

Research article/Raziskovalni prispevek

HISTOLOGICAL TYPES AND PAPILLAR GROWTH PATTERN IN BORDERLINE OVARIAN TUMORS: A RETROSPECTIVE STUDY

HISTOLOŠKI TIPI IN PAPILARNA RAST PRI MEJNO MALIGNIH TUMORJIH JAJČNIKA: RETROSPEKTIVNA RAZISKAVA

Borut Gorišek, Marija Rebolj Stare

Department of Gynecology and Perinatology, University Clinical Centre Maribor, Ljubljanska 5, 2000 Maribor

Abstract

- Background** *Our retrospective study was carried out with the aim of establishing the percentage of histologic types in borderline ovarian tumors (BLOT), bilateralism and the presence of papillary growth according to individual types.*
- Methods** *The study included 55 women treated at Maribor Teaching Hospital between January 1st, 1993 and December 31st, 2001. Data were collected up to April 1st, 2005.*
- Results** *Serous BLOT prevailed (74.5 %) while the number of mucinous BLOT was smaller (21.8 %). Borderline ovarian tumors were bilateral in 20 % of women and unilateral in 80 %. Among bilateral BLOT the serous type prevailed (90.9 %) while the mucinous were bilateral less often (9.1 %). Of the bilateral BLOT as many as 63.6 % were in stage II–IV. Papillary growth was found in 40 % of BLOT, 95.45 % of them were of the serous and only 4.45 % of the mucinous type. A statistically significant connection was established between the serous histologic type of BLOT and papillary structure ($P = 0.004$).*
- Conclusions** *Borderline ovarian tumors are mostly serous, one fourth are bilateral and more than one half have papillary growth. Serous BLOT involve peritoneal implants and positive pelvic lymph nodes more often than the mucinous. Mucinous BLOT were mostly unilateral, rarely with papillary growth, and with negative lymph nodes.*
- Key words** *borderline tumor; ovary; serous histologic type; mucinous histologic type; papillary growth*

Izveček

- Izhodišča** *Problem mejno malignih ovarijskih tumorjev (BLOT) je prvič izpostavil Taylor leta 1929, ko je opisal podvrsto ovarijskih tumorjev in jih označil za semimaligne. Svetovna zdravstvena organizacija (WHO) in Mednarodna organizacija za ginekologijo in porodništvo (FIGO) sta jih opredelila kot posebno podskupino ovarijskih tumorjev šele v začetku 70. let 20. stoletja. Predstavljajo 10–20 % vseh epitelnih ovarijskih tumorjev. Imajo nizek maligni potencial in počasno rast. Najpogostejši so serozni in mucinozni. Bolnice z BLOT imajo relativno dobro napoved, le manjša skupina ima slabšo. Zato je dobro poznati dejavnike, ki nam omogočajo, da te bolnice s slabšo prognozo prepoznamo in dodatno zdravimo. Z retrospektivno raziskavo smo želeli ugotoviti delež histoloških tipov mejno malignih tumorjev jajčnika (BLOT), bilateralnost ter prisotnost papilarne rasti po posameznih tipih.*

Corresponding author / Avtor za dopisovanje:

Marija Rebolj Stare, MD, Department of Gynecology and Perinatology, University Clinical Centre Maribor, Ljubljanska ulica 5, 2000 Maribor, Slovenia, E-mail: mitzir@email.si, mitzirs@gmail.si

Metode	<i>Vraziskavo je bilo vključenih 55 bolnic, ki so bile v obdobju 1. 1. 1993–31. 12. 2001 zdravljene v Učni bolnišnici Maribor. Uporabo podatkov za statistične namene so vse bolnice dovolile. Redno smo jih spremljali v Ambulanti za onkologijo. Zbrali smo podatke do 1. 4. 2005.</i>
Rezultati	<p><i>Vključene so bile vse bolnice. Stare so bile od 18–87 let, z mediano 48 let in povprečno starostjo $50,7 \pm 16,7$ leta. Sledenje bolnic je trajalo od 9–145 mesecev, povprečno $76,73 \pm 4,59$ meseca, mediana 73 mesecev.</i></p> <p><i>Po histološkem izvidu smo bolnice razdelili v skupine s seroznim (74,54 %), mucinoznim (21,82 %) in drugimi (Sertoli-Leydig, mešani epitelni) histološkimi tipi (3,64 %). Prevaloval je serozni tip BLOT (74,5 %), manj je bilo mucinoznega (21,8 %). Mejno maligni tumorji jajčnika so bili obojestranski pri 20 % bolnic in enostranski pri 80 %. Obojestranski so bili predvsem seroznega tipa (90,9 %) in manj mucinoznega (9,1 %). Kar 63,6 % obojestranskega BLOT je bilo pri stadiju II–IV. Papilarna rast je bila ugotovljena pri 40 % BLOT, od tega pri 95,45 % seroznega tipa in le pri 4,45 % mucinoznega. Ugotovili smo statistično pomembno povezavo med seroznim histološkim tipom BLOT in papilarno zgradbo ($p = 0,004$).</i></p> <p><i>Primerjali smo tudi načine zdravljenja. Pri 53 bolnicah (96,4 %) je bil operativni poseg citoredukcija brez rezidualnega tumorskega tkiva, pri eni (1,8 %) je bil rezidualni tumor do 2 ccm, pri drugi (1,8 %) pa večji od 2 ccm. Limfadenektomija je bila narejena pri devetih bolnicah (16,4 %). Pri vseh je bila narejena pelvična limfadenektomija, pri treh (5,45 %) pa še paraaortna. Odstranjenih je bilo do 36 pelvičnih bezgavk (povprečno 21) in 2–4 paraaortnih (povprečno 3). Pelvične bezgavke so bile pozitivne pri dveh bolnicah s seroznim BLOT (3,6 % vseh bolnic) (9 pozitivnih/35 odstranjenih, 10 pozitivnih/36 odstranjenih). Paraaortne so bile vse negativne. Adjuvantno terapijo s citostatiki je prejelo 9 bolnic (16,4 %).</i></p>
Zaključki	<i>Mejno maligni tumorji jajčnika so predvsem seroznega tipa, pri četrtini obojestranski in pri več kot polovici s papilarno rastjo. Pogosteje kot mucinozni ima implante po trebušni votlini ter pozitivne pelvične bezgavke. Mucinozni BLOT so bili večinoma enostranski, redko s papilarno rastjo, z negativnimi bezgavkami.</i>
Ključne besede	<i>mejno malignen tumor; jajčnik; serozni histološki tip; mucinozni histološki tip; papilarna rast</i>

Introduction

In 1929 Taylor was the first to expose the problem of borderline ovarian tumors (BLOT) when he described the subtype of ovarian tumors and designated them as semimalignant.¹ It was only at the beginning of the 1970's that WHO and FIGO defined them as a special subgroup of ovarian tumors.^{2,3} They represent 10–20 % of all epithelial ovarian tumors. They have a low malignant potential and slow growth. They are most frequently serous or mucinous.

With the exception of a minor group, women with BLOT have a relatively favorable prognosis. Therefore it is good to know the factors, which allow the identification and additional treatment of these women with poor prognosis.

With our study we wished to establish the percentage of histologic types of BLOT, bilateralism and the presence of papillary growth according to individual types.

Methods

In our retrospective study we analyzed the data of women treated for BLOT at the Maribor Teaching Hospital Department of Gynecologic Oncology and

Oncology of the Breasts between January 1st, 1993 and December 31st, 2001. All women consented to the use of their data for statistical analysis. They were followed regularly at the OPC for oncology. The data were collected up to April 1st, 2005 and analyzed statistically.

Results

At the Maribor Teaching Hospital Department of Gynecologic Oncology and Oncology of the Breasts, 55 women were treated for BLOT between January 1st, 1993 and December 31st, 2001. All were included in the study. Their age was between 18 and 87 years, with a median of 48 years and mean age 50.7 ± 16.7 years. Patient follow-up lasted 9–145 months, 76.73 ± 4.59 months on average, median 73 months.

In accordance with the histologic findings the women were divided into groups with serous (74.54 %), mucinous (21.82 %) and other (Sertoli-Leydig, mixed epithelial) histologic types (3.64 %).

In 20 % of our patients the BLOT were bilateral and in 80 % unilateral. The majority of bilateral BLOT were of the serous histologic type (90.9 %). Bilateral mucinous BLOT was found in one patient (9.1 %) only. We established a statistically significant connection

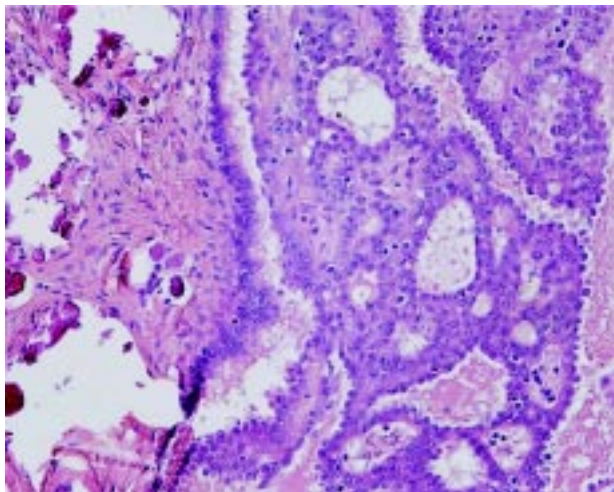


Figure 1. Serous BLOT without papillary growth (HE staining, 100× magnification).

Sl. 1. Serozni mejno maligni tumor jajčnika brez papilarnih rasti (barvanje s HE, 100× povečava).

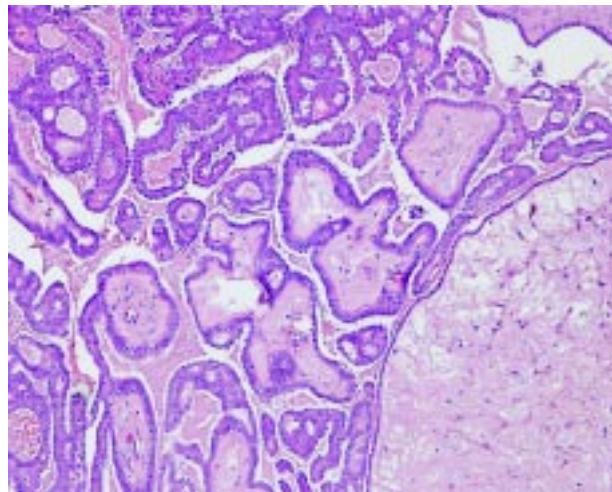


Figure 3. Serous BLOT with papillary growth (HE staining, 100× magnification).

Sl. 3. Serozni mejno maligni tumor jajčnika s papilarnimi rasti (barvanje s HE, 100× povečava).

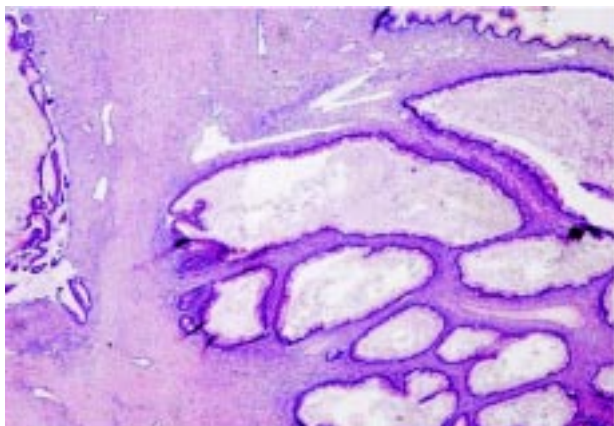


Figure 2. Mucinous BLOT without papillary growth (HE staining, 40× magnification).

Sl. 2. Mucinozni mejno maligni tumor jajčnika brez papilarnih rasti (barvanje s HE, 40× povečava).

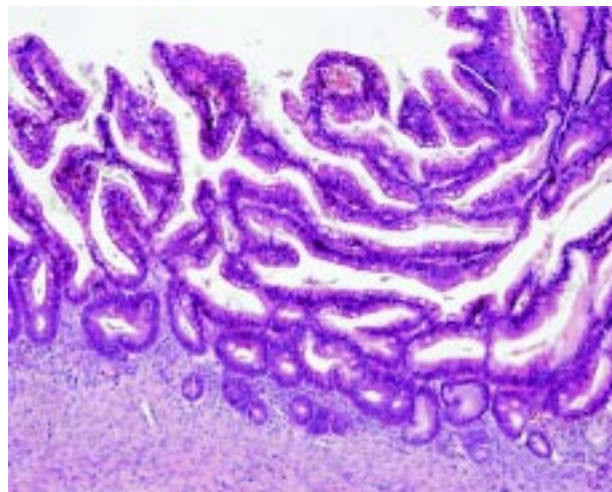


Figure 4. Mucinous BLOT with papillary growth (HE staining, 100× magnification).

Sl. 4. Mucinozni mejno maligni tumor jajčnika s papilarnimi rasti (barvanje s HE, 100× povečava).

between the presence of bilateral BLOT and staging into groups of stage I or II-IV ($P = 0.000$). In four cases (36.6 %) bilateral BLOT was found in the group with stage I and in seven cases (63.6 %) in the group with stage II-IV.

During histologic analysis papillary growth was also evaluated (Figure 1, 2). It was present in 22 samples (40 %), most of which (95.45 %) were serous BLOT (Figure 3) while there was only one case of mucinous BLOT with papillary growth (4.45 %) (Figure 4). There is a statistically significant connection between the serous histologic type of BLOT and the presence of papillary structure ($P = 0.004$). The connection between papillary structure and life performance status at the termination of follow-up did not prove statistically significant ($P = 0.057$).

The methods of treatment were also compared. In 53 women (96.4 %) the operative procedure was cyto-

reduction without residual tumor tissue, in one case (1.8 %) the residual tumor was up to 2 cc and in another (1.8 %) over 2 cc in size. Histology confirmed serous BLOT implants on the appendix (2×), omentum (1×) (Figure 5) and pelvic peritoneum (2×) as well as mucinous BLOT implants on the mesentery (1×). Metastatic invasiveness was not determined. Lymphadenectomy was performed in nine women (16.4 %). In all of them pelvic lymphadenectomy was performed, with additional paraaortic lymphadenectomy in three cases (5.45 %). Up to 36 pelvic (21 on average) and 2-4 paraaortic lymph nodes were removed. The pelvic lymph nodes were positive in two women with serous BLOT (3.6 % of all women) (9 positive/35 removed, 10 positive/36 removed) (Figure 6). All of the paraaortic were negative.

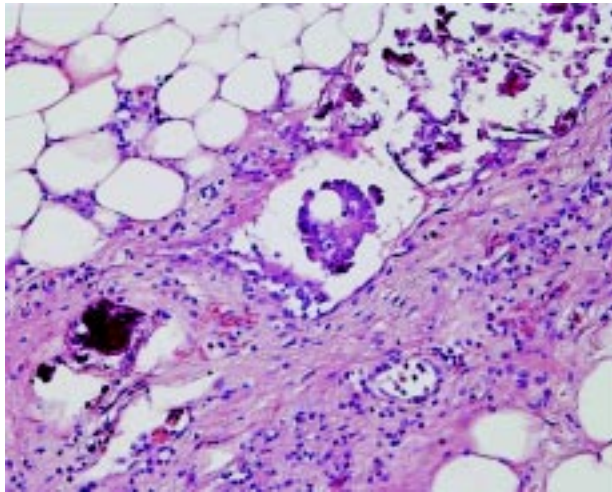


Figure 5. Metastases of serous BLOT into omentum (HE staining, 200× magnification).

Sl. 5. Metastaze seroznega mejno malignega tumorja jajčnika v pečico (barvanje s HE, 200× povečava).

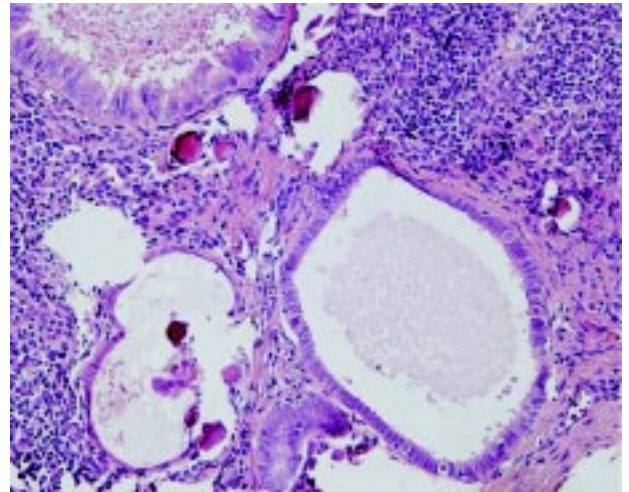


Figure 6. Metastases of serous BLOT into lymph node (HE staining, 200× magnification).

Sl. 6. Metastaze seroznega mejno malignega tumorja jajčnika v bezgavko (barvanje s HE, 200× povečava).

Adjuvant cytostatic therapy was administered to nine women (16.4 %). In all cases the disease was in stage II–IV, with only one exception. The only case of stage I BLOT, where the patient was treated with adjuvant chemotherapy, was a case of bilateral serous BLOT, evaluated macroscopically as malignant.

By the termination of follow-up, one patient with bilateral mucinous BLOT (stage IV) died nine months after surgical treatment at age 82, due to the progression of the disease, with a residual tumor exceeding 2 cc and histologically confirmed multiple mesenterial implants. On account of her age and general condition, chemotherapy was not applied. In the remaining patients there was no recurrence of the disease.

Discussion

Borderline ovarian tumors are a heterogenous group of tumors. They most often present as serous (54–55 %), more rarely as mucinous (39–40 %) and very rarely as endometrioid, clear-cell or Sertoli-Leydig.^{4,5} In our patients serous BLOT prevailed with 74.54 %. This percentage was over 50 % in other studies also (51.2 %, 52.2 %, 60.4 %).^{4–7} Mucinous BLOT comprised 21.8 % of all BLOT.

They presumably appear particularly in younger women, i. e. in over 50 % before the age of 40.⁸ According to our own results only 25.5 % of all BLOT occur up to this age and 50.9 % were found in women over the age of 50.

When evaluating the presence of papillary growth we found that it was present in 22 (40 %) BLOT – in 21 serous (51.2 % of all serous) and in one mucinous (8.3 % of all mucinous). In serous BLOT, papillary growth proved statistically significant ($P = 0.004$). Some authors believe that micropapillary growth is a reflection of an invasive tumor, despite the absence of classical signs of invasive growth.⁹ Micropapillary growth is more frequent in serous than in mucinous

BLOT.⁸ In serous BLOT with papillary growth, the ovarian surface is affected or changed more often, peritoneal implants are more frequent – invasive as well as noninvasive, which represent a negative predictive factor for recurrence.^{9–11} Therefore these tumors should be designated as micropapillary serous carcinoma.⁹ Women with micropapillary serous carcinoma have an 11 times higher risk for the occurrence of invasive carcinoma and a 19 times higher mortality rate as compared to those with serous BLOT without invasive implants.⁹

Invasive implants are distinguished from the non-invasive on the basis of their histologic appearance. They differ in their growth pattern, epithelial and stromal component, in the presence of psammoma bodies, cellular atypia and inflammation.⁹ We, however, did not assess the invasiveness of implants. Peritoneal implants were observed particularly in serous BLOT (83.3 % of all BLOT with implants), which is in agreement with other studies.^{8–10}

On the basis of the latest clinicopathologic studies some authors suggested the division of serous BLOT into those with micropapillary structure (micropapillary serous carcinoma, frequently in connection with invasive implants that are most likely its metastases) and all those remaining (atypical proliferative serous tumors, which may have noninvasive implants representing benign growth).^{9,11} The borderline category, thus subclassified into malignant and benign types, would become superfluous.¹¹ Such a classification would allow a rational approach to the diagnosis and treatment of these tumors.⁹

In our study we also evaluated the uni- or bilateralism of BLOT occurrence. In 44 women (80 %) it was unilateral and in the remaining 11 (20 %) bilateral. The majority of bilateral BLOT were serous (90.9 %), the rest mucinous (9.1 %). Bilateral BLOT occurred in 46.3 % of all serous and in 8.3 % of all mucinous BLOT, which is similar to the results obtained by Ayhana et

al. (33 % and 5.1 %).⁴ The connection between the presence of bilateral BLOT and staging into the stage II–IV group proved statistically significant ($P = 0.000$). Papillary growth occurred more frequently in unilateral serous BLOT (90.5 % of all serous BLOT) than in bilateral.

A small group of women with BLOT has a poorer prognosis.^{12,13} These cases can be identified by the combination of the presence of advanced-stage BLOT (stage III), invasive peritoneal implants and papillary growth.^{8,11} The stated criteria may be an indication for adjuvant treatment.^{14,15} Adjuvant or more aggressive treatment would be most advantageous in these women.¹⁴ Chemotherapy is not indicated in noninvasive implants since they are insensitive to chemotherapy.¹⁵

Within five years there are recurrences in 2 % of women with noninvasive and in 31 % of those with invasive implants.¹⁵ In the course of our own study no recurrence was observed.

In serous BLOT survival is almost 100 % in the localized forms (limited to the ovary) but only about 90 % in the spread forms.⁸ Older women with serous BLOT spread have a poorer survival rate than younger ones. Malignant changes of peritoneal implants – sometimes even after years of latency – and peritoneal implants that could not be distinguished from ovarian serous carcinoma have a lethal outcome. Compared to those with noninvasive implants, survival of women with invasive implants is poorer. In stage I survival is almost 100 %. In advanced stages with noninvasive implants it is 95.3 %, with invasive only 66 %.¹¹ From our group only one woman with mucinous BLOT died during the first year of follow-up.

Conclusions

Our study revealed that BLOT mostly appeared as the serous type. One fourth were bilateral and more than half with papillary growth. Compared with the mucinous, the serous BLOT had peritoneal implants and positive pelvic lymph nodes more frequently.

The mucinous BLOT were mostly unilateral, there was a single case of papillary growth, the lymph nodes were negative. Mesenteric implants were present only in one case, which was in the advanced stage (IV). In the remaining cases no implants were found.

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