritoneal biopsy was performed in 18 (23.1%) patients with TOB. Among the LB patients, 44 (28.2%) administered 3 chemotherapy courses, 19 (12.2%) – 4 courses, 14 (9.0%) 6 courses and in one case 8 courses.

More than half of the patients (43 – 55.1%) administered the Cisplatin+Cyclophosphane CP regimen, about 1/3 of the patients (25 – 32.1%) – the Cisplatin+Cyclophosphane+Adriamycin CAP regimen, 8 (10.3%) patients – Carboplatin+paclitaxel scheme and 2 (2.6%) patients – CMF scheme Cisplatin methotrexate+Cyclophosphamide.

Therefore, conservative surgical treatment was applied to 20.5% of patients with TOB from LB and radical surgical treatment – to 79.5% of patients. Among the LB patients, 28.2% administered 3 chemotherapy courses, 12.2% – 4 courses, 9.0% – 6 courses and in one case 8 courses.

In the patients from the LB study group, over the 5-year period, 71 patients (91.02%) showed no signs of borderline ovarian tumor recurrence, the presence of recurrences was determined in 7 patients (8.98%).

### **3.2 Clinical-paraclinical characteristics of patients with borderline ovarian tumors treated surgically, without adjuvant treatment**

**Socio-demographic and anamnestic data.** 78 patients were included in the LM in the study

with TOB, hospitalized in IMSP IO between January 2015 and August 2024, treated only surgically, without chemotherapy, with an average age of  $48.58 \pm 16.4$  years (from 19 years to 80 years).

Depending on the age group, 14 (17.9%) patients were between 18-30 years old, 30 (38.5%) – between 31-50 years and 34 (43.6%) were >50 years old (figure 4). More than ½ (44 - 56.4%) of the patients were from the urban environment and 34 (43.6%) - from the rural environment.

More than 4/5 of patients with TOB (70 – 89.7%) from LM did not mention exposure to factors harmful, 2 (2.6%) indicated smoking, 3 (3.8%) – alcohol consumption, 1 (1.3%) – administration of combined oral contraceptives, 2 (2.6%) – alcohol consumption and smoking

In 29 (37.2%) patients with TOB from LM, concomitant comorbidities were absent. Diseases 33 (42.3%) women recorded cardiovascular diseases in the antecedents, endocrine diseases – 35 (44.9%) and benign uterine tumors – 18 (23.1%) patients. It is important to note that 19 (24.4%) patients with TOB have 2 and 9 (11.5%) – 3 concurrent comorbidities. Heredocollateral antecedents of oncological diseases were mentioned by 16 (20.5%) patients.

**Previous obstetric status.** 26 (33.3%) indicated a regular menstrual cycle irregular menstruation – 15 (19.3%) and menopause – 37 (47.4%) patients with TOB from LB.

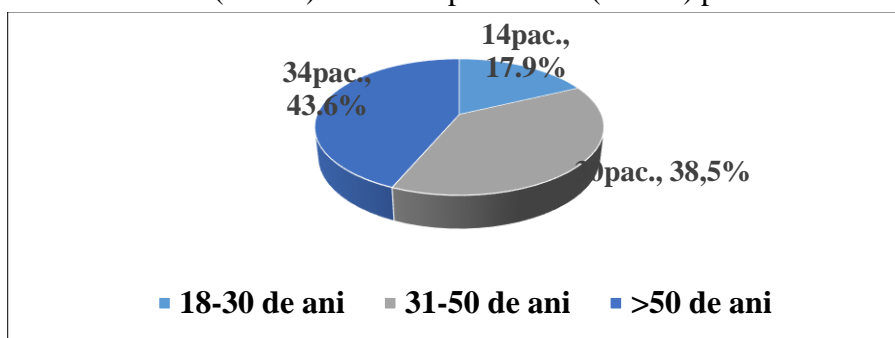


Figure 5. Distribution of patients with TOB from the control group depending on the age group.

62 (79.5%) women indicated previous births, 13 (21.0%) patients had 1 birth each, 32 (51.6%) patients with 2 births each, 9 (14.5%) patients with 3 births each, 7 (11.3%) with 4 births each and 1 (1.6%) patient with 5 births. The mean number of births was  $2.21 \pm 1.0$  births (from 1 birth to 5 births).

Abortions in the past were mentioned by 41 (52.6%) women, 12 (29.3%) patients each 1 abortion, 17 (41.5%) patients 2 abortions each, 6 (14.6%) patients 3 abortions each, 5 (12.2%) patients 4 abortions each and 1 (2.4%) patient 5 abortions. The mean value of abortions was  $2.17 \pm 1.1$  abortions (from 1 abortion to 5 abortions).

**Subjective and objective clinical data.** The patients with TOB in LM accused the impairment of the condition general in 44 (56.4%) cases, pain syndrome of the small pelvis in 62 (79.5%) cases, palpable tumor mass in the small pelvis in 42 (53.8%) cases, chronic constipation in 25 (32.1%) of cases, dyspeptic disorders (nausea, vomiting) in 16 (20.5%) cases, menstrual cycle disorders in 30 (38.5%) of cases.

During the objective examination, the following were found: abdomen increased in size in 51 (65.4%) of patients, abnormally developed external genital organs in 5 (6.4%) patients, uterus removed in history in 6 (7.7%) patients, enlarged uterus on palpation in 32 (41.0%) patients,

normal uterus on palpation in 40 (51.3%) patients. The enlarged uterus on palpation had an average size of  $8.78 \pm 2.1$  weeks of gestation (from 6 to 16 weeks of gestation).

Depending on the location, on palpation the ovarian tumor was on the right in 28 (35.9%) patients, on the left – in 25 (32.1%) patients, bilaterally – in 23 (29.5%) patients and could not be assessed in 2 (2.6%) patients. On palpation, the ovarian tumor was mobile in 65 (83.3%) cases, immobile in 13 (16.7%) cases, tender in 75 (96.2%) cases, hard in 54 (69.2%) cases and of hard-elastic consistency in 24 (30.8%) cases.

**Immunological and immunohistochemical data.** The cancer antigen CA-125 had a value mean of  $102.30 \pm 134.6$  U/mL, was within normal limits in 32 (41.0%) patients and increased in 46 (59.0%) patients. CA19-9 carbohydrate antigen had a mean value of  $29.15 \pm 38.3$  U/mL, was within normal limits in 59 (75.6%) patients and increased in 19 (24.4%) patients. The CEA carcino-embryonic antigen had a mean value of  $2.73 \pm 2.1$  U/mL, was within normal limits in 70 (89.7%) patients and increased in 8 (10.3%) patients.

Immunohistochemical investigations were performed in 20 (25.6%) patients. Inclusive, estrogen receptors were positive in 17 (85.0%) cases, progesterone receptors – in 15 (75.0%) cases, tumor suppressor p53 – in 16 (80.0%) cases and proliferation index Ki-67 – in all 20 (100.0%) cases with an average value of  $4.95 \pm 4.7\%$  (from 1% to 20%).

Therefore, 78 patients with TOB aged 19-80 years (average age  $48.58 \pm 16.4$  years), including 17.9% patients aged between 18-30 years, 38.5% - aged between 31-50 years and 43.6% - aged over 50 years. Cancer antigen CA-125 was elevated in 59.0% of patients, carbohydrate antigen CA19-9 – in 24.4% of patients and carcino-embryonic antigen CEA – in 10.3% of patients. Immunohistochemical investigations were performed in 25.6% of patients. Estrogen receptors were positive in 85.0% of cases, progesterone receptors – in 75.0% of cases, tumor suppressor p53 – in 80.0% of cases and proliferation index Ki-67 – in 100.0% of cases.

**The intraoperative appearance of the tumor.** Depending on the location, in patients from LM TOB was located on the right ovary in 28 (35.9%) patients, on the left ovary – in 26 (33.3%) patients and bilaterally – in 24 (30.8%) patients. The size of the ovarian formation was  $\leq 4$  cm in 4 (5.1%) cases, within 5-10 cm – in 37 (47.4%) cases and  $\geq 11$  cm in 37 (47.4%). The mean value of TOB size was  $14.56 \pm 9.6$  cm (from 4.0 cm to 45.0 cm). Intraoperative rupture of the tumor was found in 27 (34.6%) patients, the damage omentum – in 6 (7.7%) patients, and the damage to the lymph nodes was not detected.

The appearance of the cyst content was serous in 51 (65.4%) patients, mucinous – in 12 (15.4%) patients, endometriotic – in 8 (10.3%) patients, serous-mucinous – in 2 (2.6%) patients and serous-endometriosis – in 5 (6.4%) patients.

Vegetations on the surface of the tumor were missing in 12 (15.4%) patients, they were identified on the external surface of the tumor in 1 (1.3%) patient, on the internal surface of the tumor in 59 (75.6%) patients, on the external and internal surface of the tumor in 6 (7.7%) patients.

Afectarea peritoneului lipsea la 73 (93,6%) de pacienți și era afectat la 5 (6,4%) pacienți, inclusiv leziuni parietale au fost identificate în 2 (2,6%) cazuri, leziuni parietale și viscerale în 3 (3,8%) cazuri.

The involvement of the peritoneum was absent in 73 (93.6%) patients and was affected in 5 (6.4%) patients, including parietal lesions were identified in 2 (2.6%) cases, parietal and visceral lesions in 3 (3.8%) cases.

Abdominal free fluid was missing in 63 (80.8%) patients, it was highlighted in a volume

below 500 ml in 10 (12.8%) cases, within 500-5000 ml in 4 (5.1%) cases and >5000 ml in 1 (1.3%) case. The appearance of the free abdominal fluid was serous in 13 (86.7%) patients and mucinous – in 2 (13.3%) patients.

In our study we diagnosed the following histological forms of TOB: serous in 59 (75.7%) cases, mucinous in 16 (20.5%) cases and mixed (sero-mucinous) in 3 (3.8%) cases (figure 6).

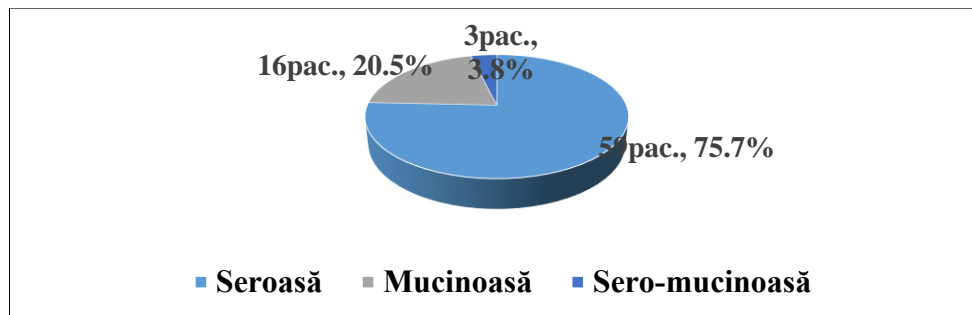


Figure 6. Distribution of patients from the control group according to function of the histological form of TOB.

Depending on the tumor stage and TNM, the patients with TOB in our study were classified as follows: stage IA T1aNoMo 35 (44.9%) cases, stage IB T1bNoMo 27 (34.6%) cases, stage IC T1cNoMo 5 (6.4%) cases, stage IIA T2aNoMo 6 (7.7%) cases, stage IIB T2bNoMo 2 (2.6%) cases, stage IIIA T3aNoMo 1 (1.3%) cases, stage IIIB T3bNoMo 1 (1.3%) cases and stage IIIC T3cNoMo 1 (1.3%) cases (figure 7).

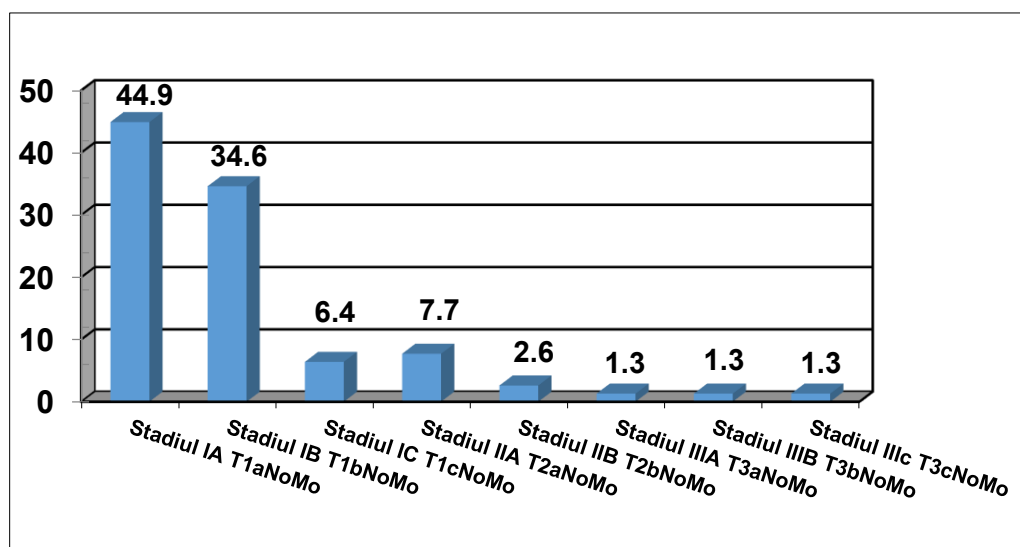


Figure 7. Distribution of patients from the control group according to function by tumor stage and TNM (%).

So, in our study we diagnosed the following histological forms of TOB: serous in 75.7% cases, mucinous in 20.5% cases and mixed (sero-mucinous) in 3.8% cases. The tumor was located on the right ovary in 35.9% of patients, on the left ovary - in 33.3% of patients and bilaterally - in 30.8% of patients. The average value of the TOB size was  $14.56 \pm 9.6$  cm (from 4.0 cm to 45.0 cm), including  $\leq 4$  cm in 5.1% of cases, within the limits of 5-10 cm – in 47.4% cases and  $\geq 11$  cm in 47.4%. Vegetation on the surface of the tumor was found in 84.6% of patients, damage to the peritoneum - in 6.4% of patients, free abdominal fluid - in 19.2% of patients.

**Treatment.** In the vast majority of cases (68 – 87.2%) the surgical intervention was performed by laparotomic approach and only in 10 (12.8%) cases laparoscopic approach was used. Conservative surgical treatment was applied to 17 (21.8%) patients with TOB and radical surgical treatment to 61 (78.2%) patients.

Among all cases of conservative surgical treatment, in 3 (3.8%) women it was performed unilateral ovarian cystectomy, in 2 (2.6%) women bilateral ovarian cystectomy, in 5 (6.4%) women ovarian cystectomy with omentectomy, in 1 (1.3%) women ovarian cystectomy with omentectomy and appendectomy, in 3 (3.8%) women ovarian cystectomy with unilateral adnexectomy and omentectomy, in 3 (3.8%) women unilateral adnexectomy and in 5 (6.4%) women unilateral adnexectomy with omentectomy.

Among all cases of radical surgical treatment, it was performed in 2 (2.6%) patients total hysterectomy with unilateral adnexectomy and omentectomy, in 4 (5.1%) patients – total hysterectomy with bilateral adnexectomy, 40 (51.3%) patients – total hysterectomy with bilateral adnexectomy and omentectomy and 10 (12.8%) patients – total hysterectomy with bilateral adnexectomy, omentectomy and appendectomy. Unilateral adnexectomy with omentectomy was performed in all 5 (6.4%) patients with TOB, who underwent total hysterectomy in the past.

Peritoneal biopsy was performed in 21 (26.9%) patients with TOB. Therefore, conservative surgical treatment was applied to 21.8% patients with TOB from LM and radical surgical treatment – in 78.2% of patients. In the patients from the LM study group, over the 5-year period, 72 patients (92.30%) did not show signs of borderline ovarian tumor recurrence, the presence of recurrence was determined in 6 patients (7.70%).

### **3.3 Analysis of the effectiveness of chemotherapy treatment in patients with ovarian borderline tumors**

**Socio-demographic and anamnestic data.** In LB and LM in our study, 78 patients with TOB were included, hospitalized in IMSP IO between January 2015 and August 2024. Although the average age of LM patients was higher, compared to LB patients, this difference did not reached statistical certainty ( $48.58 \pm 16.4$  years and  $44.44 \pm 13.1$  years, respectively;  $p > 0.05$ ).

According to the age group, also, no statistically significant differences were found, despite the fact that women aged up to 50 years predominated in LM, and women over 50 years old prevailed in LM.

No statistically significant differences were found even according to the living environment: 41 (52.6%) patients from LB and 44 (56.4%) patients from LM were from the urban environment ( $p > 0.05$ ), 37 (47.4%) and 34 (43.6%), respectively – from rural areas ( $p > 0.05$ ).

Patients with TOB from LB mentioned exposure to harmful factors significantly more frequently: 19 (24.4%) and 8 (10.3%), respectively ( $p < 0.05$ ). The analysis of the frequency of exposure to different harmful factors in the study groups revealed a statistically significantly higher smoking rate in LB patients (12 - 15.4% and 4 - 5.1%, respectively;  $p < 0.05$ ). The frequency of exposure to other harmful factors was similar in both study groups: 9 (11.5%) LB patients consumed alcohol and 5 (6.4%) patients from LM ( $p > 0.05$ ), administered combined oral contraceptives 3 (3.8%) patients from LB and 1 (1.3%) patient from LM ( $p > 0.05$ ).



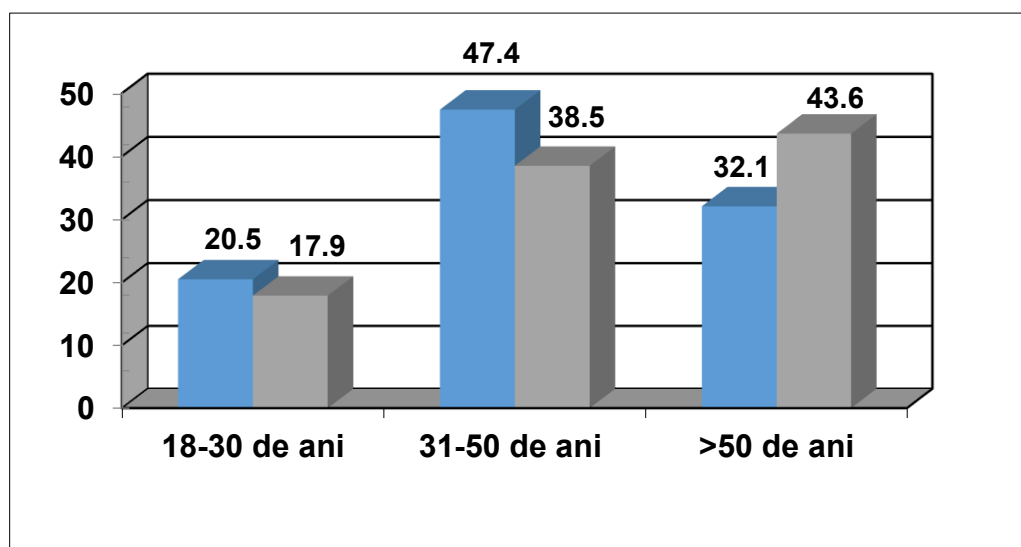


Figure 8. **Distribution of patients in the study groups by function by age group (%).**

The frequency of comorbidities was also similar ( $p>0.05$ ) in both study groups: 25 (32.1%) women from LB and 33 (42.3%) women from LM recorded cardiovascular diseases in the antecedents, respectively, endocrine disorders – 36 (46.2%) and 35 (44.9%) patients, benign uterine tumors – 22 (28.2%) and 18 (23.1%) patients, sexually transmitted diseases – 2 (2.6%) and no patients. It is important to note that 21 (26.9%) patients with TOB from LB and 19 (24.4%) patients with TOB from LM presented 2 concurrent comorbidities each, 5 (6.4%) and 9 (11, 5%) women – 3 concurrent comorbidities each, and in 24 (30.8%) patients with TOB from LB and in 29 (37.2%) patients with TOB from LM the concurrent comorbidities were missing

The difference in the rates of heredocollateral antecedents of oncological diseases, although it was higher in LB patients (27 - 34.6% and 16 - 20.5%, respectively), did not reach statistical certainty ( $p<0.05$ ).

**Previous obstetric status.** Patients with TOB from both study groups were similar in terms of regular menstrual cycle (26 (33.3%) women from LB and LM each;  $p>0.05$ ) and menopause – 26 (33.4%) ) of LB patients and 37 (47.4%) of LB patients ( $p>0.05$ ). Irregular menstrual cycle in the antecedents was recorded statistically significantly more frequently by women from LB, compared to those from LM: 26 (33.3%) women and 15 (19.3%) women, respectively ( $p>0.05$ ).

Although, the number of previous births was higher in TOB patients from LM compared to those from LB: 62 (79.5%) women and 51 (65.4%) women, respectively ( $p>0.05$ ), this difference did not reach statistical certainty. According to the number of births, no statistically significant differences were also determined ( $p>0.05$ ): 15 (19.4%) patients from LB and 13 (21.0%) patients from LM had 1 each birth, respectively, 25 (49.0%) and 32 (51.6%) patients – 2 births each, 6 (11.8%) and 9 (14.5%) patients – 3 each births, 4 (7.8%) and 7 (11.3%) patients – 4 births each and 1 (2.0%) patient from each study group – 5 births each.

The mean value of the number of births was also similar in both study groups:  $2.04\pm1.0$  births (from 1 birth to 5 births) in LB patients and  $2.21\pm1.0$  births (from 1 birth to 5 births) in LM patients.

Patients in both study groups were similar ( $p>0.05$ ) according to the number of previous abortions. Abortions in the past were mentioned by 30 (38.5%) women from LB and 41 (52.6%) women from LM, respectively, 1 abortion each – 11 (36.7%) and 12 (29.3%) patients, 2 abortions

each – 14 (46.7%) and 17 (41.5%) patients, 3 abortions each – 2 (6.7%) and 6 (14.6%) patients, 4 abortions each – 3 (10.0%) and 5 (12.2%) patients, 4 abortions each – no patient and 1 (2.4%) patient.

The mean value of the number of abortions was also similar in both study groups:  $1.90 \pm 0.9$  abortions (from 1 abortion to 4 abortions) in LB patients and  $2.17 \pm 1.1$  abortions (from 1 abortion to 5 abortions) in LM patients.

**Subjective and objective clinical data.** Patients with TOB from LB, compared to patients with TOB from LM, accused statistically significantly more frequently the impairment of the general condition (65 - 83.3% and 44 (56.4%) of cases, respectively;  $p < 0.001$ ) and palpable tumor mass in the small basin (62 - 79.5% and 42 - 53.8% of cases, respectively;  $p < 0.01$ ). The frequency of other complaints was similar ( $p > 0.05$ ) in both study groups: pelvic pain syndrome - in 69 (88.5%) and 62 (79.5%) cases, chronic constipation - in 30 (38.5%) and 25 (32.1%) cases, dyspeptic disorders (nausea, vomiting) – in 21 (26.9%) and 16 (20.5%) cases, menstrual cycle irregularities – in 27 (34.6%) and 30 (38.5%) cases, respectively.

Objective examination parameters were also similar ( $p > 0.05$ ) in both study groups. An enlarged abdomen was found in 60 (76.9%) LB patients and in 51 (65.4%) LM patients, respectively, abnormally developed external genital organs – in 6 (7.7%) and in 5 (6.4%) patients, uterus removed in history – in 4 (5.1%) and in 6 (7.7%) patients, enlarged uterus on palpation – in 29 (37.2%) and in 32 (41.0%) patients, normal uterus on palpation – in 45 (57.7%) and in 40 (51.3%) patients.

Enlarged uterus on palpation had an average size of  $9.55 \pm 2.0$  weeks of gestation (from 6 to 12 weeks of gestation) in patients with TOB from LB and of  $8.78 \pm 2.1$  weeks of gestation (from 6 to 16 weeks of gestation in patients with TOB from LB ( $p > 0.05$ )).

Depending on the location, on palpation the bilateral ovarian tumor was found statistically significantly more frequently in LB patients – 39 (50.0%) and 23 (29.5%) patients, respectively;  $p < 0.01$ . Tumor location on the right adnexa (18 - 23.1% patients from LB and 28 - 35.9% of patients from LM;  $p > 0.05$ ) or on the left adnexa (16 - 20.5% patients from LB and 25 - 32.1% of patients from LM;  $p > 0.05$ ) and the impossibility of assessing the tumor (5 - 6.4% of patients from LB and 2 - 2.6% of patients from LM;  $p > 0.05$ ) were similar in both study groups

In patients with TOB from LB and from LM, the ovarian tumor on palpation was mobile in 61 (78.2%) and 65 (83.3%) cases, respectively ( $p > 0.05$ ), immobile in 17 (21.8%) and in 13 (16.7%) cases, respectively ( $p > 0.05$ ), sensitive in 71 (91.0%) and in 75 (96.2%) cases, respectively ( $p > 0.05$ ), of hard consistency in 53 (67.9%) and in 54 (69.2%) cases, respectively ( $p > 0.05$ ), of hard-elastic consistency in 25 (32.1%) and in 24 (30.8%) cases, respectively ( $p > 0.05$ ).

**Immunological and immunohistochemical data.** The mean value of cancer antigen CA-125 was statistically significantly higher in TOB patients from LB compared to TOB patients from LM:  $181.227 \pm 212.4$  U/mL and  $102.30 \pm 134.6$  U/mL, respectively;  $p < 0.05$ . The mean values of CA19-9 carbohydrate antigen ( $55.98 \pm 73.7$  U/mL in LB patients and  $29.15 \pm 38.3$  U/mL in LM patients;  $p > 0.05$ ) and carcino-embryonic antigen CEA ( $6.09 \pm 18.23$  U/mL in LB patients and  $2.73 \pm 2.1$  U/mL in LM patients;  $p > 0.05$ ) they only had an increasing trend in LB patients, which did not reach statistical certainty.

Depending on the level, the cancer antigen CA-125 was within normal limits in 23 (29.5%) patients from LB and in 32 (41.0%) patients from LM ( $p > 0.05$ ), it had increased values in 55 (70.5%) patients from LB and in 46 (59.0%) patients from LM ( $p > 0.05$ ). The carbohydrate antigen CA19-9 was within normal limits in 49 (62.8%) patients from LB and in 59 (75.6%)

patients from LM ( $p>0.05$ ), it had increased values in 29 (37, 2%) of LB patients and in 19 (24.4%) LM patients ( $p>0.05$ ). The carcino-embryonic antigen CEA was within normal limits in 63 (80.8%) patients from LB and in 70 (89.7%) patients from LM ( $p>0.05$ ), had increased values in 15 (19, 2%) patients from LB and in 8 (10.3%) patients from LM ( $p>0.05$ ). Thus, although the increased values of these antigens were higher in LB, these differences did not reach statistical certainty.

Immunohistochemical investigations were performed statistically significantly more frequently in patients with TOB from LM: in 20 (25.6%) and in 7 (9.0%) patients, respectively ( $p<0.05$ ). However, the positive values of estrogen receptors (6 - 85.7% cases in LB and 17 - 85.0% cases in LM,  $p>0.05$ ), progesterone receptors (7 - 100.0% cases in LB and 15 - 75.0% cases in LM,  $p>0.05$ ), tumor suppressor p53 (5 - 71.4% cases in LB and 16 - 80.0% cases in LM,  $p>0.05$ ) and the Ki-67 proliferation index (7 - 100.0% cases in LB and 20 - 100.0% cases in LM,  $p>0.05$ ), but also the average value of the index of Ki-67 proliferation ( $12.9\pm 8.3\%$  in LB and  $4.95\pm 4.7\%$  in LM,  $P>0.05$ ) were similar in both study groups.

Therefore, patients with TOB in both study groups were similar according to age ( $44.44\pm 13.1$  years in LB and  $48.58\pm 16.4$  years in LM;  $p>0.05$ ), living environment, the frequency of comorbidities, the number of births and abortions in the antecedents, the parameters of the objective examination, the increased values of CA-125, CA19-9 and CEA antigens, the positive values of estrogen receptors, progesterone receptors, tumor suppressor p53 and proliferation index Ki-67.

Patients with TOB from LB, compared to patients with TOB from LM, had statistically significantly more frequent exposure to harmful factors (24.4% and 10.3%, respectively;  $p<0.05$ ), mainly smoking (15.4 % and 5.1%, respectively;  $p<0.05$ ), affecting the general condition (83.3% and 56.4%, respectively;  $p<0.001$ ), palpable tumor mass in small pelvis (79.5% and 53.8%, respectively;  $p<0.01$ ), bilateral ovarian tumor (50.0% and 29.5%, respectively;  $p<0.01$ ) and mean cancer antigen value CA-125  $181.227\pm 212.4$  U/mL and  $102.30\pm 134.6$  U/mL, respectively;  $p<0.05$ .

***The intraoperative appearance of the tumor.*** During the intraoperative examination, the bilateral localization of TOB was found statistically significantly more frequently in LB patients: 41 (52.6%) and 24 (30.8%) patients, respectively;  $p<0.01$ . The frequency of TOB localization on the right ovary (21 - 26.9% and 28 - 35.9% of patients, respectively;  $p>0.05$ ) and on the left ovary (16 - 20.5% and 26 - 33.3% of patients, respectively;  $p>0.05$ ) had only an increasing tendency in LM patients.

The size of the ovarian formation was similar in both study groups. The average value of the TOB size was  $13.67\pm 10.1$  cm (from 4.0 cm to 50.0 cm) in LB patients and  $14.56\pm 9.6$  cm (from 4.0 cm to at 45.0 cm) in LM patients ( $p>0.05$ ). Respectively, the size of the ovarian formation  $\leq 4$  cm was identified in 3 (3.8%) and in 4 (5.1%) cases ( $p>0.05$ ), within the limits of 5-10 cm – in 45 (57.7 %) and in 37 (47.4%) cases ( $p>0.05$ ),  $\geq 11$  cm – in 30 (38.5%) and in 37 (47.4%) cases ( $p>0.05$ ).

The analysis of TOB complications revealed that damage to the omentum (20 - 25.6% and 6 - 7.7% patients, respectively;  $p<0.01$ ) and damage to the peritoneum (28 - 35.9% and 5 - 6.4% patients, respectively;  $p<0.001$ ) was statistically significantly more frequent in LB patients, compared to LM patients (figure 9).

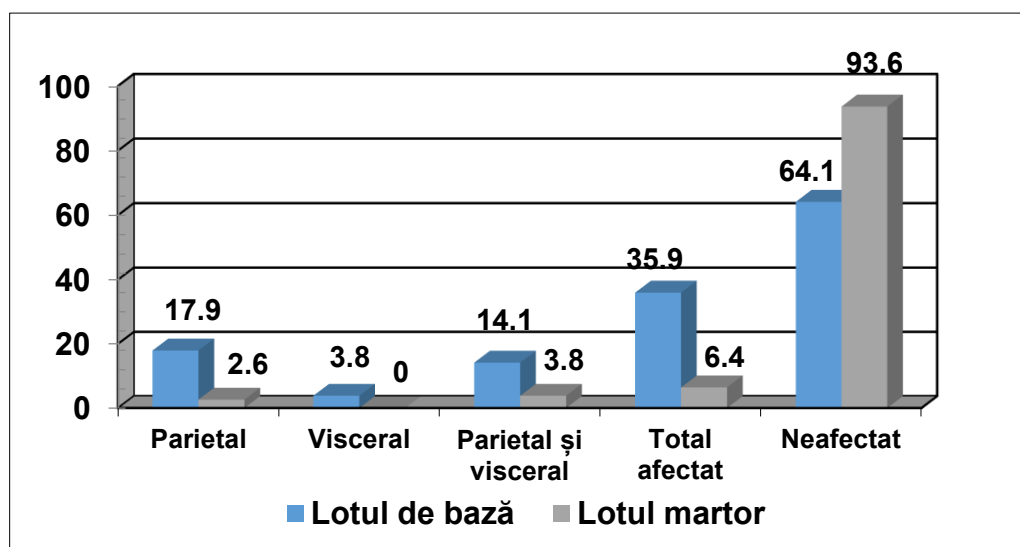


Figure 9. **Distribution of patients from the study groups according to function by affecting the peritoneum.**

Frequencies of intraoperative tumor rupture (25 - 32.1% of LB patients and 27 - 34.6% of LM patients;  $p>0.05$ ) and lymph node damage (3 - 3.8% of LB patients and no patient from LM;  $p>0.05$ ) were found similarly in both study groups.

The serous aspect of the cystic content was statistically significantly more frequently determined in patients with TOB in LM: 51 (65.4%) and 38 (48.7%) cases, respectively;  $p<0.05$ . The other types of cystic content were similar in both study groups.

Vegetation on the external and internal surface of the tumor was found statistically significantly more frequently in patients with TOB from LB (24 - 30.8% and 6 - 7.7% cases, respectively;  $p<0.001$ ), and the lack of vegetation on the tumor surface - statistically significantly more frequent in patients with TOB from LM (12 - 15.4% and 3 - 3.8% cases, respectively;  $p<0.05$ ). Vegetation on the external surface of the tumor (in 3 - 3.8% of LB patients and in 1 - 1.3% of LM patients;  $p>0.05$ ) and on the internal surface of the tumor (in 48 - 61.5% of patients from LB and in 59 - 75.6% of patients from LM;  $p>0.05$ ) were detected similarly in both study groups.

Abdominal free fluid was found statistically significantly more frequently in patients with TOB from LB (30 - 38.5% and 15 - 19.2% cases, respectively;  $p<0.01$ ), and the absence of abdominal free fluid - statistically significantly more frequent in patients with TOB from LM (63 - 80.8% and 48 - 61.5% cases, respectively;  $p<0.01$ ). Depending on the volume of free abdominal fluid, the patients in both groups were similar: volume below 500 ml was highlighted in 14 (17.9%) cases in LB and in 10 (12.8%) cases in LM ( $p>0.05$ ), respectively, volume between 500-5000 ml in 11 (14.1%) and 4 (5.1%) cases ( $p>0.05$ ), volume  $>5000$  ml in 5 (6.4%) and 1 (1.3%) case ( $p>0.05$ ).

The appearance of the free abdominal fluid was serous in 23 (76.7%) patients from LB and in 13 (86.7%) patients from LM, and the appearance was mucinous - in 7 (23.3%) patients from LB and in 2 (13.3%) patients from LM, but these differences did not reach statistical certainty.

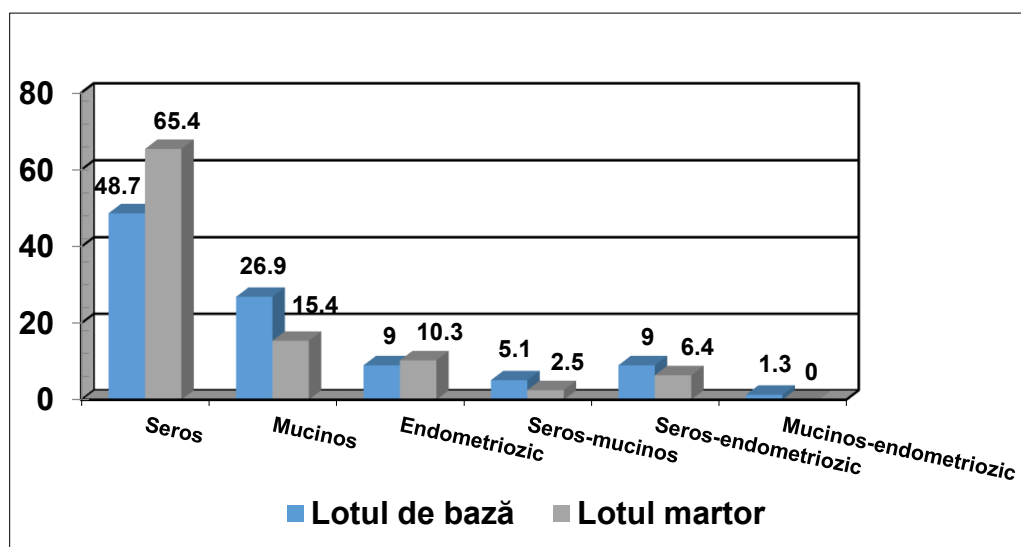


Figure 10. Distribution of patients in the study groups by function by the appearance of the cystic content.

Depending on the volume of free abdominal fluid, the patients in both groups were similar: volume below 500 ml was highlighted in 14 (17.9%) cases in LB and in 10 (12.8%) cases in LM ( $p>0.05$ ), respectively, volume between 500-5000 ml in 11 (14.1%) and 4 (5.1%) cases ( $p>0.05$ ), volume  $>5000$  ml in 5 (6.4%) and 1 (1.3%) case ( $p>0.05$ ).

The appearance of the free abdominal fluid was serous in 23 (76.7%) patients from LB and in 13 (86.7%) patients from LM, and the appearance was mucinous - in 7 (23.3%) patients from LB and in 2 (13.3%) patients from LM, but these differences did not reach statistical certainty.

In our study, we did not find statistically significant differences regarding the histological forms of TOB. The analysis according to the tumor stage and TNM found that patients with TOB from LM presented statistically significantly more frequently tumors in stage IA T1aNoMo: 35 (44.9%) and 4 (5.1%), respectively;  $p<0.001$ . On the contrary, tumors in stage II B T2bNoMo (10 - 12.8% and 2 - 2.6%, respectively;  $p<0.05$ ), in stage IIIA T3aNoMo (9 - 11.5% and 1 - 1.3%, respectively;  $p<0.01$ ) and in stage IIIC T3cNoMo (15 - 19.2% and 1 - 1.3%, respectively;  $p<0.001$ ) were statistically significantly more frequently identified in patients with TOB from LB (table 1).

**Treatment.** The treatment of patients with TOB was similar in both study groups. In the vast majority of cases, the surgical intervention was performed through a laparotomy approach: 75 (96.2%) cases in LB and 68 (87.2%) cases in LM ( $p>0.05$ ). The laparoscopic approach was applied to 3 (3.8%) patients from LB and to 10 (12.8%) patients from LM. Conservative surgical treatment was performed in 16 (20.5%) patients with TOB in LB and in 17 (21.8%) patients with TOB in LM ( $p>0.05$ ), and radical surgical treatment in 62 (79, 5%) and in 61 (78.2%) patients, respectively ( $p>0.05$ ) (table 1).

Table 1. Distribution of patients in the study groups according to histological forms of TOB and classification according to tumor stage and TNM

The parameters	The base lot		Control lot		P
	abs.	%	abs.	%	
Histological forms of TOB					

Serous	51	65,4	59	75,7	NS
Mucinous	24	30,8	16	20,5	NS
Sero-mucinous	3	3,8	3	3,8	NS
<b>Classification according to tumor stage and TNM</b>					
stage IA T1aNoMo	4	5,1	35	44,9	<0,001
stage IB T1bNoMo	27	34,6	27	34,6	NS
stage IC T1cNoMo	3	3,8	5	6,4	NS
stage IIA T2aNoMo	9	11,5	6	7,7	NS
stage II B T2bNoMo	10	12,8	2	2,6	<0,05
stage IIIA T3aNoMo	9	11,5	1	1,3	<0,01
stage IIIB T3bNoMo	1	1,3	1	1,3	NS
stage IIIC T3cNoMo	15	19,2	1	1,3	<0,001

Note: NS – not significant.

Peritoneal biopsy was performed in a similar number of patients from LB and from LM (18 - 23.1% patients 21 - 26.9% patients, respectively;  $p>0.05$ ).

Therefore, in our study we did not find statistically significant differences regarding the histological forms of TOB in both study groups. Patients with TOB from LB presented significantly more frequently bilateral tumor location (52.6% and 30.8%, respectively;  $p<0.01$ ), omentum involvement (25.6% and 7.7%, respectively;  $p<0.01$ ), damage to the peritoneum (35.9% and 6.4%, respectively;  $p<0.001$ ), vegetations on the external and internal surface of the tumor (30.8% and 7.7%, respectively;  $p<0.001$ ), abdominal free fluid (38.5% and 19.2%, respectively;  $p<0.01$ ), stage II B T2bNoMo tumors (12.8% and 2.6 %, respectively;  $p<0.05$ ), in stage IIIA T3aNoMo (11.5% and 1.3%, respectively;  $p<0.01$ ) and in stage IIIC T3cNoMo (19.2% and 1.3%, respectively;  $p<0.001$ ). Patients with TOB in LM had statistically significantly more frequently stage IA T1aNoMo tumors (44.9% and 5.1%, respectively;  $p<0.001$ ). The surgical treatment of patients with TOB was similar in both study groups.

**Table 2. Distribution of patients in the study groups by function the type of treatment**

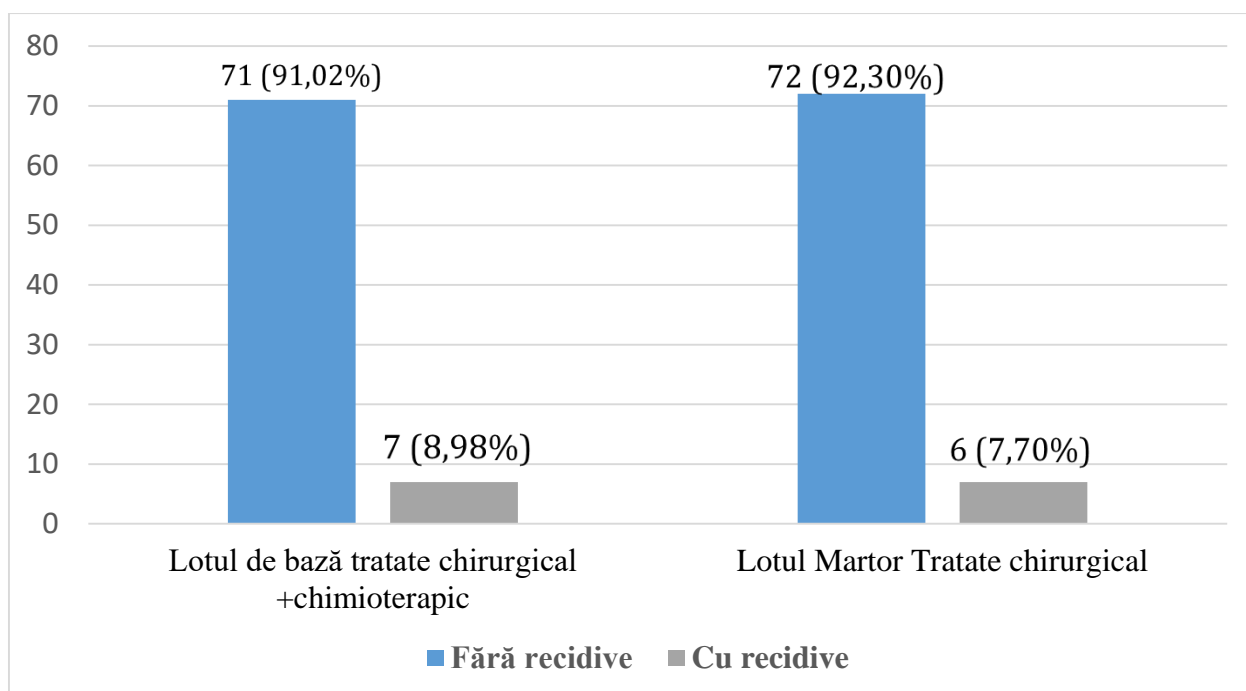
The parameters	The base lot		Control lot		p
	abs.	%	abs.	%	
Conservative surgical treatment					
Unilateral ovarian cystectomy	3	3,8	3	3,8	NS
Bilateral ovarian cystectomy	1	1,3	2	2,6	NS
Ovarian cystectomy with omentectomy	4	5,1	5	6,4	NS
Ovarian cystectomy with	1	1,3	1	1,3	NS

omentectomy and appendectomy					
Ovarian cystectomy with unilateral adnexectomy and omentectomy	0	0	3	3,8	NS
Unilateral adnexectomy	2	2,6	3	3,8	NS
Unilateral adnexectomy with omentectomy	3	3,8	0	0	NS
Unilateral adnexectomy with omentectomy and appendectomy	3	3,8	0	0	NS
<b>Radical surgical treatment</b>					
Total hysterectomy with unilateral adnexectomy and omentectomy	0	0	2	2,6	NS
Total hysterectomy with Bilateral adnexectomy	2	2,6	4	5,1	NS
Total hysterectomy with bilateral adnexectomy and omentectomy	45	57,7	40	51,3	NS
Total hysterectomy with bilateral adnexectomy, omentectomy and appendectomy	14	17,9	10	12,8	NS
Total hysterectomy in history of adnexectomy bilateral and omentectomy	3	3,8	0	0	NS
Total hysterectomy in history of adnexectomy bilateral, omentectomy and appendectomy	1	1,3	0	0	NS
Total hysterectomy in history of adnexectomy unilateral and omentectomy	0	0	5	6,4	NS

Note: NS – not significant.

La In the patients from the LB study group, over the 5-year period, 71 patients (91.02%) showed no signs of borderline ovarian tumor recurrence, the presence of recurrences was determined in 7 patients (8.98%).

In the patients from the LM study group, over the 5-year period, 72 patients (92.30%) did not show signs of borderline ovarian tumor recurrence, the presence of recurrence was determined in 6 patients (7.70%). (Figure 11).



**Figure 11. Distribution of patients in the LB and LM study groups depending on the presence of relapses (5-year period).**

During the period of our study, no patient died due to the underlying disease, 8 patients (10.25%) from LM gave birth, without signs of recurrence, and 2 (2.56%) patients are currently pregnant.

Our study supports the effectiveness of conservative treatment for patients with advanced borderline ovarian tumors (stage II, III or IV), without changing the overall prognosis. Advanced TOB with non-invasive implants can be safely treated with conservative surgery. Patients with invasive implants or with a micropapillary pattern in most cases can be offered conservative surgery, which preserves fertility, but with an individualized approach and careful dynamic monitoring.

There is no benefit of chemotherapy for patients with borderline ovarian tumors. Adjuvant chemotherapy is not necessary for these patients, even in the advanced stage with the presence of invasive implants.

## **GENERAL CONCLUSIONS**

1. Patients with borderline ovarian tumors complained of the most common pelvic pain syndrome (84.0%), impairment of the general condition (69.9%), palpable tumor mass in the pelvis (66.7%). The objective examination revealed an enlarged abdomen (71.2%) and the presence of ovarian masses on palpation (69.1%). During the intraoperative examination, the borderline ovarian tumor was predominantly located bilaterally - in 41.7% of patients. Vegetation on the internal surface of the tumor was found in 90.4% of patients, damage to the peritoneum - in 21.2% of patients, free abdominal fluid - in 28.8% of patients.



2. In our study, we diagnosed the following histological forms of borderline ovarian tumors: serous in 70.5% of cases, mucinous in 25.6% of cases and mixed (sero-mucinous) in 3.9% of cases. The immunological study in patients with borderline ovarian tumors determined increased values of the cancer antigen CA-125 (64.7%), the carbohydrate antigen CA19-9 (30.8%) and the carcinoembryonic antigen CEA (14.7%).

3. The management of borderline ovarian tumors, primarily primary surgical intervention (conservative or radical), is personalized and depends on the woman's age, the size of the ovarian mass, the type and stage of the disease, reproductive desires, the extent and nature of peritoneal implants (invasive or non-invasive).

4. There is no benefit of chemotherapy for patients with borderline ovarian tumors.

Adjuvant chemotherapy is not necessary for these patients, even in the advanced stage with the presence of non-invasive implants.

5. Based on the results of the study, we developed an algorithm for the diagnosis and treatment of patients

with borderline ovarian tumors, which will determine the application of conservative and radical surgical treatment depending on the reproductive age, tumor stage and histological type of the disease.

## **PRACTICAL RECOMMENDATIONS**

**For oncologists-gynecologists, obstetricians-gynecologists, medical oncologists.**

1. Surgical treatment represents the mandatory therapeutic conduct, the type of management chosen, conservative or radical, depending on the histological subtype, the stage of the disease at diagnosis and the desire to preserve fertility. In the case of young patients, with an early stage of the disease, who want children, conservative treatment can be adopted, followed by careful long-term surveillance, but the risk of recurrence is higher. For patients who no longer wish to give birth, the standard treatment consists of bilateral adnexectomy, with or without total hysterectomy. In the case of borderline ovarian tumors diagnosed in advanced stages with invasive implants, the treatment is similar to that of invasive ovarian carcinomas.
2. Conservative surgery is safe in young patients treated for ovarian tumors borderline and then carefully supervised. In case of recurrence of the borderline ovarian tumor on the remaining ovary, another conservative intervention (cystectomy) can be proposed to preserve fertility. Even for patients with stages II, III or IV of borderline ovarian tumor who wish to preserve reproductive function, conservative surgery may be indicated.
3. Postoperative adjuvant chemotherapy or radiotherapy does not reduce the recurrence rate and does not improve survival in both early and advanced stages of the disease, with residual tumor masses or lymph node involvement. Thus, the adverse effects of postoperative chemotherapy, radiotherapy and hormonal therapy outweigh the benefits and are not recommended for patients with borderline ovarian tumors.
4. In the case of TOB relapse, the standard treatment is only surgery; in case recurrence with invasive carcinoma, treatment includes secondary surgery and chemotherapy; only recurrence, stromal microinvasion or intraepithelial carcinoma are indications for radical surgical intervention after conservative treatment.

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## ANNEXES

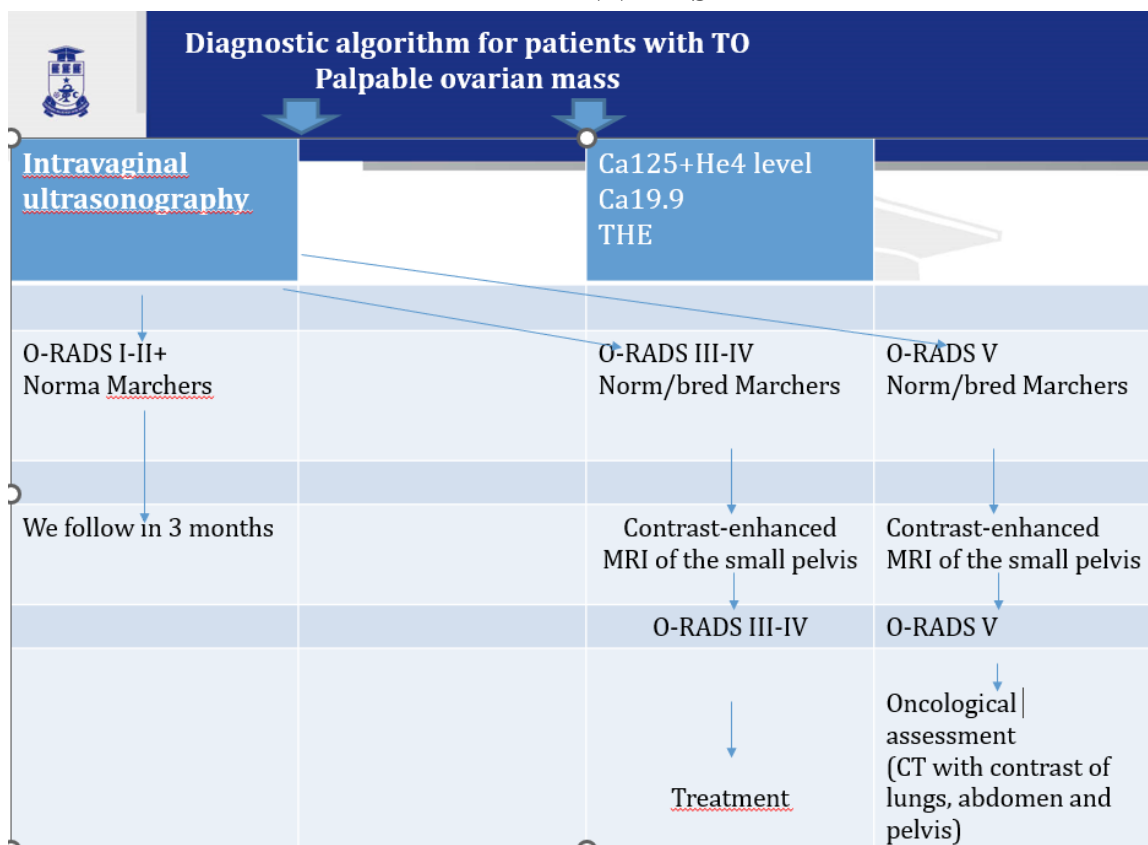


Figure 12. Diagnostic algorithm for patients with ovarian tumors.

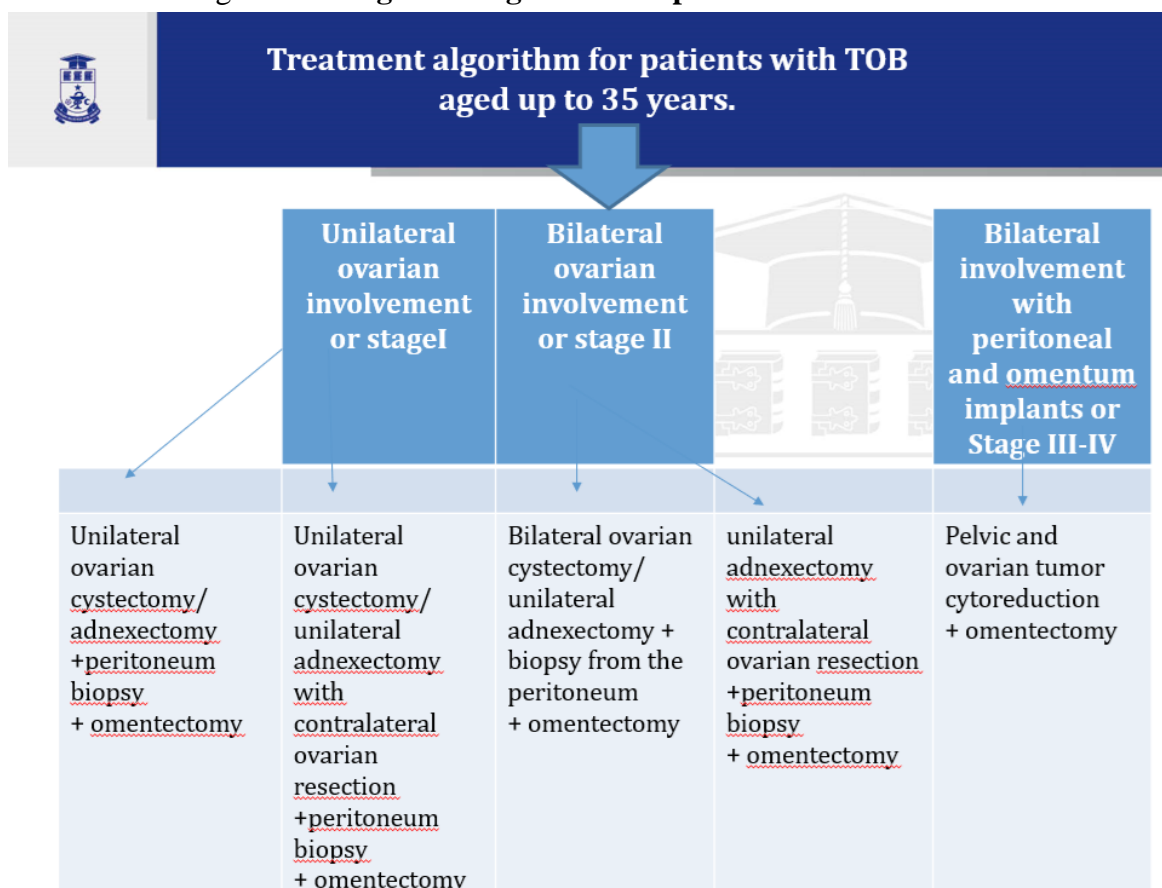


Figure 13. Treatment algorithm for patients with TOB aged up to 35 years.

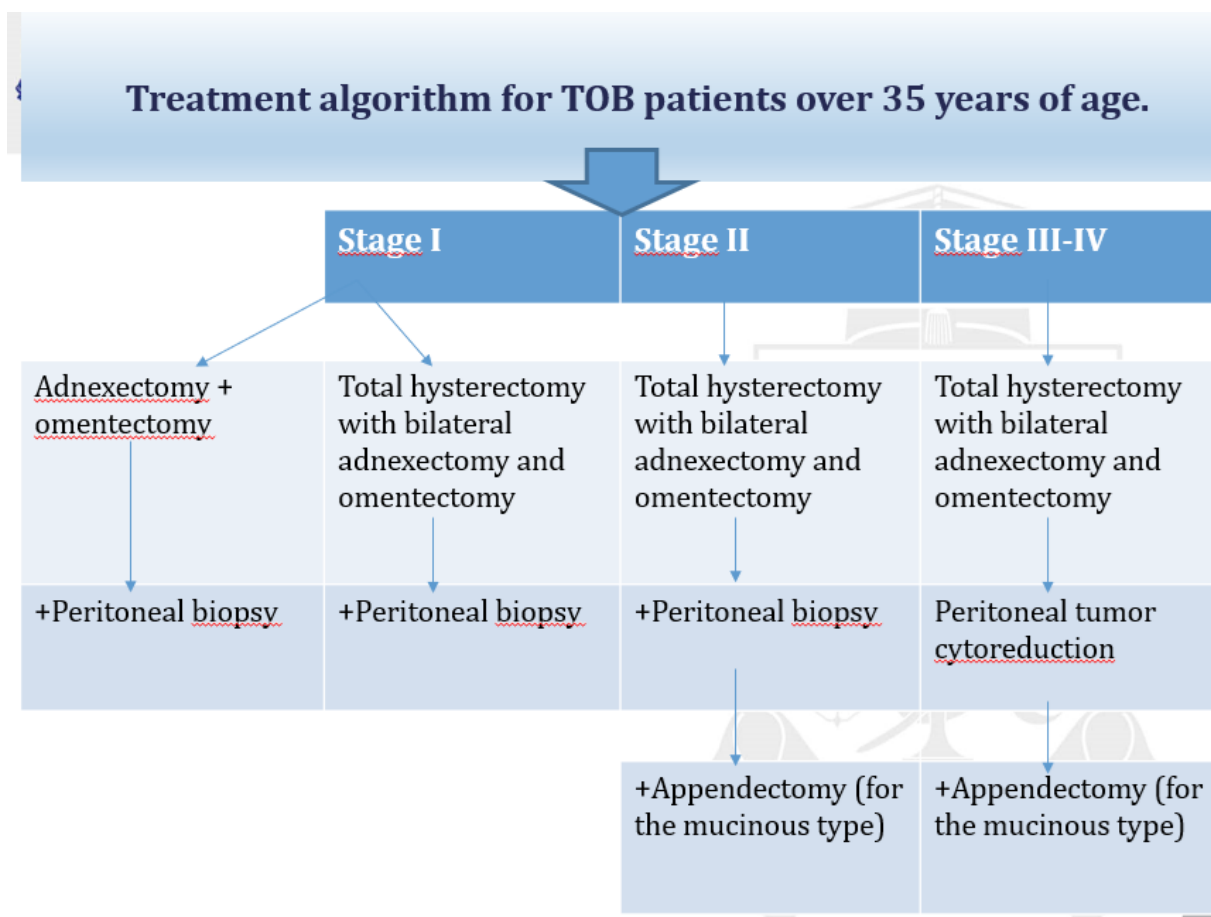


Figure 14. Treatment algorithm for patients with tob aged over 35 years.

**LIST OF PUBLICATIONS AND PARTICIPATIONS IN SCIENTIFIC FORUMS**  
**of Mrs. Mariana VÎRLAN,**  
 completed in the doctoral thesis in medical sciences,  
 with the theme: **BORDERLINE OVARIAN TUMORS, OPTIMIZATION OF**  
**DIAGNOSTIC AND TREATMENT METHODS**, 321.20 - Oncology and radiotherapy,  
 "Nicolae Testemițanu" State University of Medicine and Pharmacy from the Republic

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**VÎRLAN Mariana**

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**321.20 – ONCOLOGY AND RADIOTHERAPY**

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