

Research article/Raziskovalni prispevek

## **BORDERLINE TUMORS OF THE OVARY – TREATMENT AND SURVIVAL AT MARIBOR TEACHING HOSPITAL BETWEEN 1993 AND 2001**

MEJNO MALIGNI TUMORJI JAJČNIKOV – ZDRAVLJENJE IN PREŽIVETJE BOLNIC V SPLOŠNI BOLNIŠNICI MARIBOR V OBDOBJU 1993–2001

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### **Abstract**

**Background** *The purpose was to determine the structure of women with borderline ovarian tumors (BLOT) with respect to their age, the stage of disease at diagnosis, the treatment method, survival rate and disease-free interval.*

**Methods** *The retrospective study included all women (55), treated at Maribor Teaching Hospital between January 1, 1993 and December 31, 2001. Follow-up was completed on December 31, 2006.*

**Results** *By the age of 40 years, 25.5 % of BLOT appeared. At diagnosis 80 % were in stage I. The women were followed up for  $94.9 \pm 74.2$  months. The surgical procedure was limited to the adnexa in 23.6 %. Pelvic lymphadenectomy was carried out in 16.4 %, with positive lymph nodes in 22.4 %. Paraaortic lymphadenectomy was performed in 5.45 %; all lymph nodes were negative. Adjuvant chemotherapy was employed in 16.4 % of women, no problems were observed. One woman died of the basic disease, three more died for other reasons. Absolute survival (overall, one-, three- and five-year survival) for stage I and stage II–IV was 100 % and 98 % respectively. There was one recurrence.*

**Conclusions** *BLOT appeared in women older than those in the literature. Absolute survival was very good. The disease recurred in 1.8 %.*

**Key words** *borderline tumor; ovary; treatment; survival; recurrence; disease-free interval*

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### **Izvleček**

**Izhodišča** *Z nalogo smo želeli ugotoviti starostno strukturo bolnic z mejno malignimi tumorji jajčnikov, deleže posameznih stadijev bolezni ob diagnozi, načine zdravljenja, preživetje in bolezninski prost interval.*

**Metode** *V retrospektivno raziskavo so bile vključene vse bolnice (55), zdravljene v Splošni bolnišnici Maribor v obdobju 1. 1. 1993 do 31. 12. 2001. Redno so bile spremljane, sledenje pa se je zaključilo 31. 12. 2006.*

**Rezultati** *Do 40. leta starosti se je pojavilo 25,5 % mejno malignih tumorjev jajčnikov. Ob ugotovitvi bolezni je bilo kar 80 % v stadiju I. Sledenje je trajalo  $94,9 \pm 74,2$  mesecev. Operativni poseg je bil omejen na adneksa pri 23,6 % bolnic. Pelvična limfadenektomija je bila narejena pri*

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16,4 % bolnic, bezgavke so bile pozitivne pri 22,4 %. Paraaortna limfadenektomija je bila narejena pri 5,45 % bolnic, vse bezgavke so bile negativne. Pooperativno KT je prejelo 16,4 % bolnic, vse so jo prestale brez težav. Zaradi osnovne bolezni je umrla ena bolnica, zaradi drugih vzrokov še tri. Absolutno preživetje (celotno, enoletno, triletno in petletno) za stadij I ter stadije II–IV je bilo 100 % in 98 %. Do ponovitve bolezni je prišlo pri eni bolnici stadija IIIC z obojestranskim seroznim papilarnim mejno malignim tumorjem jajčnika 7,5 leta po zaključku primarnega zdravljenja.

**Zaključki** *Mejno maligni tumorji jajčnikov so se pojavljali v kasnejši starosti kot poročajo v literaturi. Absolutno preživetje je bilo zelo dobro. Bolezen se je ponovila v 1,8 %.*

**Ključne besede** *mejno maligni tumor; jajčnik; zdravljenje; preživetje; recidiv; bolezni prost interval*

## Introduction

Borderline ovarian tumors (BLOT) are epithelial tumors with a low malignant potential and slow growth. They represent 10–20 % of all epithelial tumors of the ovary. Compared to ovarian carcinoma they occur in younger women and survival is better.<sup>1</sup> Generally, they are diagnosed at an earlier stage than invasive cancer.

There are differences between the treatment of initial and advanced stages of BLOT. The guidelines are similar to those for treating ovarian malignancies. In the early stages the prognosis is good since the 5-year survival in stage I is as high as 95–97 % and the 10-year survival is 70–95 %. In stages II–III survival is poorer (the 5-year survival is 65–87 %). The tumor stage at diagnosis (FIGO classification) is one the most important predictors.<sup>2</sup>

With a retrospective study we wanted to determine the structure of women regarding their age, the percentage of individual disease stages at diagnosis, treatment methods, survival within groups, the disease-free interval, the percentage of recurrences in general as well as within groups.

## Methods

In our study we included women who were treated for BLOT at Maribor Teaching Hospital Department for Gynecologic Oncology and Oncology of the Breasts, between January 1, 1993 and December 31, 2001. All women signed a written consent that their data can be used for research purposes. They were regularly followed up at the OPC for Gynecologic Oncology. Information on the causes of death was obtained either from our own database or the Cancer Registry of Slovenia. The vitality status was last established on December 31, 2006. All data was statistically processed.

## Results

In the last nine years 55 women were treated for BLOT at Maribor Teaching Hospital Department for Gynecologic Oncology and Oncology of the Breast and all were included in the study. Their age was between 18–87 years. The median was 48 years and the average age  $50.7 \pm 16.7$  years. Women who were 40 years old or younger represented 25.5 % of all cases. Women

were divided into three age groups: 35 years or less (16.4 %), from 36 to 50 years (32.7 %), and older than 50 years (50.9 %).

The disease stage was determined at the beginning of treatment according to FIGO classification criteria from 1989. Women were divided into two groups regarding their disease stage. There were 44 women (80 %) in stage IA, IB, and IC in the first group and 11 women (20 %) in stage II–IV in the second.

There are no statistically significant differences between the age groups regarding the disease stages ( $p = 0.723$ ) (Table 1).

Tab. 1. Število in delež primerov glede na stadij ob ugotovitvi bolezni.

Table 1. Number and proportion of cases with regard to the stage at the time of diagnosis.

Stadij bolezni Stage of disease	IA	IB	IC	IIA	IIB	IIC	IIIA	IIIB	IIIC	IV
N	31	4	9	1	0	3	1	3	2	1
Frekvenca Frequency	56,4	7,3	16,4	1,8	0	5,5	1,8	5,5	3,6	1,8

N = število primerov, frekvenca = delež primerov (%)  
N = number of case, frequency = proportion of cases (%)

Patients were divided into groups regarding histological types – group with serous (41/55 = 74.54 %), mucinous (12/55 = 21.82 %) and other (Sertoli-Leydig, mixed epithelial) types (2/55 = 3.64 %).

The duration of follow-up lasted from 60 to 168 months,  $94.9 \pm 74.25$  months on average, the median 93 months.

We compared different treatment methods. In thirteen women (23.6 %) the ovary could be preserved at least on one side. Forty-two women (76.4 %) had a more extensive surgical procedure. Fifty-three women had no residual tumor after surgery. In one patient (1.8 %) with tumor stage IIIB the residual tumor measured up to 2 cm<sup>3</sup> and in another (1.8 %) with tumor stage IV the residual tumor measured more than 2 cm<sup>3</sup>. Histologically, implants of serous borderline ovarian tumor on appendix were confirmed twice, once on omentum and once on peritonea. Implants of borderline mucinous ovary carcinoma on mesentery were confirmed once. The invasiveness of metastases was

not established. Lymphadenectomy was performed in nine women (16.4 %), pelvic lymphadenectomy in all women, and paraaortic lymphadenectomy in three women (5.45 %).

We removed 10 out of 36 pelvic lymph nodes (21 on average) and 2 to 4 paraaortic lymph nodes (3 on average). Pelvic lymph nodes tested positive in two women with serous BLOT in stage IIIC (3.6 %). Paraaortic lymph nodes were all negative.

Nine women (16.4 %) received additional treatment with cytostatics. With the exception of one case, all women had the disease stage II–IV. In one case of BLOT in stage I, where the patient received adjuvant chemotherapy, the serous BLOT was both-sided and macroscopically diagnosed as malignant.

Chemotherapy was two-track. The following combinations were used: cisplatin – cyclophosphamide, cisplatin – paclitaxel, and carboplatin – cyclophosphamide. All women received 6 cycles of chemotherapy. Due to neutropenia occurring in two women, we had to apply granulocyte colony-stimulating factor (G-CSF) and in one case lower the dose of cytostatics. All women concluded their treatment with cytostatics successfully.

In 54 women (98.2 %) primary treatment led to complete remission.

One year after the beginning of treatment no patient in stage I died. In the first three years after treatment two women at the age of 82 and 87 died due to other causes. One woman in stage IV died already the first year after the beginning of treatment due to the progress of the basic disease. She had a residual tumor larger than 2 cm<sup>3</sup> and did not receive chemotherapy. This patient died 9 months after surgery at the age of 82. Two women at the age of 41 and 53 died in the first three years after the beginning of treatment due to other causes and with no signs of recurring borderline ovarian tumors.

Recurrence of the disease was present in one patient with both-sided serous papillary borderline ovarian tumors in stage IIIC and positive pelvic lymph nodes. Recurrence was clinically, biochemically, and cytologically confirmed. There was no residual tumor present after primary operative cytoreductive therapy with appendectomy and omentectomy. Implants were already present on appendix and omentum. Six cycles of chemotherapy with cisplatin and cyclophosphamide followed. A complete clinical and chemical remission (negative tumor marker CA 125) lasted 7.5 years when recurrence was established in the minor pelvis, retroperitoneally to the rectosigmoid and ileal loops as well as on the serosa of urinary bladder. Resection of rectosigmoid, ileum, adhesiolysis, metastasectomy and anus praeter was performed. A residual tumor was not visible. After three weeks the treatment continued with secondline chemotherapy. The patient received 6 rounds of chemotherapy with paclitaxel and paraplirin. Three months after the chemotherapy was finished, progress in vaginal cupola was clinically and cytologically established. It was additionally confirmed by the CT scan of the pelvis. The patient was additionally treated with brachioradiotherapy of the vaginal cupola with a total dose of 54G.

## Discussion

According to previous studies, borderline ovarian tumors appear in more than 50 % of women before the age of 40.<sup>1,3,4</sup> In our case the percentage was lower and amounted to only 25.5 %. A higher percentage of BLOT (50.9 %) was present in women older than 50 years.

Almost 80 % of borderline ovarian tumors were in stage I at diagnosis (56.4 % in stage IA, 7.3 % in stage IB, and 16.4 % in stage IC). The remaining 20 % were in stages II–IV. This corresponds with the results of previous studies, where BLOT in stage I accounted for 66–83.4 % and 34–16.6 % in stages II–IV.<sup>3,5</sup> There were no statistically significant differences regarding the disease stages in individual age groups ( $p = 0.723$ ).

The principle treatment of BLOT is a complete surgical removal of the tumor mass. The surgery can be conservative or radical. Since 1995 it is no longer necessary to perform paraaortic lymphadenectomy to determine the disease stage.<sup>6</sup> Lymphadenectomy is performed only in women with serous BLOT and increased lymph nodes. In our study most women received surgical treatment only. The surgeons decided on the nature of surgery regarding the clinical status at operation. In 13 women (23.6 %) the surgery was limited to one ovary whereas in the remaining 42 women (76.4 %), it was more extensive. In one patient the residual tumor was bigger than 2 cm<sup>3</sup> while in the other it was smaller than 2 cm<sup>3</sup>. The remaining 52 women (96.3 %) had no tumor. Pelvic lymphadenectomy was performed in 9 women (16.4 %), two women with serous BLOT had positive lymph nodes (3.6 % of all borderline ovarian tumors or 22.2 % of borderline ovarian tumors with lymphadenectomy or in 25 % of women in stages II–IV). Paraaortic lymphadenectomy was carried out in three women (5.45 %) and all lymph nodes were negative. The percentage of positive lymph nodes in our study is concordant with the study of Camatte et al.<sup>7</sup> They diagnosed positive lymph nodes in 19 % of women. Rao et al.<sup>8</sup> diagnosed positive pelvic lymph nodes in only 1 % of the removed lymph nodes, paraaortic being all negative.

Postoperative treatment with cytostatics (chemotherapy) of borderline ovarian tumors is employed for adjuvant treatment of advanced disease stages. In stage I it does not increase the survival rate.<sup>4,9</sup> The expected effect of chemotherapy is small since the majority of cells in borderline ovarian tumors are in the latent phase and therefore insensitive to chemotherapy.<sup>10</sup> In our study 9 women (16.4 %) received postoperative adjuvant chemotherapy. They concluded the therapy successfully without any major problems, and are alive. Some studies report of women dying due to complications occurring during adjuvant treatment (leukemia after chemotherapy, chronic radiation enteritis after radiotherapy).<sup>4,7</sup>

Primary treatment resulted in complete remission in all patients except one. This patient died 9 months after primary operative treatment of advanced left and right mucinous BLOT in stage IV, which was the only death caused by progressed basic disease. In one case recurrence was established after several years. During the follow-up, which lasted 94.9 months on average,

another four women – two with BLOT in stage I and two in stage II-IV – died due to other causes during the first three years after treatment.

The entire relative survival rate was 90.9 % for all groups, 95.5 % for women in stage I and 72.7 % for women in stages II-IV. One-year survival was in 98.2 % for all stages, 100 % for stage I, and 90.9 % for stages II-IV. The 3-year relative survival accounted for 92.7 % for all stages, 95.5 % for stage I, and 72.7 % for stages II-IV. The 5-year survival has the same statistics as the 3-year survival.

After we exclude women who died due to other causes, we get the absolute survival rate. Complete, one-, three-, and five-year absolute survival rate for all stages is 98 %, for stage I 100 %, and 98 % for stages II-IV. Our results are somewhat better than the ones described in literature where the 5-year survival for all stages was almost 93 % and the 10-year survival 99 % for stage I, 98 % for stage II, 96 % for stage III, and 77 % for stage IV (3, 11). In the study by Seidman and Kurman<sup>12</sup> the survival of women in stage I was 100 % (6.7 years of follow-up), 95.3 % in advanced stages with non-invasive implants, and 66 % in cases with invasive implants (7.4 years of follow-up). In women with positive lymph nodes five- and ten- year survival is 100 % and 83 % respectively, in comparison to 100 % and 92 % in women with negative lymph nodes or without lymphadenectomy.<sup>7</sup>

According to data provided in literature, recurrence of the disease is also possible several years after the beginning of treatment. The chance of recurrence is up to 3 % or 12 % in stage I.<sup>3,5</sup> In our study there was no recurrence of the disease in stage I (0 % chance of recurrence). The disease was diagnosed once again in a patient with serous papillary BLOT in stage III C. The case accounted for 1.8 % chance of recurrence. Since the disease recurs relatively late, a long-term follow-up is required in order to establish possible recurrence.

## Conclusions

Our study clearly shows that BLOT in the group of women treated at Maribor Teaching Hospital occurred at somewhat older age than elsewhere.

The 5-year survival was very good, independent of the women's age and disease stage at the beginning

of treatment. The disease recurred in one patient with serous papillary BLOT in stage III C after complete remission, 7.5 years after primary treatment was finished.

With regard to good survival and the recurrence of the disease in only 1.8 % of women, we believe that these patients were properly and successfully treated at our hospital. The question of lymphadenectomy, however, still remains open. It seems reasonable that surgery is performed in cases of advanced stages of serous BLOT with invasive implants.

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