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ScienceDirect
EJSO xx (2008) 1–6
EJSO the Journal of Cancer Surgery
www.ejso.com

Behaviour of ovarian tumors of low malignant potential treated with conservative surgery

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Accepted 30 September 2008

Abstract

Objective: Fertility-sparing surgery has been proposed for the treatment of borderline ovarian tumors. The aim of this study was to evaluate the outcome of patients submitted to cystectomy (CYS) compared with patients treated by unilateral salpingo-oophorectomy (USO) or bilateral salpingo-oophorectomy with/without total hysterectomy (radical surgery, RS).
Methods: We reviewed retrospectively the data of patients treated in 3 institutions for borderline ovarian tumors. One hundred and sixty-eight patients underwent laparoscopic or laparotomic surgical treatment from 1985 to 2006. Tumor recurrence rate, disease-free survival and site of recurrences were evaluated. Specific prognostic factors, such as stage, histology, micropapillary subtype, exophytic tumor growth, intraoperative spillage, endosalpingiosis, staging procedures, and route of surgery were analysed.
Results: Thirty-five patients underwent cystectomy, 50 unilateral salpingo-oopohorectomy, and 83 radical surgery. Twelve patients in the CYS group (34.3%), 10 in the USO group (20.0%), and 5 (6.0%) in RS group relapsed. Five-year progression-free survival (PFS) was 59.6%, 78.4%, and 93.5% in CYS, USO and RS groups, respectively. None of the relapsed patients died of disease.
Conclusions: Cystectomy is an effective surgical strategy for patients with borderline ovarian tumor. The higher risk of local relapses is not associated with a reduction in the overall survival. The procedure should be offered to young patients with bilateral tumors and to very young ones, considering the higher risk of local relapse.

Keywords: Ovarian low malignant potential tumor; Fertility-preserving surgery; Cystectomy; Relapse

Introduction

Borderline ovarian tumors (BOTs), or low malignant potential tumors (LMPT), account for 10–15% of all ovarian tumors. They are characterized by a degree of cellular proliferation and nuclear atypia in the absence of destructive growth or stromal invasion. The most common histological type is serous (50–65%) followed by the mucinous one (35–46%). Serous LMPT are bilateral in 30% of cases and associated with extra-ovarian lesions, so-called ''implants'', in 35%. According to their microscopic characteristics, implants can be divided into non-invasive (papillary structure similar to LMPT) or invasive (structure similar to infiltrating well-differentiated adenocarcinoma), the latter influencing prognosis.[1–3]

In most cases BOTs present at an early stage, usually 1a, and their prognosis is good. Nevertheless, recurrences can occur even more than 10 years after diagnosis. The 5-year survival rate is around 96%, although studies with long-term follow-ups describe overall survivals of 99.7% and over at 5 years and 80–90% at 15 years.[4]

Since their original description in 1929, our knowledge of the natural history of LMPT has advanced over recent decades.[4] As a consequence, management has changed from radical surgery to a more conservative therapy. Surgical removal is the cornerstone in the management of BOTs, but the surgical approach and the extent of the staging

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doi:10.1016/j.ejso.2008.09.011

procedure are currently debated.[2] In the last two decades laparoscopy has become a good alternative to laparotomy. Laparoscopic surgery has greatly changed the approach to ovarian masses and laparoscopic management is considered to be safe and adequate even in early invasive ovarian cancer.[5,6] The mean age that LMPT present is in the childbearing period and a fertility-sparing approach is an important issue. However, at least as important as fertility is whether we can reduce the morbidity caused by radical surgery and whether a more conservative approach is a safe alternative from an oncologic point of view.[2]

The aim of this study is to evaluate the outcome of patients treated by cystectomy compared to those treated by unilateral salpingo-oophorectomy or bilateral salpingo-oophorectomy with/without total hysterectomy (radical surgery).

Patients and methods

One hundred and sixty-eight patients with BOTs were treated in three Italian Institutions (Bologna, Torino, and Parma) from January 1985 to June 2006. Databases of the surgical reports, histological diagnosis, and clinical outcome were obtained.

Surgical procedures and staging

All patients underwent surgery via laparoscopy or laparotomy according to the surgeon's experience. The patients were grouped according to three different surgical treatments: 1) simple removal of the ovarian cyst sparing the residual ovarian tissue and the contralateral ovary (fertility-sparing surgery: cystectomy group, CYS); 2) complete removal of the ovary containing the borderline tumor (fertility-sparing surgery: unilateral oophorectomy group, USO); and 3) bilateral oophorectomy with/without total hysterectomy (radical surgery, RS).

Cystectomy was performed as follows: after visualisation of the affected ovary by means of a laparotomic or laparoscopic approach, the ovarian cortical tissue was incised, the cleavage plane was identified and the cyst was stripped off the remaining ovarian parenchyma through traction exerted in opposite directions by using atraumatic grasping forceps. Every effort was made to avoid rupture of the cyst and spillage of its content inside the abdomen. During laparoscopic procedures the cyst was then removed through an endo-bag.

The patients were staged according to the International Federation of Gynecology and Obstetrics classification.[7] Staging procedures were performed in 90 patients (53.6%) and consisted of peritoneal washing, infracolic omentectomy, random peritoneal biopsies in at least six different areas of the abdomen, contralateral ovarian biopsy, and appendectomy in mucinous tumors.

Histological assessments

Histological diagnosis was performed according to the WHO criteria[8]; peritoneal implants were studied for the presence of stromal invasion (invasive implants). Micropapillary serous borderline tumor was defined when an area of micropapillary growth measuring >5 mm in maximum diameter was found and in the absence of stromal invasion.[9] The presence of tumor on the surface of the ovary (exophytic borderline tumor) was assessed to evaluate the recurrence risk. Endosalpingiosis, consisting of benign glandular inclusions in the peritoneum, was considered.

Follow-up

Follow-up was performed by clinical assessment, CA125 testing and transvaginal sonography every three months for two years, and every six months up to five years from diagnosis, then annually.

Statistical analyses

Tumor recurrence rate, progression to carcinoma rate, disease-free survival, site of recurrence and histological type were evaluated.

Specific prognostic factors, such as age, stage, histology, micropapillary subtype, exophitic tumor growth, intraoperative spillage, endosalpingiosis, staging procedures, route of surgery were analysed.

Pearson's χ^2 test, one way ANOVA, and Kruskal Wallis test were used for statistical analysis. Cumulative survival curves were analysed by Breslow's test. Cox's regression with Wald's statistics was used to verify specific risk factors. Statistical significance was set at $p < 0.05$.

Results

Patients' characteristics

The characteristics of the patients are presented in Table 1. According to the macroscopic appearance at surgery, 85.1% of the patients had a stage I disease. Among the patients that received complete staging procedures 69 were stage I: 49 stage Ia, 5 Ib, 15 Ic; 4 patients were stage II, and 17 stage III.

Patients' characteristics according to surgical procedures

Laparoscopy was used in 57 patients and laparotomy in 112 patients. Laparoscopy was performed in younger patients (40.3 ± 15.6 vs. 48.3 ± 15.2 years); stage I tumors were treated by laparoscopy in 36.4% of cases or by laparotomy in 63.6%; stage II disease was treated by laparoscopy in 2 cases and by laparotomy in 3 cases, and stage III disease was treated by laparoscopy in 3 cases and by

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Table 1
Patients' characteristics.

Total number of patients	168
Mean age, years	45.5 (range 14–85)
Age ≤ 40 years	75
Menopausal	64
Apparent stage	
Stage Ia	119
Stage Ib	6
Stage Ic	18
Stage II	5
Stage III	20
Histological type	
Serous	102
Mucinous	40
Others	26
Serous subtype micropapillary	7
Endosalpingiosis	23
Peritoneal implants	21
Non-invasive	17
Invasive	4
Exophytic	28
Spillage	51
Mean follow-up, months	60.5 (range 4–240)

laparotomy in 17 cases. Cyst rupture during surgery was reported in 42.1% of laparoscopic procedures and in 24.3% of laparotomic surgery. Twenty-seven patients were completely staged in the laparoscopic group and 63 in the laparotomic group.

Patients' characteristics according to surgical aggressiveness are shown in Table 2.

Bilateral borderline tumors were present in 25 patients, and they were treated with bilateral cystectomy in 1 case, with monolateral oophorectomy plus cystectomy in 3 cases, and with bilateral oophorectomy in 21 cases.

Risk factors for recurrence according to surgical aggressiveness

16.1% of the patients had a recurrence, with a mean time to recurrence of 25.1 months.

Description of the relapses according to the treatment group is shown in Table 3. Tumor relapses occurred in 22 cases out of 143 in stage I disease, in 1 case out of 5 in stage II and in 4 cases out of 20 in stage III. Relapses occurred in the same ovary in 5 cases, in the other ovary in 13 cases, in both ovaries in 3 cases, and in the peritoneal cavity in 6 cases. The rate of recurrences did not differ significantly according the approach: 14% for the laparoscopic group and 17% for the laparotomic group ($p > 0.05$). Histotype was serous borderline in all patients with relapse. Among the group of relapses 13 had intrasurgical rupture, 8 were exophytic, and 5 presented endosalpingiosis. Relapses in patients with peritoneal implants were observed in 6 out of 21 cases.

There were 5 relapses in the same ovary in the cystectomy group, 3 contralateral ovarian relapses, 3 bilateral ovarian relapses and one peritoneal relapse. In the USO group all 10 relapses occurred in the remaining ovary; in one case the ovarian relapse was associated with peritoneal recurrence. In the RS group all 5 relapses occurred in the peritoneal surface in the pelvis. All cases of relapse in the CYS group were retreated conservatively.

Table 2
Patients' characteristics according to surgical aggressiveness.

	Cys	USO	RS	*p*
Patients	35	50	83	n.s.
Mean age, years (range)	33.5 (17–64)	37.2 (14–77)	55.7 (23–85)	<0.0005
Stage I	31	43	69	
Stage II	–	1	4	
Stage III	4	6	10	n.s.
Serous	29	25	48	0.015
Mucinous	5	17	18	
Others histology	1	8	17	n.s.
Micropapillary	–	4	5	n.s.
Cyst rupture/spilling	21	16	14	<0.0005
Exophytic growth	2	6	20	0.026
Endosalpingiosis	5	7	11	n.s.
Peritoneal implants	2	8	11	n.s.

Among patients with bilateral tumors local relapse was observed in all the three patients treated with cystectomy and monolateral oophorectomy, in no case treated by bilateral oophorectomy, and in the only patient treated by bilateral cystectomy.

Univariate analysis

All risk factors were analysed by univariate analysis with Cox's regression with Wald's statistics, which emphasizes only large differences between groups (Table 4). Cystectomy, exophytic growth and age less than 35 years were the only factors associated with an increased risk of local relapse.

Progression-free survival

The overall 2-year and 5-year progression-free survival (PFS) was 83.6% and 82.7%, respectively. Two-year progression-free survival in the CYS, USO and RS group was 64.2%, 78.4% and 93.5%, respectively; five-year survival in the CYS, USO and RS group was 59.6%, 78.4% and 93.5%, respectively (Fig. 1); both conservative groups had significantly lower PFS compared to the radical group, while the difference between PFS of cystectomy and monolateral oophorectomy did not reach statistical significance. None of the relapsed patients died of disease.

Discussion

Staging procedures

Guidelines for the surgical treatment of LMPT are similar to those of ovarian cancer and, in women without reproductive desire, include peritoneal washing, hysterectomy

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Table 3
Risk factors for recurrence according to surgical aggressiveness.

	Cystectomy		Oophorectomy		BSO	
	Recurrence	No recurrence	Recurrence	No recurrence	Recurrence	No recurrence
Disease relapses (%)	12 (34.3)	23 (65.7)	10 (20.0)	40 (80.0)	5 (6.0)	78 (94.0)
Stage						
I	11	20	8	35	3	66
II	–	–	–	1	1	3
III	1	3	2	4	1	9
Histology						
Serous	10	19	9	16	4	44
Mucinous	1	4	0	17	0	18
Others	1	0	1	7	1	16
Micropapillary	0	0	2	2	0	5
Cyst rupture/spilling	7	14	5	11	1	13
Exophytic	1	1	4	2	3	17
Endosalpingiosis	2	3	2	5	1	10
Peritoneal implants	1	1	3	5	2	9

with bilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies and appendectomy for mucinous tumors. Lymphadenectomy can be omitted even for advanced disease.[1,2] Complete staging is only performed in 50% or fewer patients.[2] Nevertheless, Camatte et al. reported that the absence of peritoneal staging in patients with an ''apparent stage I'' does not modify survival even if the recurrence rate is increased.[10] In a French multicenter study no difference in recurrence rate was observed between women who underwent restaging and those who did not.[11] In our series 53.6 % of the patients underwent complete staging procedures. The percentage of apparent stage I diseases was similar to that of real stage I (85.1 vs. 76.7%). Staging was not a risk factor for relapse.

Laparoscopic approach

Laparoscopic restaging as well as total laparoscopic management of LMPT has been reported to be safe and feasible with excellent immediate and late results.[12] In our study recurrence rate did not differ according to laparoscopic or laparotomic approach. Local relapses were seen in 16.1% of our cases, being similarly distributed in the laparoscopic (14%) and in the laparotomic (17%) group, consistent with the data observed by others.[13,14] Laparotomic approach is generally reserved to larger tumors, but possibly the easy manipulation of the mass by laparotomy reduces the risk of tumor spilling.[15]

In our experience the cystectomy procedure caused intraoperative spilling in 60% of the patients, corresponding to the incidence of intraoperative rupture seen by Fauvet et al. in the patients treated by laparoconversion.[13] Nevertheless, this factor was not associated with a significant increase in local relapses (HR: 1.3), suggesting that the biological characteristics of LMPT and the protected removal of the cyst via an endo-bag were sufficient to avoid wound metastasis and a significant increase in local relapses.

Recurrence features

Conservative surgery is complicated by a higher rate of relapse. In the literature relapse rates are between 0 and 20% after adnexectomy, between 12 and 58% after cystectomy, and between 3 and 6% after radical surgery.[2,3] In our series the rate of recurrence was 34% in the cystectomy group, 20% in the USO group and 6% in the radical group. This confirmatory result is of value since the number of patients that underwent fertility-sparing surgery in our series is among the highest in the literature. Recurrences after fertility-sparing surgery are characterized by an excellent long-term survival,[1] and this is confirmed by our data, as none of our relapsed patients died of disease.

Previous reports have shown that recurrence after cystectomy does not necessarily occur ipsilaterally.[16–18] Zanetta et al. in a series of 164 patients treated

Table 4
Factors independently associated with recurrence by univariate Cox's regression with Wald's statistics.

	Odds ratio	95% CI	*p*
Laparoscopy/laparotomy	1.28	0.80–2.06	n.s.
Staged/unstaged	1.30	0.83–2.05	n.s.
Stage I/stage III	1.36	0.55–3.36	n.s.
Surgical aggressiveness			0.001
-Bilateral oophorectomy /cystectomy	0.31	0.16–0.61	0.001
-Oophorectomy/cystectomy	1.36	0.79–2.35	n.s.
Histology			n.s.
-Mucinous/serous	0.33	0.08–1.35	n.s.
-Others histology/serous	1.82	0.63–5.22	n.s.
Micropapillary	1.01	0.40–2.57	n.s.
Endosalpingiosis	1.09	0.63–1.91	n.s.
Spillage/no spillage	1.21	0.76–1.93	n.s.
Exophytic/endophytic	2.19	1.23–3.88	0.007
Age <35 years/>35 years	2.16	1.16–4.02	0.015
Peritoneal implants	1.43	0.91–2.26	n.s.

CI: 95% confidence interval.

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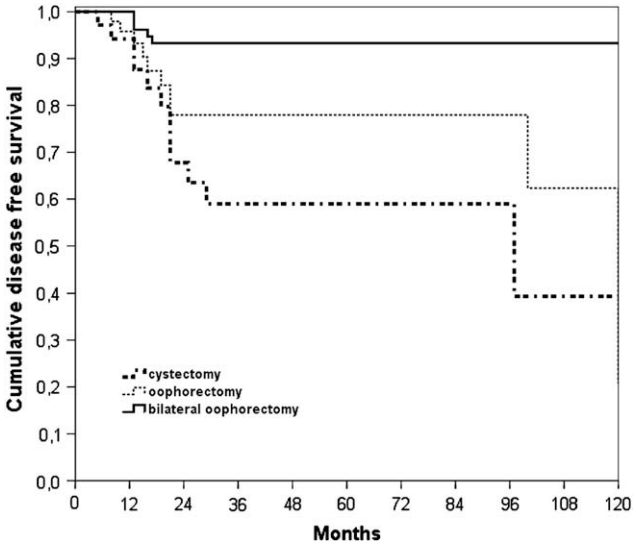

Figure 1. Progression-free survival in patients with ovarian borderline tumor according to type of surgery. Breslow test: bilateral oophorectomy vs. cystectomy: 0.038; bilateral oophorectomy vs. oophorectomy: 0.0003; cystectomy vs. oophorectomy: 0.187.

conservatively, reported 11 recurrences in the contralateral ovary and 9 in the same ovary.[17] Yinon et al. in a single center retrospective study observed 4 ipsilateral and one contralateral serous borderline recurrence in 22 patients treated with cystectomy.[19] Our data show that, after cystectomy, contralateral relapse was seen in 6 (3 single contralateral and 3 bilateral) out of 12 cases of relapse. Recurrence is therefore not only caused by a local residual tumor after cystectomy but can be due to tumor localization in the other ovary.

According to the literature, at diagnosis LMPT are bilateral in 25–50% and in 5–10% of the serous and mucinous histotypes respectively.[1] Our data show bilateral LMPT in 19.6% of serous histotype, in 2.5% of mucinous type and in 21% of mixed histotype. In a randomised trial, Palomba et al. compared the effects of 2 laparoscopic fertility-sparing surgical procedures (bilateral cystectomy vs. oophorectomy plus contralateral cystectomy) for the treatment of bilateral BOTs.[20] The cumulative probability of first recurrence was not statistically different in the 2 groups ($p = 0.358$). The majority of our patients (21 out of 25) were treated with bilateral oophorectomy; only 4 patients were treated with fertility-sparing surgery, bilateral cystectomy in 1 case and monolateral oophorectomy plus cystectomy in 3 cases, with local relapses in all cases.

The literature reports a 2% rate of invasive recurrence and 30% in patients with invasive peritoneal implants.[2,17] We observed no cases of invasive recurrence and a 100% 5-year overall survival; malignant recurrences generally appear within the first three years following surgery,[3] therefore our 60 months of follow-up was long enough to obtain viable results.

Risk factors for recurrence

Survival is generally associated with stage; Leake reported a 20-year survival rate of 99%, 96% and 45% in stage I, stage II and stage III disease respectively.[21] The risk of recurrence is also associated to stage; a review of 1001 cases by Massad et al. showed a recurrence rate of 2.1% in stage I, 7.1% in stage II and 14.4% in stages III–IV.[22] Romagnolo et al. observed a significant correlation between progression-free survival (PFS) and stage, which at 10 years was 89.2%, 66.6, and 45% for stage Ia, II and III, respectively.[14] Our series did not support these studies, but the number of advanced stage patients is probably insufficient to draw any conclusion.

Women with exophytic serous LMPT are at higher risk of extra-ovarian disease and as a consequence at higher risk of relapse.[23] In our series exophytic growth was independently associated with recurrence, with an odds ratio of 2.194. This feature was most frequently observed in the radical surgery group (24.1%) vs. the cystectomy (5.7%) and the monolateral oophorectomy (12.0%) groups ($p = 0.026$). Exophytic growth is therefore a significant risk for recurrence, but is generally associated with characteristics (age, volume of the tumor, stage) that induce surgeons to perform the laparotomic procedures.

Micropapillary serous subtype has been proposed as a risk factor of relapse. Shih and Kurman consider this histological identity as a transition from atypical proliferative serous tumors to non-invasive micropapillary serous carcinoma, which can be observed in 75% of cases. The latter can be associated with invasive low grade serous carcinoma that pursues an indolent course, with a 50–60% survival.[24] On the contrary, Prat and de Nictolis in a series of 137 cases of serous LMPT including 18 patients with micropapillary pattern reported no influence on prognosis.[25] In the small group of patients with micropapillary pattern, our results did not show a prognostic value of this factor.

Although endosalpingiosis is generally considered benign and does not seem to influence the prognosis in serous LMPT, Moore et al.[26] suggested that in some instances it may actually be a metastase, and Silva et al.[27] noted a significantly higher frequency of endosalpingiosis in extra-ovarian sites in women with stage I serous BOTs who experienced recurrence compared with a control group of women with no recurrence after a minimum follow-up of 15 years. Similar to previous studies the rate of endosalpingiosis in our series was 13%. Our study supports the claim that endosalpingiosis is not a risk factor for tumor relapse.

The risk of relapse has been correlated with age. In a large series of LMPT, published in 1992, Kaern et al. observed with multivariate analysis a fivefold higher risk of dying of disease in patients older than 70 years compared with patients younger than 40 years.[28] On the contrary, our data show that age less than 35 is significantly associated with higher rate of recurrence; this might be influenced by the bias of different treatments for younger and older

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patients, the latter being more frequently treated by radical surgery.

Conclusions

Previous studies have suggested the safety of conservative surgery with unilateral salpingo-oophorectomy or cystectomy for patients with stage I LMPT. Recurrences are more frequent, but do not affect survival. In a recent review on the conservative surgery of LMPT, Tinelli et al.[1] concluded that unilateral salpingo-oophorectomy must be considered as the first choice of conservative treatment, which can be performed by laparoscopy. The authors reserve unilateral cystectomy for patients with a history of contralateral adnexectomy and advocate the use of this procedure in the incidental histological discovery of an LMPT. In another recent review Cadron et al.[2] investigated whether fertility-sparing surgery in the management of LMPT was good clinical practice from an oncologic point of view. They considered it safe to perform conservative surgery (i.e., salpingo-oophorectomy, infracolic omentectomy, multiple peritoneal biopsies and cytology) for stage I disease. They only recommended performing cystectomy when there is a bilateral tumor or when there is a previous history of unilateral adnexectomy.

We think that monolateral cystectomy is feasible, and the higher risk of local relapses is not associated with an impairment of the overall survival. The procedure should be limited to young patients with bilateral tumors and very young ones, after comprehensive counselling about the higher risk of local relapse.

Conflict of interest

The authors have no conflict of interest.

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