

# Borderline ovarian tumors – literature review

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## Summary

Borderline ovarian tumors (BLOTs), also called semi-malignant ovarian tumors, despite a clear classification, represent one of the most controversial topics in oncogynecology. Although it is not a rare diagnosis, there are no prospective randomized studies showing clear recommendations regarding the management of this disease. The disease incidence reaches its peak when women attain their reproductive age, thus, a fertility sparing approach is often the goal of the treatment. Surgery remains the main therapeutic strategy. A clear definition for low- or high-risk patients requiring more or less aggressive treatment is lacking. Nowadays, the main factors deciding the range of therapeutic approach depends upon the histopathological features; particularly the presence of invasive implants and microinvasion, as well as the staging of the disease. Recent genetic assessment has brought new knowledge, but the extrapolation to clinical practice is still missing.

*Key words:* Borderline ovarian tumor; Peritoneal implants; Fertility sparing surgery; Invasive implants.

## History of borderline ovarian tumors

Borderline ovarian tumor (BLOT), also called tumors with a low malignant potential, belong to the group of epithelial ovarian tumors showing some features of malignancy [1]. Interest in a clear classification was conducted over 75 years ago. The first mention was from 1898, when Hermann Johannes Pfannenstiel described papillary cystadenoma with borderline malignant properties [2]. A similar description was put forth in 1901 by Carl Abel to the group of proliferative papillary cystadenomas; he marked their growth on the border between benign and malignant lesions [3]. The term, semi-malignant or borderline tumors, was presented by Howard Taylor in 1929. Serous cystadenocarcinomas was ranked between the main groups of the two previously classified tumors [4]. The first comprehensive reference to the mucinous BLOT was in 1955, which was described in a study by the Cleveland clinic [5]. The definitive form of the classification of BLOT was determined by the International Federation of Gynecology and Obstetrics (FIGO) in 1971 [6]. The World Health Organization in its classification of ovarian tumors in 1973 substituted for BLOT, the synonym “tumors with low malignant potential” with BLOT [7].

## Introduction

Currently, despite a clearly defined classification, BLOT is one of the most controversial topics in oncogynecology, especially in terms of the choice of therapeutic approaches. The indicators of incidence show a relatively wide range, i.e. 4-14% of all ovarian tumors are BLOT. This fact is due to the uncertainties in histopathological definitions, mainly

of the early stages of BLOT. Leitaó *et al.* in 2004, reclassified up to 29% of early ovarian cancer patients to BLOT from a study involving 20 years of patient investigations (1980-2000) [8]. The above facts, as well as the proactive approach to diagnostic processes, have led to a 500% increase in the incidence of BLOT in last 40 years [9]. A clear understanding of the specific etiological factors remains unexplained. Among the predisposing factors, according to some authors, include: menarche, age of first conception, age of first pregnancy, age of first birth, smoking, and a positive family history of ovarian cancer. It is not rare that a mucinous BLOT was confirmed as a metastatic focus from an appendical carcinoma. Compared to the malignant ovarian tumors, BLOT occurs mainly in younger patients, i.e. in patients about ten years younger than in the case of malignant ovarian tumors (53 vs. 63 years) [9, 10]. The incidence during the reproductive age represents the main factor influencing surgical treatment. The symptoms of the disease are non-specific and include abdominal pain and an increase in the waist circumference; however up to 23% of the patients are asymptomatic [11]. Imaging studies (USG, CT, and MRI) help with the diagnosis, but only in terms of the detection of the suspected tumorous mass. Although Bent *et al.* in their study using MRI for the diagnosis of BLOTs, showed that serous BLOTs are significantly smaller than mucinous BLOTs. Nevertheless clear characteristic features for different BLOTs were absent [12].

There are two different types of BLOT regarding histological classification, i.e. serous and mucinous type. The incidence of serous BLOT is higher when compared to mucinous BLOT. Other histologic subtypes such as endometrioid, clear cell BLOT, BLOT from transitional cells,

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as well as BLOT from mixed epithelial cells, represent rather rare occurrences. It is expected that serous types are derived from the germinal epithelium. The origin of the mucinous types has not been clearly defined [13].

The results of genetic studies are still unclear, although the pilot studies demonstrated some correlation [14]. Currently, the main approach for women during their reproductive age is fertility sparing treatment.

### Serous borderline ovarian tumors

There is a higher incidence of serous BLOT in the population compared to mucinous BLOT. Borderline tumors represent 9-15% of all serous ovarian tumors [15]. It is a disease affecting predominantly women in their reproductive age, although, the occurrence in postmenopausal women is not rare. The median age for serous BLOT is 38 years [16]. Due to its slow growth, most cases are diagnosed in their early stages. Regarding FIGO statistics, up to 68% of all serous BLOTs are diagnosed in Stage I; in Stage II it is 11%. Almost one quarter of all diagnosed serous BLOTs are in advanced stages, i.e. 21% in Stage III and only 1% in Stage IV [17]. Although most of the cases are detected in early stages, bilateral occurrence represents up to 40% [18].

Cystic and papillary tumors are usually macroscopically seen. The sizes of the tumors are different; Segal *et al.* in a study of 98 serous BLOT patients detected a size of 2-25 cm, median 10 cm [18]. In approximately half of the patients, a papillary tumor is located on the surface of the ovary. The origin of this tumor is directly from the surface epithelium, not from a tumor inside the ovary. In 10% of the cases, only an exophytic tumor is seen, without any intraovarian tumor components [18]. The typical serous BLOT represents a non-invasive proliferative disease with the cells including a mild to moderate nuclear atypia. The presence of high nuclear atypia represents an important histopathological criterion characterizing conventional serous papillary carcinomas. Psammomatous bodies (in the case of the serous BLOT) are often present in parts of the stromal invasion.

There is a specific variant in the group of serous BLOTs regarding the histopathological features. Micropapillary variants represent 6-18% of all serous BLOTs [19, 20]. This subgroup of BLOT is characterized by specific histopathological findings of micropapillary features, as well as by a worse prognosis. Compared to the classical serous BLOT, in the micropapillary variant (more frequent bilateral occurrence) exophytic growth as well as faster growth has been seen. Some studies showed a higher incidence of peritoneal implants and shorter disease free interval in the case of micropapillary variant compared to the classical type of serous BLOT [19-21]. Due to these mentioned facts, advanced stage of micropapillary serous BLOT is often diagnosed. On the other hand, there are studies that did not

confirm a significant difference in overall survival between micropapillary and classic BLOT [19, 20].

### Microinvasion

One of the most important histopathological diagnostic criteria of BLOT is the absence of clear stromal invasion. However, the areas of stromal microinvasion containing the same cells like the original cells of BLOT, can be present. There are slight differences in the literature regarding the criteria of stromal microinvasion. Most of the studies concluded that a microinvasion of three mm (with total range up to ten mm<sup>2</sup>) constitutes a maximal size [22, 23]. Only a few of the studies showed the size of five mm for microinvasions [13]. The incidence of stromal microinvasion in the group of serous BLOTs represents 9-10% [24,25]. A slightly higher percentage of stromal microinvasions (13%) was seen using an immunohistochemical assessment by epithelial markers [26]. Although the presence of stromal microinvasion predicts the local spread of the disease, it does not represent a significant prognostic factor compared to the staging of the disease and the presence of peritoneal implants. Looking at the overall results of a number of studies, the stromal invasion represents the main risk factor in the advanced stages [19, 24, 25, 27].

### Peritoneal implants

Peritoneal implants (PI) presented in a BLOT diagnosis represent an extraovarian disease located on the serous surfaces of the abdominal cavity or the omentum. There is a wide range of the PI incidence in the literature, i.e. 20-46% [24]. This fact is due to a controversy in the histopathological criteria used for the diagnosis of PI, as well as due to the need to decide when a precise surgical intervention is necessary. A close connection between the incidence of PI and the presence of exophytic BLOT has been documented. Peritoneal implants were diagnosed in 75% of the exophytic BLOTs, while additionally up to 94% of the patients initially diagnosed with PI have confirmed exophytic ovarian tumors [18]. Based on the histological criteria, two different types of the PI with different prognostic influence are known, i.e. invasive and non-invasive. Eighty-three to 94% of all PI are usually non-invasive and can be epithelial, desmoplastic or have both components. The predilection site of the non-invasive PI is the peritoneum. The incidence of invasive PI is significantly lower compared to non-invasive PI. Their diagnosis is still controversial, often confronted with the possibility of over-diagnosis or under-diagnosis due to well differentiated serous carcinoma and therefore includes in part, the subjectivity and experiences of the pathologist. Only 4-13% of all PI are stated as invasive [19, 24, 28]. The different types of PI usually do not occur independently, and often both invasive and non-invasive PI are seen simultaneously. Therefore, the precise surgical staging,

as well as experiences of the pathologist, are inevitably needed.

Questions regarding the origin of PI remain unanswered. A close connection with exophytic tumor is the disintegration of the exophytic cells and the subsequent affectation of the serosa or the surface of the omentum. However, PI have also been confirmed in cases of the absence of any exophytic ovarian tumor. They have also been seen if endosalpingiosis is diagnosed. Therefore, it is possible for PI to exist without the influence of an exophytic tumor [29, 30]. Molecular genetic studies have confirmed both mechanisms, although a correlation with an exophytic tumor may often be seen [31, 32].

### Prognosis

Based on the BLOT incidence, there are only indicative data regarding survival and mainly in cases of advanced BLOT. The slow growth leads usually to the detection of early stages, thus the advanced stages are diagnosed less often. The problem involves, “understaging”, which is mainly due to insufficient surgical treatment and partially due to insufficient pathological examination. Excellent results of overall survival in Stage I BLOT after 15 years were seen (95-100%). However, disease recurrence can occur even years after the primary diagnosis. Latent intervals have been described as 7-50 years [19, 33, 34]. The decrease in overall survival is inevitably in the advanced stages, although it is strongly influenced by the number of patients studied. A Norwegian study demonstrated a 15-year overall survival reaching 77% in Stage II and 64% in Stage III of the disease. However in both groups, only 13 patients were included [34].

The disease prognosis is differently affected by the presence, as well as by the absence of PI. Non-resected non-invasive PI can latently persist even years; their spontaneous regression may also be seen. Thus, the morbidity is caused mainly by adhesions and recurrent bowel obstructions due to PI or as a consequence of their treatment. The presence of invasive PI represents a negative prognostic feature. Invasive growths as well as the presence of nuclear atypia are the main indicators [35].

Discrepancy in the literature regarding the prognosis of micropapillary variants of serous BLOT has been found. In some studies, a higher probability of invasive PI presence, as well as a shorter interval to disease recurrence has been seen in cases of micropapillary BLOT compared to classic serous BLOT, although there are studies showing no significant difference in the overall survival when classic and micropapillary variants of BLOT were compared. Nonetheless, a higher incidence of bilateral occurrence as well as exophytic growth may be connected with adverse prognosis of micropapillary BLOT [19-21]. Genetic studies have confirmed that fact as well. While 95% of BLOTs have diploid DNA (thus connected with an excellent prognosis), a micropapillary variants of BLOTs have aneuploid DNA

(leading to higher risk of disease recurrence). Other genetic studies have shown that p53 mutation and HER2 overexpression are connected with an adverse prognosis in the invasive ovarian cancer. Nevertheless, their mutations lead to a better prognosis if BLOT is diagnosed.

There is no clear predictive value of oncomarker CA-125 in BLOT patients. An initial elevation is not typical for BLOT, only values higher than 100 IU/ml are suspected from invasive ovarian cancer. The use of CA-125 in the follow-up is controversial as well, since in up to 65% of the patients with BLOT recurrence, normal levels of CA-125 were detected.

### Treatment

Surgical treatment represents the main therapeutic strategy for BLOT patients. Since BLOT affects predominantly women in their reproductive age, fertility sparing surgery is often required. A good prognosis in the detection of the early stages allow for conservative treatment.

Ovary sparing tumorectomy is reserved for Stage I patients with a unilateral exophytic tumor and intact ovaries [36]. Unilateral adnexectomy is indicated in the early stage of patients, but in up to 15% of the patients, recurrences in the contralateral ovary were confirmed [24]. Advanced stages require radical surgical treatment. In a study conducted by Shih *et al.*, complete surgical staging was also needed when the size of the tumor was more than eight cm or if rapid pathology confirmed micropapillary, endometrioid or clear cell variant [37]. Complete surgical staging include: cytology of ascites or peritoneal lavage, hysterectomy, bilateral adnexectomy, regional lymphadenectomy, omentectomy, and appendectomy, followed by precise pathological examinations. Observation after surgery is sufficient in the case of the absence of residual tumor or invasive PI. Adjuvant chemotherapy is therefore reserved for patients with residual tumor, confirmed invasive PI, as well as for clinically progressive disease. The chemotherapeutic algorithms used in treatment are usually the same as in case of the epithelial ovarian cancer. However, the benefit of adjuvant chemotherapy was not confirmed by a prospective randomized study [38].

### Mucinous borderline ovarian tumors

Mucinous types represent a minority group of BLOTs. The biology of these tumors is significantly different compared to the group of serous BLOTs. There were two basic types defined, i.e. intestinal type and endocervical-like type (Müllerian type) [39].

The occurrence of the endocervical-like type is rather rare. In general, the incidence represents 5-14% from all mucinous BLOT [22]. The histopathological features, as well as the clinical presentation, are similar to the serous BLOTs, with a tendency to occur concurrently, known as mixed or seromucinous BLOT. In both, Müllerian or mixed types, the

association with endometriosis has been confirmed.

The incidence of the intestinal type of BLOT is significantly higher than the primary invasive mucinous ovarian carcinoma. Similar to serous BLOT, it predominantly affects women in reproductive age with a median age of 35 years. Usually, bulky masses (median 17 cm) with a smooth surface are seen macroscopically occupying not only the pelvis but also substantial parts of the abdomen. Typically, a unilateral tumor is found, with only 10% of the cases being bilateral mucinous BLOT [40]. Also, a heterogeneous composition of the intestinal types of BLOT is often seen. In histology, the structures of a non-invasive carcinoma, cystadenoma or even an invasive carcinoma can co-exist. Thus, the precise histological assessment of the tumor is necessary. Due to the bulky masses, sufficient time for the precise pathology is needed, which is not a problem, if a definitive pathology is performed. The inability to examine a whole tumor during rapid perioperative pathology can often lead to an erroneous or incomplete diagnosis.

Microinvasion, in the case of mucinous BLOT, occurs in 9% of the diagnosed cases [22, 23]. The criteria for a microinvasion classification are similar to a serous BLOTs, although the foci in mucinous BLOT usually reach a diameter of 1-2 mm [41]. In the literature, the presence of in situ invasive structures is reported discrepantly. The incidence varies between 15% to 55% [22, 23].

Advanced stages of mucinous BLOTs have been diagnosed rarely and often the occurrence of pseudomyxoma peritonei may be seen [34, 42]. Pseudomyxoma peritonei arises usually after the rupture of a mucinous adenoma of the appendix. Thereafter, with implantation of mucinous epithelium on the surface of peritoneum, mucin is subsequently produced. Thus, the advanced stages of mucinous BLOTs, with coincidence of pseudomyxoma peritonei, originate from the gastrointestinal tract, not from the ovaries [43, 44].

### Treatment

Despite bulky masses, mucinous BLOTs are usually diagnosed in Stage I. Surgical treatment represents the main therapeutic strategy. The disease recurrence in Stage I after surgical treatment (if mucinous BLOT without structures of non-invasive carcinoma is found) is reported to be 0-3%. The presence of non-invasive carcinoma in the mucinous BLOT pathology increases the risk of disease recurrence up to 7% [13, 45]. Therefore, the negative prognostic factors for the disease recurrence are the presence of microinvasion and the presence of the structures of an invasive carcinoma. The five-year overall survival in Stage I mucinous BLOT, without microinvasion or non-invasive carcinoma, is reported to be up to 98%. There are just minimal differences in the ten-year overall survival, i.e. 96% [40]. The strategy of the treatment is the same as in the case of serous BLOT. The risk of the origin from the appendix leads to the necessity of an appendectomy, if mucinous BLOTs are diagnosed.

### Conclusion

Nowadays, the increase in the incidence of BLOT is due to specification of histopathological features seen. The main therapeutic strategy remains surgery in order to reduce its range and thus preserve fertility of the treated woman. Genetic studies represent an experimental field, with the potential help of benefits the future.

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