Long-term follow-up after ovarian borderline tumor: Relapse and survival in a large patient cohort

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1. Introduction

The borderline tumor of the ovary (BOT) accounts for 10–20% of epithelial ovarian tumors [1]. BOT and invasive carcinomas show differences in their genetic aberrations suggesting that invasive tumors of high grade do not arise from pre-existing borderline lesions [2]. BOT has an incidence of 4.8/100,000 per year [3] and generally occurs 10 years earlier than ovarian cancer. About a third of patients are diagnosed under the age of 40. It has been recognized that the preservation of fertility is of great importance, especially in young patients [4]. During the last decades, operative management of BOT has changed with regard to radicality [5]. Historically, BOT had been described as a precursor malignancy of ovarian cancer and was consequentially operated in the same way to avoid recurrent invasive disease [6]. Over the years many studies have shown that a radical operative treatment including lymphadenectomy is not superior in terms of relapse or survival [7]. Further investigations have postulated even fertility sparing surgery to be appropriate in women at childbearing age, especially when diagnosed at an early stage of disease [8].

In this retrospective study we analyze risk factors for long-term survival and relapse in patients diagnosed with a borderline tumor of the ovary (BOT) with special focus on the surgical approach.

2. Materials and methods

All women diagnosed and treated for BOT at our institution between 1983 and 2006 were included in this retrospective study.

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Clinical data, demographic, diagnostic and treatment information were primarily collected from the patients' charts. Patients were seen at 3-month intervals after initial diagnosis for a 2-year period, thereafter at 6-month intervals for another 2 years and then once a year to evaluate for sonographic and clinical signs of relapse. The patients' data were further reviewed for the surgical procedure performed. Radicality varying from unilateral adnexectomy, in this study referred to as fertility sparing surgery, to hysterectomy with bilateral adnexectomy, omentectomy and lymphadenectomy were recorded. Bilateral adnexectomy, hysterectomy, omentectomy, cytology, and several peritoneal biopsies were regarded as full staging. Tumor typing and staging were performed by the department of pathology according to the criteria of the International Federation of Gynaecologists and Obstetricians (FIGO) and the International Union against Cancer (IUCC).

The following parameters were registered for each patient: age at primary diagnosis, menopausal stage, age at menopause, surgical procedure performed, tumor type and stage. Also, the presence of BOT cells in ascites was recorded. In follow-up, the occurrence of relapse, time to relapse, death and survival time were registered. The main outcomes assessed were disease recurrence and survival.

Statistical analysis was performed using MedCalc (Version 8.1; MedCalc Software, Mariakerke, Belgium). All values are given as mean and standard deviation. To test differences between continuous variables for statistical significance, the Mann–Whitney test for unpaired variables was applied. For categorical data, the chi-square test was used. For the comparison of survival times, Kaplan–Meier curves were drawn for different patient groups. The chi-square statistic of the log-rank test was calculated to test differences between survival curves for significance. p values less than 0.05 were considered as statistically significant.

3. Results

Altogether, 113 patients could be identified, including 19 women with fertility sparing surgery. Mean follow-up time was 9.6 ± 6.6 years (minimum 6 months, maximum 23.5 years, median 7.9 years). Mean age at primary diagnosis was 51.2 ± 16.6 years; altogether 36 women (32%, 36/113) were under the age of 40. About half of the patients were premenopausal (56/113). Histology revealed a serous tumor in 73 women (64.6%), mucinous in 39 (34.5%) and endometrioid in one case (0.9%). 63 patients (55.8%) were diagnosed at FIGO stage Ia, 13 (11.5%) at stage Ib, 18 (15.9%) at stage Ic, 7 (6.3%) at stage II and 12 (10.6%) at stage III (Table 1). Cytology was positive for tumor cells in five cases (4.4%, 5/113). Implants were found in 19 patients: 11 were invasive (57.9%) and 8 non-invasive implants (42.1%). Localization of implants was the omentum (42.1%), the peritoneum (31.6%), diaphragm (10.5%) and bladder (10.5%). The mesosalpinx, uterus, umbilicus and kidney were affected in less than 10%.

An adjuvant platinum-based chemotherapy was recommended to 11 patients diagnosed with invasive implants. Only one patient did not follow this treatment recommendation.

Lymphadenectomy was performed in 35 cases (30.9%, 35/113). The surgical approach was laparoscopic in 15.9% (18/113), and no conversion from laparoscopic to laparotomic approach occurred. All patients had been staged by multiple peritoneal biopsies and cytology. In 74% (n = 84/113) an omentectomy was performed, and only 15.4% (n = 6/39) of all patients with mucinous tumors had had appendectomy, resulting in a complete operative staging in 76.1% (86/113) of all patients. Second-look surgery was chosen in 12 cases (10.6%, 12/113), never revealing macroscopic or microscopic tumor tissue (Table 1).

Table 1
Patient and tumor related characteristics for all patients, fertility sparing operated patients and radical operated patients, NA = not applicable.

	Total	Fertility sparing	Radical surgery
Total number of patients	113	19	94
Age at primary diagnosis (years)	51.2	34.2	54.7
Age at diagnosis (years)			
<40	36	17	19
≥40	77	2	75
BMI (kg/m^2)	24.8	23.5	25.1
Menopause status			
Premenopausal	56	19	37
Postmenopausal	57	0	57
Menarche (years)	13.4	13.0	13.5
Tumor marker CA-125 U/ml (mean)	128.0	55.1	142.8
Histology			
Serous	73	14	59
Mucinous	39	5	34
Endometroid	1	0	1
Stage by FIGO			
Ia	63	12	51
Ib	13	0	13
Ic	18	5	13
IIa	3	0	3
IIb	3	0	3
IIc	1	0	1
IIIa	10	1	9
IIIb	1	0	1
IIIc	1	1	0
IV	0	0	0
Cytology			
Positive	5	0	5
Negative	108	19	89
Implants	19	3	16
Invasive	11	1	10
Non-invasive	8	2	6
None	94	16	78
Laterality			
Left	38	9	29
Right	44	9	35
Bilateral	20	1	19
NA	11	0	11
Surgical approach			
Laparoscopy	18	4	14
Laparotomy	95	15	80
Lymph-node sampling			
Done	35	1	34
Not done	89	18	61
Second-look surgery	12	3	9
Adjuvant chemotherapy	10	1	9
Relapse	10	2	8
Death	10	0	10

3.1. Relapse and survival

Of all patients, 10 died during follow-up time. One death is known to be tumor-associated. Mean survival time of the patients who died was 7.7 ± 4.2 years (range 2–14 years). The general 5- and 10-year survival rates were 98.0 and 92.9%, respectively.

Altogether, relapse occurred during the follow-up period in 10 patients (10.1%, 10/99) with a mean time to recurrence of 2.0 ± 1.7 years (range 0.3–6.2 years). In six of the patients relapse was detected by sonography, in two by clinical symptoms and in two by CA-125 elevation. Patients with recurrent disease had a statistically significantly worse survival rate compared with those without: 5- and 10-year survival were 90.0 and 80.0% (patients with relapse) vs.

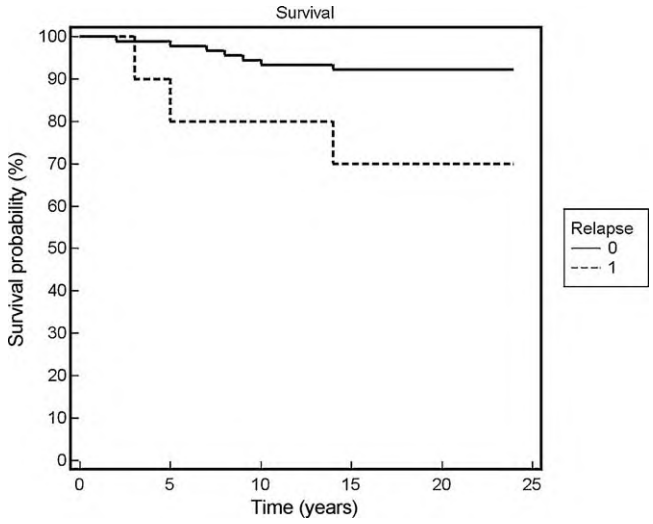

Fig. 1. Overall survival in patients with recurrent BOT vs. those without relapse.

98.9 and 94.4% for those without ($p = 0.0208$) (Fig. 1); mean survival time of the patients who died during follow-up was 7.3 ± 5.9 years in the patients with relapse and 7.9 ± 3.8 years in those without relapse ($p > 0.05$).

3.2. Histology

Of all patients with pT1a BOT ($n = 63$), 41 had been fully staged (65.1%), while operative staging was incomplete in 22 patients, so that the apparent pT1a stage (34.9%) was not definitely confirmed. Seven patients (12.5%, 7/56) with stage Ia BOT disease died during the follow-up period after a mean survival of 7.7 ± 3.7 years after primary diagnosis. Of those seven patients, complete operative staging was performed in only two cases, since omentectomy had not been performed in the remaining five. Therefore, the group of pT1a stage patients who died during follow-up may be classified as definite pT1a in two cases and apparent pT1a in the other five. Three deaths (6.0%, 3/43) occurred in the patient cohort with tumor stages greater than FIGO Ia; mean survival was 7.7 ± 6.0 years. For overall survival, statistical analysis did not reveal a significant difference between the patient groups. Altogether, 5- and 10-year survival rates were 94.8

Table 2
Patient and tumor related characteristics for patients diagnosed with a serous, mucinous or endometrioid ovarian borderline tumor, NA = not applicable.

	Total	Serous (%)	Mucinous (%)	Endometrioid
Total number of patients	113	73	39	1
Age at primary diagnosis (years)	51.2	49.2	54.4	55
Age at diagnosis (years)				
<40	36	26 (35.6)	10 (25.6)	0
≥40	77	47 (64.4)	29 (74.5)	1
Menopause status				
Premenopausal	56	36 (49.3)	20 (51.3)	0
Postmenopausal	57	37 (50.7)	19 (48.7)	1
Menarche (years)	13.4	13.5	13.4	13
Tumor marker CA-125 U/ml (mean)	128.0	154.8	80.6	21.0
Stage by FIGO				
Ia	63	32 (43.8)	31 (79.5)	0
Ib	13	10 (13.7)	3 (7.7)	0
Ic	18	16 (21.9)	2 (5.1)	0
IIa	3	2 (2.7)	1 (2.6)	0
IIb	3	2 (2.7)	0	1
IIc	1	1 (1.4)	0	0
IIIa	10	8 (11.0)	2 (5.1)	0
IIIb	1	1 (1.4)	0	0
IIIc	1	1 (1.4)	0	0
IV	0	0	0	0
Cytology				
Positive	5	5 (6.8)	0 (0)	0
Negative	108	68 (93.2)	39 (100)	1
Implants	19	18 (24.7)	1 (2.6)	0
Invasive	11	11 (15.1)	0 (0)	0
Non-invasive	8	7 (9.6)	1 (2.6)	0
None	94	55 (75.3)	38 (97.4)	1
Surgical approach				
Laparoscopy	18	11 (15.1)	7 (18.0)	0
Laparotomy	95	62 (84.9)	32 (82.0)	1
Fertility sparing surgery	19	14 (19.2)	5 (12.8)	0
Lymph-node sampling				
Done	35	26 (35.6)	9 (23.1)	0
Not done	89	58 (64.4)	30 (76.9)	1
Second-look surgery	12	9 (12.3)	3 (7.70)	0
Adjuvant chemotherapy	10	10 (13.7)	0 (0)	0
Relapse	10	6	4	0
Death	10	4	6	0

Table 3
Characteristics for patients with recurrent disease.

Age	Surgery	FS	HE	Adnectomy	OE	LNE	Pelv.	Paraa.	App.	PB	PW	PI	Invas. PI	FIGO	Histology	Chemo	Survival
41	Laparotomy	No	Yes	Bilateral	Yes	No	No	No	Yes	Yes	Yes	No	No	Ia	Mucinous	No	Alive
52	Laparotomy	No	Yes	Bilateral	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	IIc	Serous	Yes	Alive
58	Laparotomy	No	Yes	Bilateral	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Ib	Serous	Yes	Dead
38	Laparotomy	No	Yes	Bilateral	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	IIIb	Serous	Yes	Alive
79	Laparotomy	No	Yes	Bilateral	No	No	No	No	No	Yes	Yes	No	No	Ia	Mucinous	No	Dead
60	Laparoscopy	No	Yes	Bilateral	Yes	No	No	No	Yes	Yes	Yes	Yes	No	IIIa	Mucinous	No	Alive
57	Laparotomy	No	Yes	Bilateral	Yes	No	No	No	No	Yes	Yes	Yes	Yes	IIIa	Serous	Yes	Alive
35	Laparotomy	No	Yes	Bilateral	Yes	No	No	No	No	Yes	Yes	No	No	Ib	Mucinous	No	Alive
52	Laparotomy	No	Yes	Bilateral	Yes	No	No	No	No	Yes	Yes	No	No	Ic	Serous	No	Alive
35	Laparotomy	No	Yes	Bilateral	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Ia	Serous	No	Alive

Abbreviations: FS = fertility sparing, HE = hysterectomy, OE = omentectomy, LNE = lymphadenectomy, Pelv. = pelvine LNE, Paraa. = paraaortal LNE, App. = appendectomy, PB = peritoneal biopsy, PW = peritoneal washing, PI = peritoneal implant, Invas. = invasive PI and Chemo = adjuvant chemotherapy.

and 89.7% for stage Ia ($n = 56$) disease and 97.6 and 95.1% for all higher tumor stages ($n = 43$) ($p = 0.447$).

Relapse rate was 7.1% in early borderline tumor patients (Ia: 4/56) and 14% (>Ia: 6/43) for all others ($p = 0.436$). Mean relapse free interval was 1.5 ± 0.9 years for stage Ia ($n = 4$) and 2.3 ± 2.0 years for those greater than Ia ($n = 6$).

There was a higher relapse rate of 21.1% (4/19) noted in patients with implants compared with 7.5% (6/80) in those without ($p = 0.181$). 11 patients had invasive implants. Of those, four had a relapse (36.4%, 4/11 with invasive implants), indicating a significantly higher relapse rate compared with the patients without invasive implants (6.8%, 6/88) ($p = 0.0112$). Only one patient with an invasive implant died during the follow-up period. With a follow-up time of 13.1 ± 6.2 years (minimum 4.7 years, maximum 21.3 years) for patients with invasive implants, no statistically significant differences in survival rates were observed with regard to the presence or absence of implants or their invasivity.

Patients with a mucinous borderline tumor tended to be older than those with serous tumors (54.4 years vs. 49.2 years) and to have lower tumor stages. Patients with serous tumors presented at FIGO stage Ia in 43.8% ($n = 32$), while mucinous tumors were diagnosed at that stage in 79.5% ($n = 31$). Only one patient with a mucinous tumor had a peritoneal implant which was non-invasive. Regarding relapse and survival, no statistically significant differences were found between serous and mucinous tumors (relapse: $p = 0.990$, survival: $p = 0.161$, chi-square test) (Table 2).

Mucinous tumors were further differentiated into intestinal and endocervical type. Of mucinous tumors which relapsed, two were found to be intestinal and one of endocervical type. In the six patients with a mucinous tumor and death during follow-up, there were four tumors of intestinal type (66.7%, 4/10) and one of endocervical type, and one patient showed both intestinal and endocervical type.

3.3. Surgical procedure

Of the 99 patients assessable for follow-up, 19 had been operated in a fertility sparing way (19.2%) and 80 had been operated in a non-fertility sparing way (80.8%). Of the 80 patients with bilateral adnexectomy, 27 (33.8%) had been operated with and 53 (66.3%) without lymph node dissection. In the group of patients operated with lymphadenectomy, relapse incidence was even higher, although not statistically significant: 14.8% (4/27) vs. 7.5% (4/53); ($p = 0.528$). Altogether, the relapse rate was 10.0% (8/80) for all patients operated in a non-fertility sparing way. Regarding the relapse free interval for patients operated with lymphadenectomy and those without, there is again no statistically significant difference (33.3 months vs. 21.5 months, Mann–Whitney U test, $p = 0.686$). Two deaths occurred in the patient group treated with lymphadenectomy (2/27, 7.4%) and eight in the patient cohort without (8/53, 15.1%) ($p = 0.532$). In terms of survival, there was no statistically significant difference in 5- and 10-year survival rates: 97.1 and 97.1% with vs. 96.2 and 91.0% without lymph node dissection ($p = 0.427$).

All but one patient with recurrent disease had been operated by laparotomy at primary diagnosis. None of the patients were operated on in a fertility sparing way, meaning that bilateral adnecectomy and hysterectomy had been performed in all of them. Moreover, omentectomy had been included in all but one patient. Lymphadenectomy had been completed in 40% of patients with recurrent disease which is a higher percentage compared with the patients who did not experience recurrence in whom the rate of lymphadenectomy was 31.0%. Appendectomy had been performed in half of the patients diagnosed with a mucinous borderline tumor and recurrent disease ($n = 2/4$). All patients with relapse had been staged with multiple peritoneal biopsies and cytology (Table 3). For those 10 patients who experienced relapse, 20% had not undergone full operative staging (2/10). Therefore, staging in this patient cohort should be described more precisely as pT1a in two cases, apparent pT1a in one case, pT1b in one and apparent pT1b in another case since underestimation of tumor stage due to incomplete staging is possible.

Five- and 10-year survival rates of women treated with fertility sparing surgery were 100% and thus not worse than those of patients treated with radical surgery (95.1 and 90.1% for 5- and 10-year survival) ($p = 0.125$). Relapse rates in both groups were comparable with 10.5% (2/19) vs. 10.0% (8/80) ($p = 0.723$). Mean relapse free interval was 0.7 ± 0.3 years after fertility sparing surgery vs. 2.3 ± 1.8 after non-fertility sparing surgery ($p = 0.267$). The surgical access by laparoscopy or laparotomy did not show a significant effect on either relapse or survival ($p > 0.1$ for both).

4. Discussion

BOT generally occurs about 10 years earlier in life than invasive ovarian cancer [8,9]. Therefore, fertility preservation is a major issue for relevant numbers of patients. In our patient cohort, about half of all patients were premenopausal and a third was confronted with the loss of ovarian function under the age of 40. Especially for those women, the most appropriate surgical approach remains a matter of discussion.

Over the decades, operative procedures have changed. BOT used to be treated like invasive ovarian cancer. Thirty percent of the patients in the study population had been operated with lymph node dissection. There was no difference in outcome with regard to survival or relapse if operated with or without lymphadenectomy. This finding is in agreement with the data published by others who do not promote systematic lymphadenectomy in early stage disease [7,10,11]. Though lymph nodes are described to be afflicted in 21–29% of patients [12–15], recurrence rates and survival data do not differ with or without lymph node involvement.

Nevertheless, proper staging is still recommended and should be performed by exploration of the entire abdominal cavity with peritoneal washing, infracolic omentectomy, removal of all macroscopically suspicious peritoneal lesions and sampling of peritoneal biopsies [5]. Even appendectomy is recommended in mucinous tumors [16]. The need for taking multiple biopsies for proper staging is underlined by the fact that implants were spread widely in the analyzed patient collective: 42.1% were localized in the omentum, 31.6% in the peritoneum and about 10% in diaphragm and bladder. Implants were even found in the mesosalpinx, uterus, umbilicus and kidney in our study population. We observed a two-fold higher relapse rate in patients with a stage greater than Ia. Still, three patients with FIGO stage Ia disease experienced recurrence, which is relatively high. All of them had been operated by laparotomy and not fertility sparingly. In two patients, lymph node sampling had not been performed, in one with a mucinous tumor appendectomy and omentectomy had not been done. The high relapse rate of early stage disease in our patient group may be caused by suboptimal staging and consecutive pathological underestimation of FIGO stage. On the basis of a large meta-analysis, Seidman et al. postulate that the surgical pathologic stage and sub-classification of extra-ovarian disease into invasive and non-invasive implants represent the most important prognostic indicators of serous BOT [12]. In our patient cohort, invasive implants show a statistically significant correlation to recurrence, and these patients should therefore be watched closely in clinical follow-up. With regard to histologic subtype, we did not find statistically significant differences for relapse or survival. Though the number of patients with endometrioid ovarian borderline is relatively low, one should keep in mind the need to perform a uterine curettage in those patients since coexisting endometrioid carcinomas have been described [17].

Standard therapy of BOT used to be bilateral salpingo-oophorectomy, and a fertility sparing approach was considered individually. There is a higher demand for fertility preserving surgery with the generally raising age when giving birth, and patients frequently demand to have cystectomy only. In a large French retrospective study published by Poncelet et al. on women diagnosed with early stage BOT, different operative procedures were compared. In patients operated by cystectomy they observed a higher rate of intraoperative cyst rupture and more recurrences in comparison to women who had unilateral or bilateral oophorectomy [18]. Therefore, cystectomy remains controversial since several studies report of recurrence rates of 12–58% [4,19,20]. Our results did not indicate a worse outcome for women with fertility sparing surgery, though one has to keep in mind that none of our patients were operated by cystectomy only. Relapse rate and long-term survival were not statistically different from patients who had been operated in a non-fertility sparing manner. In literature, relapse generally seems to be increased if a fertility sparing approach is chosen: the numbers vary between 0 and 25% compared with about 5% in radically operated women [8,21–23]. On the other hand, comparable survival rates are reported for women operated in a fertility sparing vs. non-fertility sparing way [6,24], which is in agreement with our results. Still, women with fertility sparing surgery should be looked at carefully in follow-up. Data by Borgfeldt et al. showed that fertility can be preserved in women diagnosed with stage Ia borderline tumors until completion of childbearing, but found a low acceptance of secondary surgery, i.e. prophylactic oophorectomy of the contralateral ovary and hysterectomy, in this patient group [25].

The strength of this study is the long follow-up of 23 years, the persistent high standard of operative procedure by gynecologic oncologists at a specialized academic institution and the consistent pathologic histology review by expert gynecologic oncology pathologists. A limitation is obviously the retrospective, non-randomized study design.

5. Conclusion

Ovarian BOT has a good prognosis in general. The histological diagnosis at primary diagnosis and especially the presence of invasive implants identify patients at risk for recurrence. Fertility sparing surgery can be an adequate treatment option for women at childbearing age in early stage disease.

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