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Borderline Ovarian Tumors – Diagnostic and Treatment Modalities

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1. Summary

Ovarian tumors occur in one third of all women gynecology organs. Out of that borderline ovarian tumors occur in 10 – 15% out of all ovarian tumors. They are tumors with low malignant potential, which are different from benign lesions and malignancies by its' biological behavior and by histological structure.

2. Introduction

In comparison with invasive ovarian tumors borderline ovarian tumor occur in women of younger age. According to this patients are asking to that overall treatment must be leading to sparing character to prevent fertility.

Prognosis of this disease depends on stage and on the time of staging it. Apart from invasive tumors of ovarian cancers there is early diagnostic in borderline ovarian tumor and for it's low malignant potential, these diseases have good prognosis of survival rate with very low risk of recurrence.

3. Histopathological and Biological Behavior

Epithelia tumors of ovary have generally histological cylindric-cellular glandular character and macroscopic tendency into cystic configuration. Biologically borderline ovarian tumors have behavior like less aggressive malignant tumor with low tendency into invasion into stroma and tendencies to create peritoneal implants [1].

Primary tumor shows mostly atypic proliferation than cystadenoma, but doesn't have a destructive character of stromal invasion, therefore unlike in WHO classification it is described by Seidmann as atypically proliferative tumors [2].

Histological criteria include proliferation of epithelia, stratification of epithelia of papilla, mitosis, and cell core atypia without invasion into stroma [3].

Reason why superficial epithelia of ovary is derived from coelom epithelia, from which the Mullerian cells are created, is why the borderline ovarian tumors have histological subtypes:

- Serous
- Mucinous
- Endometroid
- Clear cell
- Transitory epithelia tumors
- Mixed epithelia tumors [4]

Majority of borderline ovarian tumors are serous or mucinous. For determination of the type of borderline ovarian tumor there is importance to clarify the types of cells from which the tumor is created, because different histological types of tumors have different clinical behavior [5] (Figure 1).

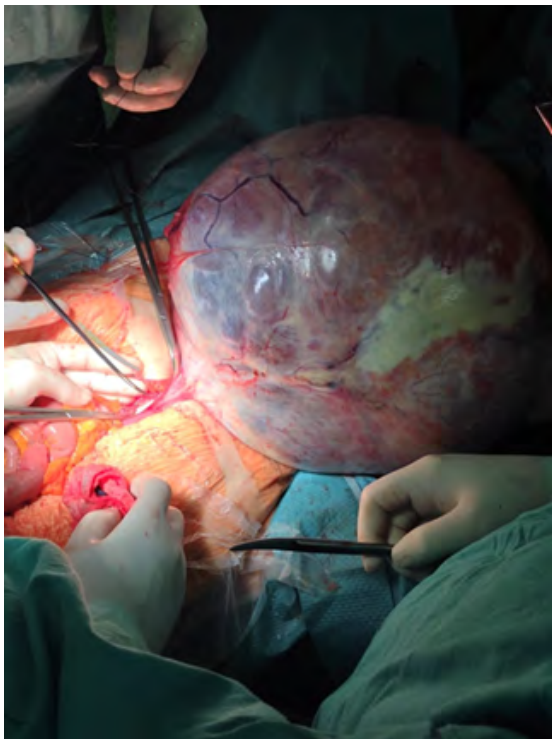


Figure 1: Precise preparation of mucinous borderline tumor on the vascular stem and fallopian tube

4. Symptomatology and Diagnostic

4.1. Clinical Symptomatology

Borderline ovarian tumors are very difficult to detect in clinical practice until they reach certain size and stage. The clinical symptoms are nonspecific. Approximately 23% of patients were asymptomatic [6]. In these patients the findings were random with the use of examination or ultrasound by screening exam.

Among first clinic symptoms there is pain in lower pelvic or sacral part of the body. Torsion of the ovarian mass causes sudden and excruciating pain. Rupture of the mucinous cystadenoma causes tumor cells dissemination, which contain mucin out of which there is created pseudomyxoma peritonei.

Growing ovarian tumorous mass causes patients, the feeling and appearance of "blowing up" doesn't disappear after urination and by palpable examination it has subdued sounds. The pressure on urinary bladder causes urological problems as urgency, incontinence and pollakiuria. Also, by the significant growth of the tumorous mass it can lead to venous resumption and occurrence of varicosities or edemas of lower extremities [6, 7, 8].

4.2. Oncomarkers

None of the potential biooncomarker is typical for ovarial carcinoma and didn't show and significant growth of the levels. Probably because the borderline ovarian tumors are diagnosed in early stages I. Elevation of marker CA 125 corellates with TNM/FIGO stage of the tumor [9].

No recommendation can be made about the use of serum tumour biomarkers (CA125, CA19-9, CEA, CA72-4, HE4) or specific score in order to distinguish benign ovarian tumor/borderline ovarian tumor/ovarian cancer in case of indeterminate the mass. In case of suspicion of mucinous ovarian tumour on imaging, the systematic dosage of serum CA19-9 antigen can be proposed (grade C). In case of an ovarian indeterminate mass on imaging; dosage of serum HE4 and C125 is recommended. If preoperative dosage of serum tumor biomarkers is normal, their systematic dosage is not recommended in the follow-up of BOT (grade C). If preoperative dosage of CA125 is high, the systematic dosage of CA125 is recommended in the follow-up of BOT with no precisions about the rhythm and the duration of the follow-up (grade B). Among the three markers, CA-125 provided the highest diagnostic performance in differentiating between benign, borderline, and malignant mucinous ovarian tumors. Preoperative elevation of CA19-9, CA-125, and CEA, along with tumor size, can serve as useful predictors in distinguishing tumor types [10] (Table 1).

CA 125 - before preoperational differencial diagnosis between borderline ovarian tumor and invasive carcinoma it has significant meaning and it's manifestation of disease in early age and lower levels of CA 125 have significance in borderline ovarian tumors [7]. Levels of CA 125 are no use for diagnostics of patients with borderline tumors. Because BOT are diagnoses mostly in, I stage the levels are not that increased. Thus, raised level of CA-125 in benign ovarian cyst should be followed-up more closely, demanding assessment of fallopian tubes for early diagnosis of ovarian cancer. Also, algorithms can be explored to include size of ovarian cyst and CA 125 levels to predict ovarian cancer.

CA 19-9 - This marker is increased especially in mucinous type of borderline ovarian tumor [9]. Isolated low-level elevation of CA19-9 has been described in benign ovarian dermoid cysts (teratomas) in three case reports,3 - 5 and also reported in up to 50% of teratomas with malignant change, 3 but our case is the highest reported rise associated with benign ovarian pathology (the previous being 1430 U/ml). Isolated low-level elevation of CA19-9 has been described in benign ovarian dermoid cysts (teratomas) in three case reports, 3 – 5 and also reported in up to 50% of teratomas with malignant change, 3 but our case is the highest reported rise associated with benign ovarian pathology (the previous being 1430 U/ml).

CEA - None of the serous borderline ovarian tumors shown positivity of CEA, the positivity was found in mucinous types of BOT [11]. Although CEA was significantly raised in patients with a variety of tumours, the highest incidence (77 %) was found in those with serious cystadenocarcinoma. Nearly all (%) of the poorly differentiated tumours were associated with a positive CEA result. CA-125/CEA at >30, the sensitivity, specificity, and both the predictive values are better and I recommend a ratio of >30 for distinguishing epithelial ovarian malignancies from non-ovarian malignancies in my study population. Independently of histological

type of ovarian tumour, CA 125 and CEA values were significantly higher in cyst and ascitic fluid than in corresponding patients' serum. The higher values of both markers were also found in malignant than benign ovarian cysts.

HE4 - When a woman is in menopause age and if the HE4 level is <147 pmol/l, and what is very similar to the internationally accepted value of <140 pmol/l, there is a 9% chance of cancer. If HE4 is higher than 147 pmol/l and eGFR is not below 48 ml/min/1.73m2, 95% of cases are probably malignant. When a woman is in menopause age and if the HE4 level is <147 pmol/l, and what is very similar to the internationally accepted value of <140 pmol/l, there is a 9% chance of cancer. If HE4 is higher than 147 pmol/l and eGFR is not below 48 ml/min/1.73m2, 95% of cases are probably malignant. HE4 has shown a sensitivity and specificity of 72.9 and 95%, respectively, for differentiating between types of ovarian masses, which is better than that of CA-125 detection. HE4 is highly expressed in ovarian cancer, endometrial cancer tissues and in the adjacent tissues, normal tissues and benign tumors

CA 72-4 - Independently of histological type of ovarian tumour, CA 125 and CEA values were significantly higher in cyst and ascitic fluid than in corresponding patients' serum. The higher values of both markers were also found in malignant than benign ovarian cysts. CA 72-4 is indicated as a type 1 tumor marker to monitor treatment response and recurrence of gastric cancer, and as a type 2 tumor marker for the diagnosis of mucinous ovarian cancer. When gastric cancer is suspected, besides CA 72-4 testing, other tests must be done to confirm the diagnosis [11].

Table 1: Tumor markers

Tumor marker	*CA125, CA19-9*, CEA, CA72-4, HE4
Blood test	Blood serum marker (except where noted)
„Normal" results	< 2,5 νγ/μλ ιν νον σμοκερσ > 5 νγ/μλ ιν σμοκερσ γενεραλψ > 100 νγ/μλ σιγνιφιεσ μεταστατιχ χανχερ
Method	Chromogranin A

4.3. Ultrasonography

Basic ultrasound examination should differentiate benign from malignant ovarian tumors. The most difficult is to differentiate cyst adenofibromas, atypical endometrioid cysts and borderline ovarian tumors from early stages of malignancies. Using Doppler sonographic examination completes information about the biological behavior or the tumor. Ultrasonography is used to identify tumorous masses, but it is not able to predict the definite pathology.

The basic condition to determine exact diagnosis is precise definition of anatomy-topographic relationship of the mass according to the tissue around it and organs surrounding it. Pathologic process and neoplastic neo forms in lower pelvis vary too much from the point of view of ultrasonographist because of its' origin, localization, size, structure, and shape (Figure 2-4).

o Qualitative DUI examination - characteristic sign of malignant growth is appearance of neovascularization

Neovascularization – newly formed vascularity is characterized by irregular branching, erratic lumen, absence of lamina muscularis, dead-ending of veins and intervascular shunts especially in mucous type of tumor.

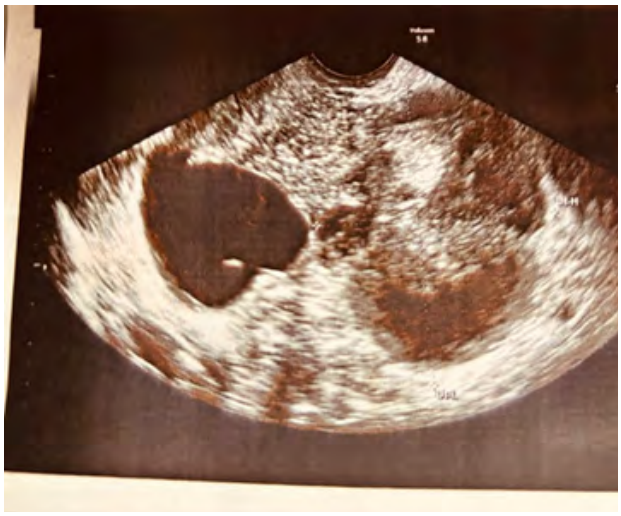
o Quantitative DUI examination – changed veins show failure of vasa-motoric control with following significant heterogeneity of flow. These changes are being able to capture and measure by using doppler ultrasound. We use to describe:

Resistance index – Using color Doppler ultrasound, Wu et al. 11 reported a significant gradual decrease in the mean value of the resistance inex (RI) from benign tumors (0.695), to borderline malignancy (0.535) and early stage ovarian carcinoma (0.485), to advanced stage ovarian malignancies (0.398). The intratumoral artery resistance index (RI) represents the blood flow impedance distal to the sampling point. It expresses the resistance to flow within the tumor and is lower in malignant tumors in comparison with benign ones.

Pulsatility index - to the ovary. Absent Doppler flow was characterized by the A special kind of ultrasound, color-flow Doppler, is sometimes used to measure blood flow to the ovaries. Blood flow is usually increased in ovarian cancers, although it may also be increased by other benign conditions. Normal Doppler flow was characterized by no decrease in arterial or venous flow absence of vascular flow to the ovary. Decreased Doppler flow was characterized by a decrease in vascular flow to the ovary, but flow was still present.

Absence of diastolic notch - The suspicion of malignancy is raised if the nodule is ill-defined, hypoechoic, has a thick irregular capsule and chaotic intranodular vascularity. The only reliable signs of malignancy on ultrasound include frank vascular invasion to adjacent vessels (such as internal jugular vein and common carotid artery). Even more suspicious is the absence of diastolic notch

Measure of detection of intra-tumorous flow in borderline tumors (90%) is comparable with malignant neoplasms (92%). The indices of resistance and pulsatility are significantly higher in carcinomas and borderline ovarian tumors, especially in mucinous types, comparing to benign tumors [12].



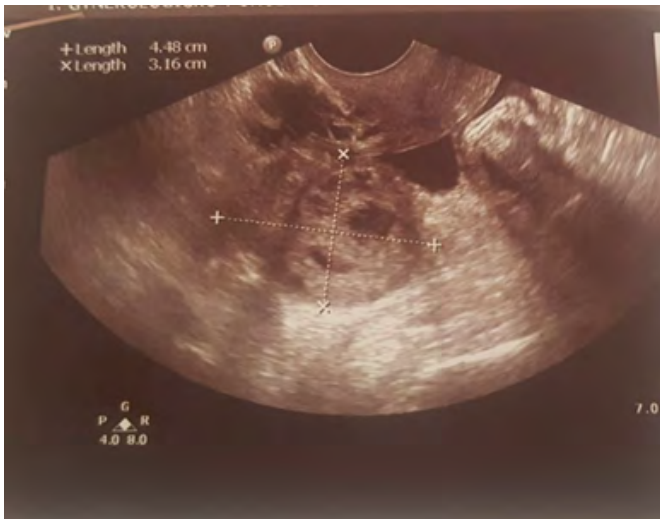


Figure 2 and 3: Ultrasound of the ovarian mass

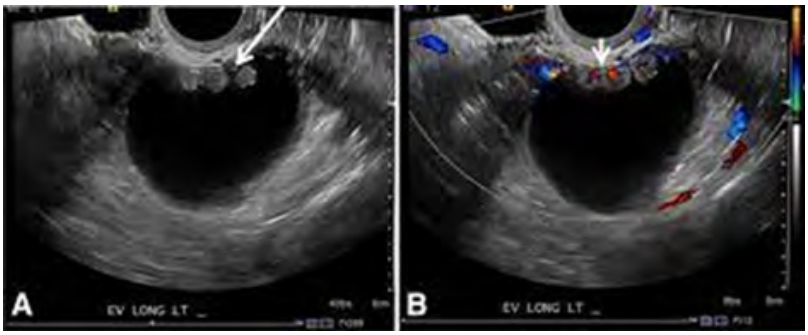


Figure 4: doppler ultrasound of ovarian mass (14)

4.4. Computer Tomography

Computer tomography is less precise method for differential diagnosis of ovarian tumorous processes according to lower contrast of the soft tissue, except differentiating fat from calcifications. By CT we can confirm

o Invasion into the urinary bladder

o Infiltration of lymph nodes

o Metastatic process into the parenchymatous organs

o Presence of ascites

The disadvantage of this method is radiational load and low detection of small peritoneal implants (15) (Figure 5).

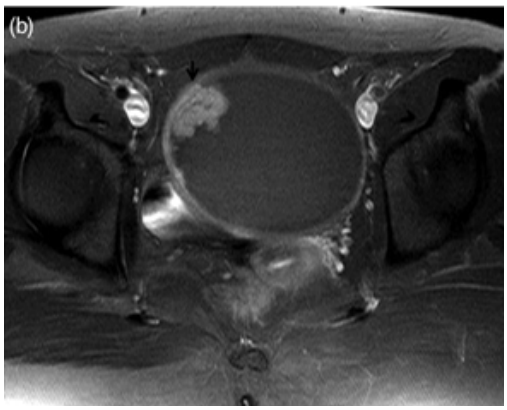


Figure 5: CT of ovarian mass

4.5. Magnetic Resonance Imaging

There is 93% accuracy of differentiating benign and malignant ovarian lesions in centers, which are specialized on this type of diagnostic. MRI differentiates for example fibroma with much higher probability than computer tomography and it's preferred in cases of suspected endometriosis.

With MRI we can precisely determine:

o Thickening of the ovarian mass wall more than 3 cm

o Papillarity of cystic lesion

o Necrosis of the tumor mass

o Imaging of the inner structure of the tumor

o Evaluating spreading of the process into surrounded area (urinary bladder, GIT)

o Evaluating lymphatic system

Not even MRI is able to characteristically differentiate borderline tumors from other types of ovarian tumors (Figure 6).

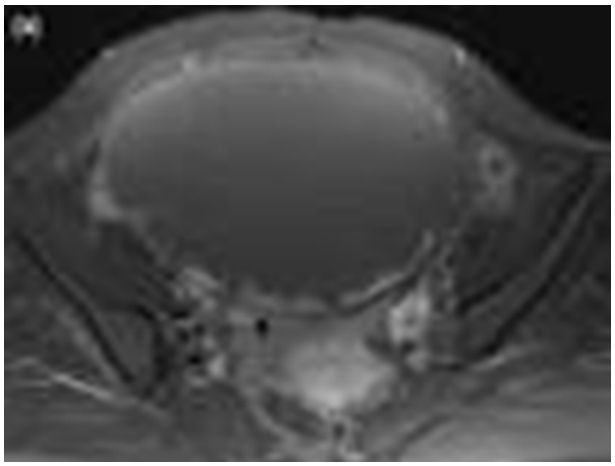


Figure 6: MRI of serous borderline ovarian tumor

4.6. Preoperational Frozen Biopsy

According to the fact that diagnosis of borderline ovarian tumor is not able to be determined preoperative, there is a possibility to determine the range of surgical treatment or any treatment modality. It is only possible by doing per-operative frozen section biopsy. Frozen section biopsy is used by surgeons in oncologic surgeries for having perioperative pathologic microscopic analysis. Frozen section biopsy has sensitivity 65 – 89% and specificity 97 – 100% in differentiating between invasion or non-invasion of the stroma of the primary tumor [16].

In cases where the tumor is larger than 10cm there can be a mistake and the presence of suspected structure in frozen section biopsy then has risk of falsely negative outcome. These kinds of false diagnoses or not diagnosing the carcinoma itself, where borderline ovarian tumor is interpreted as benign, usually leads to the second surgery – restaging – or increasing the risk of recurrences, in the worst case leads to the death of the patient. On the other side, false positive frozen section biopsy, overrated perioperative diagnosis, when benign tumor is mistaken for borderline tumor, leads to higher morbidity because of extending the surgical treatment (hysterectomy, bilateral adnexectomy, omentectomy or more). So, if the pathologist says during the surgery that it is probably borderline ovarian tumor, it's more probable, that in definitive description it will be carcinoma and not benign cyst. Diagnostic of borderline ovarian tumor is precise in 62,8% [17]. This diversity of the results between frozen biopsy and definitive histopathologic analysis is not case of wrong pathologist, but the other examinations need to be supplemented as a purpose to evaluate mitotic activity of cell cores, presence, or absence psammomatous bodies and imunochemic profiling.

4.7. Facultative Examinations

Supplementary examinations are not realized routinely, each such exam has precise indication

- Uretherocystoscopy – in determination of infiltration of urinary bladder

- Recto/colonoscopy – suspicion of infiltration of recto-sigma, these exams are followed by endoscopic examination with bioptic verification

- Gastroscopy – in suspicion for Krukenberg tumor

- PET – isn't the best sufficient method for differential diagnostic of benign and malignant tumors according to the fact of false negativity of borderline ovarian tumors [7].

5. Therapy

a) Surgical treatment and staging of borderline tumors

Surgical treatment has crucial role in determination of the diagnosis of borderline ovarian tumors and follow-up primary treatment and also treatment of recurrences of borderline tumors. From laboratory or other imaging, it is not possible to expect the definite pathology.

In the past borderline ovarian tumors were considered as pre-tumorous status before invasive carcinoma. From this comes out a therapeutic strategy, which is not different from therapy of invasive carcinomas, including complete staging-surgical treatment and indication of adjuvant chemotherapy.

Until now the surgical treatment strategy is unclear and is not unified, for example NCCN (National Comprehensive Cancer Network) states the surgical treatment for borderline ovarian tumor just like the same staging treatment for invasive ovarian carcinoma, including systematic lymphonodectomy [7].

Diagnosis of borderline ovarian tumor is based on histopathologic examination of samples.

Guidelines recommend following range of staging treatment for

1) Early stage of borderline ovarian tumor

o Bilateral adnexectomy

o Hysterectomy

o Biopsy of peritoneum – from both pelvic sides, plica of urinary bladder, both paracolic sides, subdiafragmatic area

o Infracolic omentectomy

o Lavage – lavage of pelvis, both paracolic sides and subdiafragmatic area

o Appendectomy

2) In less usual advanced stages, the target of the surgical treatment is only staging of the disease, eventually cytoreductive operation, that means removing tumorous masses, which we call "debulking". According to number of tumorous masses left, we differ optimal (less than 20%) and suboptimal (more than 20%) debulking.

b) Conservative Therapy

Borderline ovarian tumors are more likely to occur in women in reproductive age and therefore it is needed to preserve the fertility and reproductive functions.

Patients in stage I with unilateral exophytic tumor and intact ovaries can be treated for fertility-sparing surgery, which is preferred as adnexectomy instead of cystectomy in cases of recurrences.

Random biopsy is not recommended in the left ovary in case of normal macroscopic finding, because it can lead to adhesions and negatively influence fertility of the patient.

In case the tumor invades both ovaries it is not possible to identify the healthy tissue, but it has meaning to left uterus in situ and then include the patient in the oocyte donation program.

In these patients with indicated fertility sparing surgery is followed by risk of recurrence much higher than in those with radical surgical treatment. Number of recurrences after adnexectomy is around 0 – 20%, after cystectomy 12 – 58% and after radical surgical treatment 2,5 – 5,7%.

High risk of recurrence after conservative treatment occurs in cases of tumors with invasive implants in 15 – 30%. That is why in advanced there aren't conservative types of surgery recommended [18].

c) Laparoscopic Surgery

Laparoscopic treatment is not considered as a standard approach because in these cases there is higher probability of rupture of the tumorous cyst and incomplete staging. In case of the rupture of the cyst there comes dissemination of the disease in peritoneal implants and also occurrence of implantation metastases in places after insertion of ports. So, the instillation of CO_2 and increased intraabdominal pressure are considered as predisposition factors of formation of peritoneal dissemination of the disease [19].

d) Adjuvant Treatment

Borderline ovarian tumors can reoccur even after 10 years after initial diagnosis. The ratio of recurrences is higher in advanced stages.

Recommendation for adjuvant therapy of borderline tumors comes from very few studies. Presence of residua is not decision-making process for adjuvant chemotherapy. In case of adequate surgery and non-invasive implants is the surgical treatment sufficient. Indication for adjuvant chemotherapy is presence of invasive implants.

Borderline ovarian tumors have quite slow growth fraction and higher ratio of cells in G0 phase, which is the disadvantage for most cytostatic, which work on proliferating cells.

In the studies there are more types of chemotherapy. Chemotherapy is based on platina derivate and taxans. Indication for adjuvant chemotherapy is related to the prognostic factors. The only prognostic factor is histological type of implant. In 5-year observation the progression increased in 2% in patients with non-invasive implants and in 31% in those with invasive implants [20].

Gershenson recommended these criteria for postoperative therapy [21]:

o Invasive implants

o Non-invasive implants with macroscopic residua

Sevcik indicated adjuvant chemotherapy in these cases [22]:

o Unusual type of tumor

o Micropapillary growth pattern

o Presence of invasive implants

o Aneuploidy of the tumor

e) Lymphonodectomy

Disabling of the lymphatic system in patients with borderline ovarian tumors are happening very often, especially in advanced stages it's around 20 – 30%. Most studies surprisingly didn't confirm the prognostic meaning of the positivity of lymph nodes. The opinions on performing the lymphonodectomy varies from author to author [7].

Most studies didn't show any significant difference in rate survival in patient with regional lymphonodectomy performed, but thankfully to the progress of lymphonodectomy didn't increase through the modern technical instruments use in lymphonodectomy itself.

According to latest conclusions the status of regional lymph nodes doesn't represent negative prognostic factor. Other studies with higher number of patients are needed [23] (Figure 7-10).

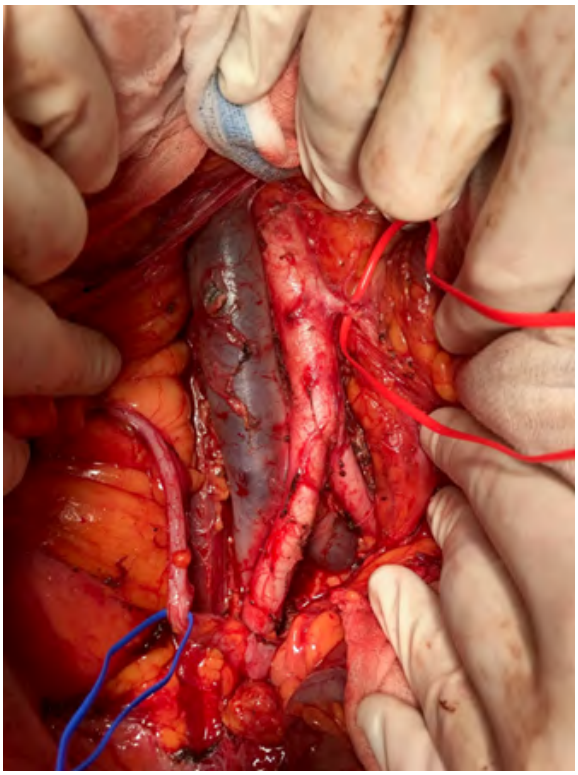
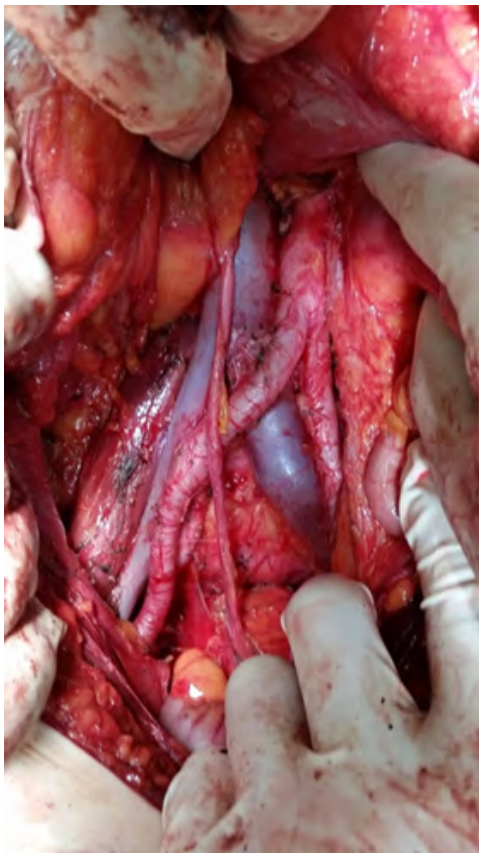


Figure 7: para-aortal dissection of lymph nodes



Figures 8: Staging dissection

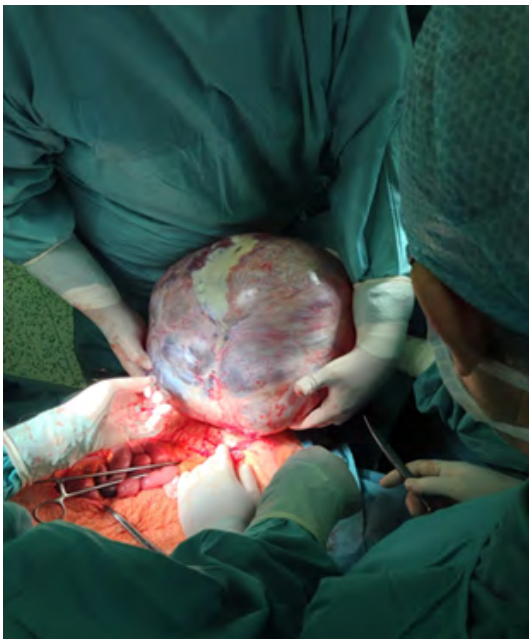


Figure 9: Tumor in situ – precise preparation

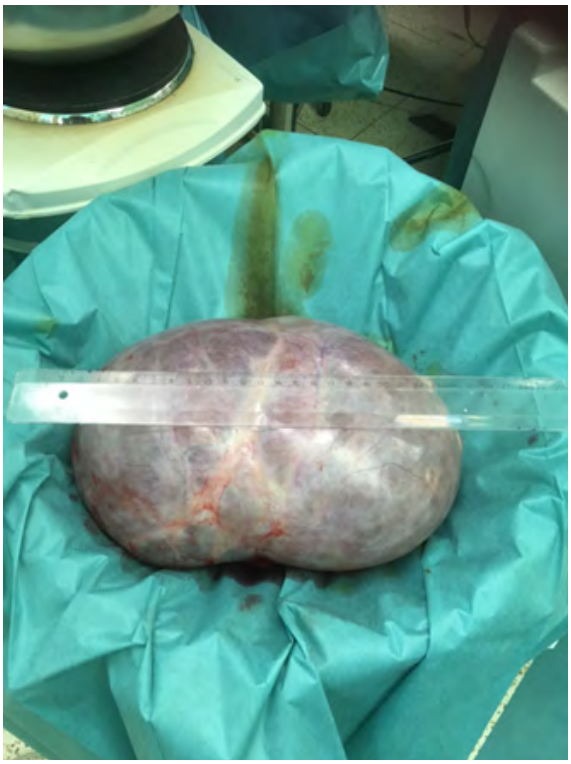


Figure 10: Intact tumor cut out

f) Therapy of Recurrences

Recurrences more often occur in cases of bilateral tumors (stage 1B) or rupturing of the capsule during surgery [24].

Most of recurrences are localized only to peritoneum and lymph nodes, although in one patient, who underwent unilateral adnexectomy, we found recurrence on the contralateral ovary. Further metastases are rare (lungs, mediastinum, brain, bones, liver). Relapsed tumors with invasive implants are primary the most important prognostic factor. In recurrences on ovary after previous conservative surgery usually the adnexectomy is finished.

Indications for conservative treatment are identical with the primary treatment, but the patient must be informed about the risk of this conservative approach.

Opinions on chemotherapy in recurrences of borderline ovarian tumors vary [24] (Table 2).

Table 2: % of recurrences within 4 years according to the stage and type of therapy

Stage and type of therapy	*% of recurrences*
Stage I and conservative therapy	15,2%
Stage II and radical therapy	2,5%
Stages III and IV and conservative therapy	40%
Stages III and IV and radical therapy	12,9%

g) Dispensarisation after Treatment

In invasive carcinomas the recurrence occurs mainly withing 2 years after finishing the treatment, but in borderline tumors this period is quite longer. Recurrences occur usually long time after surgery. Silva in 1996 studied 80 patients with borderline ovarian cancer, in who the recurrence occurred approximately 15,7 years after treatment. In most of these patients there had been performed bilateral adnexectomy. But the recurrences were up to 44%, in 10% within 5 years, in 19% within 5 – 10 years and in 15% more than 10 years after diagnosis [25]. Therefore it is recommended to dispensarize the patients with borderline ovarian tumor, by using combination of ultrasound or staging CT with examination of oncomarkers [26] (Figure 11).

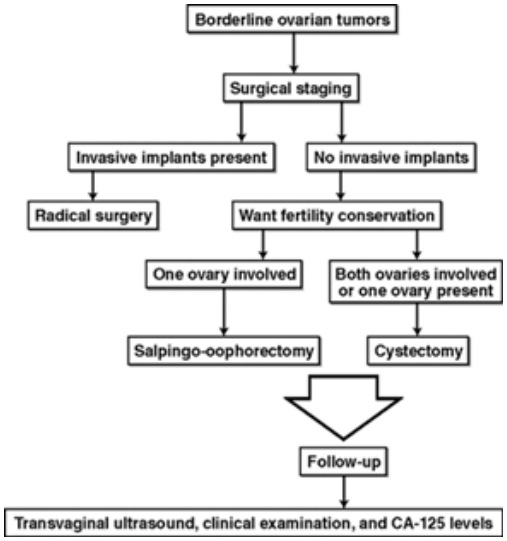


Figure 11: Diagnosis to treatment to dispensarisation – management of borderline ovarian tumors

6. Prognosis and Prognostic Factors

The most important prognostic factor of borderline ovarian tumors from the view of recurrences is the range of performed surgical treatment [7].

Prognostically important factors are DNA ploidy, TNM stage and histological type of tumor (better prognosis is in serous borderline ovarian tumor type). Invasive implants are also important prognostic factor which makes the prognosis worse [27].

Patients with adequate examined of serous borderline ovarian tumor (typical and micropapillary) in FIGO I stage (without microinvasion) have 5-year survival rate prognosis almost 100% with a very low risk of reoccurrences [28].

Micropapillary variant differs from the typical one by occurring more often bilaterally, affecting surface of the ovary, mainly diagnosed in advanced stages and with the occurrence of invasive peritoneal implants [29].

Prognosis of the patients in advanced stage without non-invasive implants is 95% 5-year survival rate. Prognostically negative factor is occurrence of invasive peritoneal implants, which decrease the 5-year survival rate down to 55 – 60% [30].

7. Discussion

The basic treatment of borderline ovarian tumors is surgical resection. In surgical treatment it is necessary to determine the way and range of the treatment individually case by case according to the potential unclear findings and precise histological staging. In cases of advanced forms and presence of infiltration of the large intestine or presence of peritoneal infiltration it is needed to extend and modify the resection. Local dissection of lymph nodes does have significant prognostic it is the safe method therefore it's needed to be done for precise staging of the disease and clarifying the presence or absence of metastasis into lymphatic nodes. It doesn't mean any higher surgical risk for patient.

Long time dispensarisation and observation of the patients is important because of the possibility of the recurrence of the disease after many years.

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