

Conservative treatment of borderline ovarian tumors: the experience of one clinical center

Leczenie zachowawcze guzów o granicznej złośliwości: doświadczenie jednego ośrodka badawczego

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Abstract

Objectives: Borderline ovarian tumors have favorable survival rates, however, prognostic factors are still discussed. The aim was to investigate the outcome for women treated conservatively with respect to different tumor-dependent and tumor-independent prognostic factors.

Material and methods: 194 women treated surgically between years 1978 and 2007. Influence of conservative or radical surgical treatment on survival was evaluated.

Results: The overall 5-year survival rate was 93.1% and 96.8% respectively for radical and conservative treatment. The mean time of survival was longer in women treated conservatively ($p = 0.03$), but this was an outcome of their younger age; when age was eliminated as a determining factor, the type of treatment had not influenced the length of postoperative survival ($p=0.57$). Conservative treatment was chosen more frequently for younger women. Factors that are detrimental to survival are age, postmenopausal detection of borderline ovarian tumors, an advanced stage of progression, a bilateral localization of tumors, the occurrence of invasive peritoneal implants and a serous rather than a mucinous histological type of borderline ovarian tumor, more frequently occurred in women treated radically. Borderline ovarian tumors recurred in 16.7% of women after conservative treatment and in 3.5% of women after radical treatment. Of women with preserved fertility 25.7% became pregnant at least once and 21.2% of the group as a whole delivered children at term; none of the pregnancies were fertility-assisted.

Conclusions: Conservative treatment does not have a deleterious effect on the prognosis of women provided that unfavorable prognostic factors are identified.

Key words: **ovarian neoplasms / gynecologic surgical procedures / women / survival rate /**

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Streszczenie

Cel: Guzy o granicznej złośliwości charakteryzują się korzystnymi współczynnikami całkowitego przeżycia chorych, chociaż wciąż dyskusyjne jest znaczenie czynników prognostycznych. Celem pracy była analiza porównawcza wyników leczenia chorych leczonych oszczędzająco w odniesieniu do różnych czynników rokowniczych zależnych i niezależnych od nowotworu.

Materiał i metody: Przeanalizowano przebieg choroby u 194. kobiet leczonych operacyjnie w latach 1978-2007. Oceniono wpływ leczenia operacyjnego oszczędzającego względem radykalnego.

Wyniki: Całkowite pięcioletnie przeżycie wynosiło 93,1% i 96,8% odpowiednio dla radykalnego i zachowawczego leczenia. Mediana czasu przeżycia była dłuższa u kobiet leczonych zachowawczo ($p = 0,03$), ale było to związane z ich młodszym wiekiem. Gdy wyeliminowano czynnik wieku jako czynnik determinujący, rodzaj leczenia nie wpływał na czas przeżycia chorych ($p = 0,57$). Leczenie zachowawcze częściej wybierano u młodszych kobiet. Czynniki pogarszające przeżycie to wiek chorych, wykrycie guzów o granicznej złośliwości w wieku pomenopauzalnym, zaawansowanie choroby, obustronne występowanie guzów, obecność inwazyjnych wszczepów, typ surowiczy guza; były one częściej stwierdzane w grupie leczonej radykalnie. Wznowy guzów o granicznej złośliwości następowały u 16,7% chorych po leczeniu oszczędzającym oraz u 3,5% chorych po leczeniu radykalnym. Wśród kobiet z zachowaną płodnością 25,7% zaszło w ciążę przynajmniej raz, a 21.2% urodziło o czasie. Żadna z ciąż nie była efektem technik wspomagającego rozrodu.

Wnioski: Leczenie zachowawcze nie miało niekorzystnego wpływu na rokowanie chorych, przy założeniu że negatywne czynniki ryzyka u chorych były wcześniej zidentyfikowane.

Słowa kluczowe: **nowotwory jajników / chirurgia ginekologiczna / kobiety /
współczynnik przeżycia /**

Abbreviations:

Borderline ovarian tumors (BOTs)

Introduction

Borderline ovarian tumors (BOTs), classified as a distinct group of ovarian tumors of epithelial origin, have a good prognosis, with a five-year survival rate that stands at 90-98%, while for recurrence the rate is 7-10% [1-4]. The percentage of serous tumors which are actually borderline, given as 15-20%, itself appears to have been underestimated [5]. BOTs affect a younger group of women, often of reproductive age [1, 2, 6], and are more likely to be at an early stage (approximately 50-85 % represent stage I of the disease [4, 7, 8]).

All these factors weigh in favor of conservative surgical techniques that avoid "overtreatment" of the patient. The prevailing procedures for ovarian cancer such as peritoneal washing, hysterectomy with bilateral salpingo-oophorectomy, omentectomy and multiple peritoneal biopsies are then reserved for postmenopausal women or premenopausal women who have completed their families or do not wish to preserve fertility [9], whereas less radical fertility-sparing surgery, including cystectomy, partial ovariectomy or unilateral salpingo-oophorectomy [9, 10] is used to treat young women who still attach importance to their child-bearing potential and in whom the disease is at stage I. However, while this may apply at an early stage of the disease, the question then arises as to whether proceeding conservatively with advanced BOTs is safe. When the neoplasm has advanced to a more advanced stage the prognosis is less favorable and the risk of progression or of recurrence is higher.

Objectives

The aim of the research has been to investigate the outcome for women treated conservatively with respect to different tumor-dependent and tumor-independent prognostic factors.

Material and methods

The research was carried out among 194 women treated surgically at the Clinic of Gynecology at the Gdańsk University Hospital between 1978 and 2007. Each patient was assigned to either radical or conservative surgical treatment on the basis of her age and desire to preserve fertility, together with the result of an intraoperative cryosection. In five cases the qualification criterion was that the patient withheld consent for radical treatment until the final result of the pathological examination had been obtained. An intraoperative examination in the Department of Pathology at the University Hospital was performed on all but 37 of the women (the reasons for not carrying out this test are explained below in the results).

As a result, 66 women (34%) were regarded as eligible for conservative treatment. This consisted of unilateral cystectomy in 14 women (7.2%), unilateral adnexectomy in 27 women (13.9%), unilateral adnexectomy with cystectomy of the opposite ovary in two women (1.0%) and unilateral adnexectomy with a partial resection of the opposite ovary in 23 women (11.9%). The remaining 128 women received radical treatment as follows: bilateral adnexectomy in six women (3.1%), total abdominal hysterectomy with bilateral salpingo-oophorectomy in 76 women (39.2%) and total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy and appendectomy in 46 women (23.7%). Adjuvant chemotherapy was administered to 13 women.

The primary treatment was completed by close gynecological

follow-up over two years, during which the women were examined every three months, followed by systematic six-monthly check-ups over the next three years and finally annual check-ups in the Outpatient Clinic of our Department. The concluding evaluation of the postoperative course and of the overall survival rate was made in September 2013.

The study was submitted to the university ethical committee and deemed to be within the confines of Polish law for such studies and exempt from formal approval.

The groups that had been designated according to the type of treatment they had received were compared statistically with respect to metrical data, features of the reproductive period, pathological features, disease stage and overall survival. All the calculations were performed by a commercial program STATISTICA.PL by means of the following: Pearson's chi-squared test, Yates' chi-squared test and the Mann-Whitney U test. Survival was evaluated according to the Kaplan-Meier method of analysis and the differences were compared by the log-rank and Cox F tests. In order to determine the respective influence of conservative or radical surgical treatment on survival, comparisons were made of the following three age-related subgroups: women younger than 40 years, those aged between 40 and 45 years and those aged between 45 and 50. The significance of the statistical differences was taken as $p < 0.05$.

Results

The patient characteristics are set out in Table I. The women who received conservative treatment were younger and, as they were less likely to have reached the menopause, their mean parity was lower. The differences were statistically significant. Of the women treated conservatively seven women had been diagnosed and treated conservatively for BOT during the course of a pregnancy.

The histological features of the BOTs are presented in Table II. The serous histological type was the most frequent, although in women treated conservatively the majority of BOTs were of the mucinous type ($p=0.01$). In the fertility-sparing group BOTs were more frequently diagnosed at earlier stages of progression ($p=0.01$) and were usually unilateral ($p = 0.004$) with the outer layer having a smooth surface ($p=0.01$ with respect to comparison of the surface only). Peritoneal implants were discovered only in one patient with preserved fertility, compared to nine women in the group that had undergone radical surgery ($p=0.02$).

In women with peritoneal implants the prevalence of recurrence was high (six out of 10 women), and in four of these (two with invasive and two with non-invasive implants) the course of the disease ended in death between 5 months and 3½ years from the initial diagnosis. Radical measures were taken where a return of peritoneal implants was seen in women that had been treated conservatively.

The intraoperative histopathological examination was omitted in 35 women (18.2%) as an ultrasonographic view of the tumor gave no cause for concern and either Ca-125 levels were normal (31 women) or it was not possible to perform the test for this owing to systemic problems (four cases). In the women in whom the examination was performed promptly, a BOT was identified in 78.5% cases, a benign tumor of the ovary in 15.9% cases, and ovarian cancer in 5.6% cases. In this last category only one patient withheld consent to radical surgery during the preoperative

evaluation before a final pathological assessment had been made.

There was a recurrence of BOT in 8.3% of women and at a higher prevalence in women treated conservatively (16.7% vs. 3.5%, $p=0.002$). The relapse after fertility-sparing surgery most frequently involved the remaining ovarian tissue, while after radical surgery it occurred in the region of the small pelvis. In general the recurrence of BOT did not influence the overall survival rates. In three of the women treated for BOT a transition of the tumor to ovarian cancer was observed. In two cases this followed radical treatment, while in one case it was found after unilateral adnexectomy with contralateral cystectomy.

The overall 5-year survival rate was 93.1% and 96.8% respectively for radical and conservative treatment. The mean time of survival was longer in women treated conservatively than in those treated radically (16.5±9.5 years vs. 12.5±7.7 years; $p=0.03$). However, calculations revealed that overall survival decreased independently with age. Therefore, if statistical analysis is made taking into account the influence of age on survival, it would appear that there is no difference in the overall survival-rate between women treated radically and those treated conservatively ($p=0.57$). Further analysis revealed that the prognostic factors in BOT were the stage of the disease ($p=0.0001$) and whether the tumor was unilateral or bilateral ($p=0.001$). All the factors that could possibly influence survival are listed in Table III.

After analysis of the effect on survival of radical excision of ovarian tissue, it turned out that there were no differences in survival between women in whom the ovary was removed with the BOT and those in whom only the tumor was enucleated with preservation of the ovarian tissue ($p=0.2$).

Of 66 women with preserved fertility 17 (25.7%) became pregnant at least once and 14 of these (21.2% of the group as a whole) delivered of a total of 18 children at term. None of the pregnancies were fertility-assisted.

Discussion

Our research revealed that where BOTs are concerned conservative treatment does not have a deleterious effect on the prognosis of women. Indeed these women survived longer, but this was an outcome of their younger age at the time of the surgical procedure. Nevertheless, when age was eliminated as a determining factor, it was shown that the type of treatment had not influenced the length of postoperative survival.

Evaluation of the factors affecting the overall survival of women with BOT is difficult [11] because of the very high survival rates for this tumor (99% at stage I in our study and in the literature [12]). Moreover, recurrence is relatively rare; in our material BOTs recurred in 16.7% of women after conservative treatment and in 3.5% of women after radical treatment. The frequency of relapses as presented in papers on BOT and systematically reviewed by Darai et al. is similar [12], although the overall relapse rate was up to 25% after conservative and up to 5% after radical treatment. The increased incidence of recurrence after conservative treatment must be associated with the fact that these arise in the spared ovarian tissue. However, recurrence does not influence the survival of women, as borne out by our results.

In the literature there is a single piece of randomized research on BOT by Palomba et al. [13, 14] comparing conservative to radical treatment, while all other studies, including our own, are retrospective [4, 15-17].

Table I. Characteristics of women treated for borderline ovarian tumors with a distinction to the type of surgical treatment.

Feature [mean ± SD (min – max)]	all		conservative		radical		p-value
Age at surgery	48.2 ± 16.0 16 – 85		33 ± 12.2 16 – 72		56 ± 11.5 28 – 85		< 0.0001
Number of deliveries	1.5 ± 1.5 0 – 8		0.7 ± 1.0 0 – 5		1.9 ± 1.6 0 – 8		< 0.0001
Number of miscarriages	0.4 ± 1.0 0 – 9		0.2 ± 0.8 0 – 5		0.5 ± 1.1 0 – 9		0.03
Reproductive status	n	%	n	%	n	%	< 0.0001
- premenopausal	100	55.2	50	76.9	50	43.1	
- pregnancy	7	3.9	7	10.8	0	0.0	
- postmenopausal	74	40.9	8	12.3	66	56.9	

Table II. Tumor-dependent features in women treated conservatively and radically for borderline ovarian tumors.

Feature	all		conservative		radical		p-value
	n	%	n	%	n	%	
Histological type							0.01
- serous	91	47.9	25	37.9	66	53.2	
- mucinous	68	35.8	31	47.0	37	29.8	
- endometrioid	8	4.2	2	3.0	6	4.8	
- mesothelial	6	3.2	3	4.5	3	2.4	
- Brenner's tumor	17	8.9	5	7.6	12	9.7	
FIGO stage							0.01
- Ia	143	73.7	60	90.9	83	64.8	
- Ib	19	9.8	4	6.1	15	11.7	
- Ic	15	7.7	1	1.5	14	10.9	
- IIa	4	2.1	0	0.0	4	3.1	
- IIc	1	0.5	0	0.0	1	0.8	
- IIIc	12	6.2	1	1.5	11	8.6	
Tumor site - unilateral	164	85.4	63	95.5	101	80.2	0.004
- bilateral	28	14.6	3	4.5	25	19.8	
Tumor surface							0.08
- smooth	137	72.9	54	83.1	83	67.5	
- papillar	34	18.1	6	9.2	28	22.8	
- rupture of the cyst	17	9.0	5	7.7	12	9.8	
Peritoneal implants							0.02
- noninvasive	174	95.1	65	100.0	109	92.4	
- invasive	6	3.3	0	0.0	6	5.1	
- not defined	3	1.6	0	0.0	3	2.5	
Intraoperative frozen section							0.3
- BOT,	128	66.7	44	66.7	84	66.7	
- other benign tumor,	22	11.5	5	7.6	17	13.5	
- ovarian cancer,	7	3.6	1	1.5	6	4.8	
- not performed.	35	18.2	16	24.2	19	15.1	
Frequency of staging procedure	62	32.1	13	19.7	49	38.6	0.008
Adjuvant treatment							0.003
- none,	172	92.0	66	100.0	106	87.6	
- chemotherapy,	13	7.0	0	0.0	13	10.7	
- radiotherapy.	2	1.1	0	0.0	2	1.7	
Frequency of Second Look Operation	8	4.3	3	4.5	5	4.2	0.9
Frequency of recurrence	15	8.3	11	16.7	4	3.5	0.002

The worse survival rate of women after radical surgery in our studies was a consequence of the characteristics of this group, in whom unfavorable prognostic factors were more frequently present. It has been found independently that the factors that are detrimental to survival are age, postmenopausal detection of

BOTs, an advanced stage of progression, a bilateral localization of tumors, the occurrence of invasive peritoneal implants and a serous rather than a mucinous histological type of BOT. The neoplasm stage is, according to the FIGO classification, considered the strongest and most objective prognostic factor for

BOTs, followed by histological type and patient age at diagnosis [11, 18, 19].

The profiles of the women designated for conservative or radical treatment are dissimilar. Conservative treatment was chosen more frequently for younger women whose fertility was, in the majority of cases, at its greatest and, in view of the fact that more than half were under the age of 40 and that half were nulliparous, of considerable importance to the women. The profile of the women corresponds to the features of BOTs, which are most prevalent in relatively young women during their reproductive years [20]. Women aged under 40 years in our study constituted 31% of the group analyzed. This corresponds to the results reported by Sherman et al. [21] and Skirmisdottir et al. [22], who showed that the incidence of BOTs in women aged under 40 years is 29% and 34% respectively. As a consequence of their youth, the majority of women treated for BOT still are planning to have a family. In our study more than half the women treated conservatively were nulliparous. In our study approximately 25% of the women conceived at least once postoperatively, and the rate of births at term reached about 12%. Moreover, a high staging of the BOT observed in one patient was not an obstacle for having a term birth, nor did it affect the patient's survival.

Fertility outcomes for women treated for BOT with conservative procedures have been evaluated and published in a series of at least 55 studies. The results of these studies show that the proportion of women who achieved a pregnancy after fertility-sparing surgery falls within the range of 7–45% [12]. It should, however, be noted that a pregnancy rate of 40–88% is given, considerably higher than in our studies, but this percentage represents the percentage of women actively trying to conceive. Following Darai et al. [12], the pooled estimate for spontaneous pregnancies after conservative treatment is 54%, which is significantly lower if compared to the general population.

There may be several reasons for this. Firstly, the surgical procedures may reduce the ovarian reserve, as shown by Palomba et al in the only randomized studies on BOTs [13, 14]. They showed that the pregnancy rate was higher following cystectomy than after adnexectomy and that the prevalence of recurrence was similar in both groups. After cystectomy, however, the time of relapse formation was shorter and its occurrence more frequently resulted in radical treatment [14]. Another reason for the reduced percentage of spontaneous pregnancies after treatment for BOT is the age of women at the time they conceived. Fauvet et al. [23] and Kanat-Pektas et al. [24] have shown that an age of 40 marks the boundary beyond which the chances of conception decline rapidly. It should be borne in mind, however, that this team of writers did not measure two parameters known to influence fertility, namely the number of antral follicles and Serum anti-Müllerian hormone concentration. The third factor influencing the fertility rates is the histological type of BOT. As shown by Kanat-Pektas et al. [24], in women with the mucinous type the number of pregnancies achieved was very high compared to women with serous BOTs. This may be a consequence of the fact that serous BOTs are more likely to occur bilaterally with a peritoneal spread, usually in women that have a history of infertility treatment [25, 26].

Attention is increasingly being drawn to the presence of peritoneal implants as a prognostic factor, and especially to the significance of their type [11, 12]. Although our study gave little

Table III. The influence of chosen tumor-dependent and tumor-independent factors on the overall survival rates in women treated for borderline ovarian tumors.

Features	p-value
- age at surgery	0.01
- age at <i>menarche</i>	0.9
- premenopausal vs. postmenopausal period	0.01
- number of deliveries before surgery	0.01
- having a pregnancy after surgery	0.06
- histological type: serous vs. mucinous	0.01
- stage of the disease	0.001
- unilateral vs. bilateral site of BOT	0.001
- cystectomy vs. adnexectomy	0.2
- performing the staging procedure	0.8
- rupture of the cyst	0.05
- recurrence	0.06

opportunity to evaluate the safety of conservative treatment in women with peritoneal implants (as only one patient was concerned), two major studies by Zanetta et al. [27] and Uzan et al. [28] have revealed that conservative treatment may be safely used in women with non-invasive implants provided that these are totally excised. In view of the fact that there is a paucity of literature on the conservative treatment of women with invasive implants, the safety of this method must still be open to doubt [27-30].

Tailored surgery in women with ovarian tumors is based on correct decisions regarding eligibility for a particular type of treatment on the basis of the ultrasonographic view of the ovarian lesion and the level of Ca-125 marker, together with the patient's age at diagnosis, reproductive plans and consent to treatment. Intraoperative frozen section diagnosis of BOT is, however, decisive. In our study this test revealed borderline tumor histology in only two thirds of cases. Approximately a sixth of women did not undergo this test initially, mainly owing to an absence of pre-operative clinical indications. However, in approximately a fifth of women the diagnosis had been incorrect. In 5.6% ovarian cancer had been diagnosed and in 15.0% benign tumors, resulting in overtreatment or undertreatment respectively. Studies by Gultekin et al. [31], Tempfer et al. [32] and Liu et al. [33] have revealed that the underdiagnosis rate for BOTs is 29.3%, 28% and 25.7% respectively. The retrospective multicenter pooled analysis reported by Tempfer et al. [32] showed that in 280 women with a final diagnosis of BOT as many as 25% women had been diagnosed for benign lesions and 3.6% for ovarian cancer in the intraoperative cryosection. On the other hand, of women who received a final diagnosis of ovarian cancer an intraoperative diagnosis of BOT had been given for 11.4%. The intraoperative evaluation of BOT is known to be difficult, especially when the tumor is large, as a limited invasive component of such a lesion may be easily missed [11].

Conclusions

The results presented support the theses that tailored surgical treatment guarantees the best outcome and that conservative treatment is not a choice between a good prognosis over procreative success and a reduced risk of later complications.

Oświadczenie autorów

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