Borderline ovarian tumors: laparoscopic treatment

M. Candiani, C. Vasile[1], M. R. Sgherzi, A. Nozza, F. Maggi, R. Maggi
2nd Clinic of Obstetrics and Gynaecology "L. Mangiagalli", University of Milano
Cucesc (Universitary Center of Experimental and Clinical Endoscopic Surgery) - University of Milano
[1]Clinic of Gynaecology and Obstetrics, University of Padova

Introduction

The benefits of laparoscopic surgery in the treatment of benign ovarian lesions are clearcut and well documented by many Authors [1, 2]. Almost 90% of adnexal masses are histologically benign and may be adequately treated by laparoscopy. Problems may arise in the management of suspect adnexal masses: inappropriate surgical procedures, incomplete staging and delays in definitive therapy might have a significant impact on subsequent outcome of an adnexal mass found to be malignant. The current trend in the management of adnexal cysts includes an accurate preoperative workup (clinical and ultrasound examination, serum markers detection and eventual Doppler evaluation) in order to exclude inadvertent laparoscopic treatment of ovarian malignancy. The French school (Bruhat and coworkers) suggests laparoscopy may play an important role as a diagnostic preoperative tool as it permits an accurate magnified macroscopic definition of the lesion, a good inspection of the pelvic and abdominal organs allowing target biopsies. The advantages of the laparoscopic approach in defining an adnexal mass are related to a strict intraoperatory protocol which includes performing peritoneal washings, accurate evaluation of the location, size, macroscopic aspects of the cysts as well as of the contralateral ovary and of the abdominal cavity.

Since it is universally accepted that a benign ovarian cyst can be treated laparoscopically and that an ovarian cancer requires laparotomic conversion the management of borderline ovarian tumors represents a puzzling chapter in the treatment of adnexal masses. There are a number of conceptual and practical problems involving the terminology and staging of ovarian borderline tumors [3].

Borderline ovarian tumors, known as tumors of low malignant potential (LMP) or, more recently as atipically proliferating tumors (APT) are a group of tumors sharing an excellent prognosis despite peculiar histological aspects which may mimick malignancy (presence of cellular stratification, atypical cell clusters, high mitoses and nuclear atypia) [4, 5, 6]. They represent 10-15% of all ovarian neoplasias and have a long natural history, an indolent course characterized by slow growth and late recurrences. LMP ovarian tumors occur in younger patients with respect to epithelial frank malignancies, are usually detectable in early stages, lack stromal invasion and present high overall survival rates – 95% five year survival and 80% twenty year survival – [7, 8, 9, 10, 11]. Since borderline ovarian tumors frequently occur in women of reproductive age, they may pose difficult management problems because many of these wish to preserve their fertility. Surgery is the cornerstone of treatment for these tumors. Recent trials have established the important role of a conservative approach with the preservation of the ovarian tissue and reproductive function in fertile age patients. *Table 1* summarizes the results of 4 case series with a long follow-up. Lim Tan *et al.* [8] in their case series performed ovarian cystectomy for serous borderline tumors: follow up of the 35 patients showed that despite the occasional complication of persistence or recurrence of tumor, all were alive without evidence of disease 3-18 years after the initial surgery with an average follow up of 7.5 years. The recent GOG report [12] suggests that even cystectomy as opposed to oophorectomy may be adequate therapy, because the risk of recurrence or the development of a new LMP tumor appears to be only 10-15% and can be succesfully managed by reoperation. The need of adjuvant therapies has been questioned and the result of four prospective randomized trials revealed that they did not seem to improve the overall corrected survival [13]. *Table 2* shows the main prognostic factors cited in literature as: residual disease after primary surgery, invasive extraovarian implants, stage at initial surgery [14], involvement of the resection margins of the cystectomy and multifocality [8], histological type [13], high grade [16], DNA ploidy, pseudomyxoma peritonei [15], findings associated with a high risk for recurrence. In agreement with Bell and Scully [16] other Authors [17] found that stromal microinvasion is not an adverse prognostic factor. Subclinical node involvement in 14-23% of patients who underwent retroperitoneal lymphnode sampling for serous borderline tumors was present but this finding did not significantly affect survival [18]; however, recurrence was more likely for those patients with positive nodes. Finally, available data suggest that borderline tumors maintain their histological pattern and do not undergo malignant transformation. Kurman and Trimble [19] have estimated malignant transformation to occur in 0.75% of ovarian serous LMP tumors and some Authors have postulated that these cases represent "de novo" development of invasive serous carcinoma from the peritoneum rather than progression of a borderline lesion [20].

The laparoscopic treatment of borderline ovarian tumors was first reported by Nezhat [21] then by other Authors [22, 23]. The aim of our study was to evaluate the efficacy of laparoscopic surgery in the removal and staging of borderline ovarian tumors.

Table 1 – *Borderline ovarian tumors follow-up: Cases series*

Authors	N. Cases	Mean follow-up yrs	NED %	DOD %	Conservative surgery	REC.
Casey	39	11.8	69	2/39	21	3/39
Lim Tan	35	7.5	100	none	100	4/35
Rice	80	4.1	95.8	none	40	1/71
Tazelaar	61	7.4	100	none	32.7	5/61

NEO = no evidence of disease DOD = dead of disease REC = recurrences

Patients and Methods

From 1993 through 1998 fifty eight (n=58) patients with borderline ovarian tumors were surgically treated in our Department. The mean age of the patients was 42 years (range 19-79). A total of 70 ovarian cysts (9 bilateral) with a mean cystic diameter of 8.6 cm were present. Preoperative assesments included clinical examination, ultrasound scoring (Sassone) and serum markers detection. In

47.5% of the cases elevated markers (> 35UI/ml) were present (*Table 3*). A suspicious echografic pattern was present in 70.05% of the patients and subsequently confirmed by intraoperatory examination in 83.3% of these cases. Twenty six patients (44.8%) underwent laparoscopic treatment while 32 (55.17%) underwent laparotomy. Eight patients in the laparotomy group had a previous diagnostic laparoscopy; laparotomic conversion was decided for suspicious ovarian cysts subsequently found to be histologically borderline tumors. The patients in the two groups (laparoscopic and laparotomic) presented a homogeneous distribution regarding age and fertile status. Despite of the type of surgery, cytological evaluation of pelvic and abdominal washings before the surgical procedure, inspection of the contralateral ovary, targeted multiple peritoneal biopsies and accurate abdominal inspection to obtain an intraoperatory stadiation of the disease were performed.

Conservative treatment was performed in 32 patients (55.71%) – laparoscopically in 19 cases and by laparotomy in 13 cases while demolitive procedures were carried out in 26 cases (44.8%) – 7 by laparoscopy and 19 by laparotomy. The indication for conservative treatment (cystectomy or monolateral oophorectomy) in the laparoscopy group included stage I borderline ovarian tumors in patients wishing to preserve their fertility. Enucleation of the cyst was performed in early stages (IA and IB) tumors, when the resection margins at frozen section were free and the patient was previously informed about the possibility of late recurrences and therefore the necessity of a long term follow up.

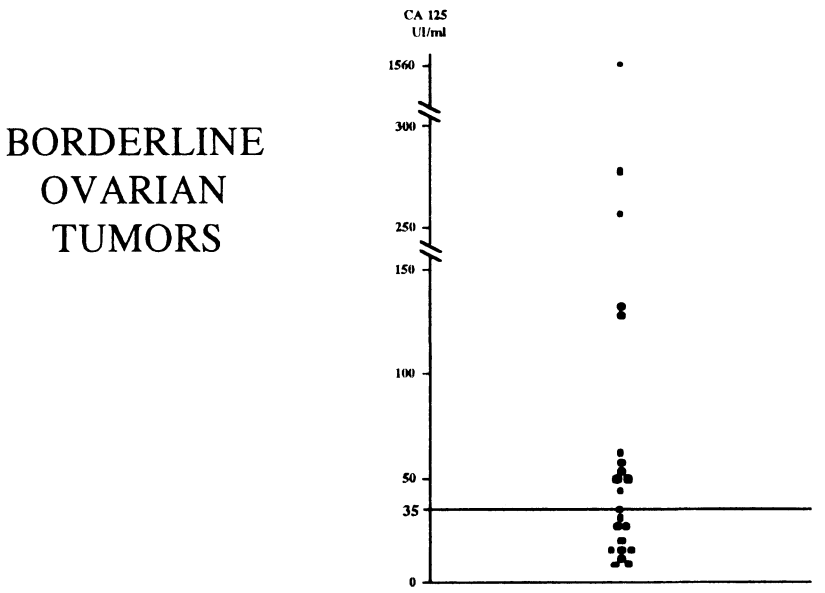
Demolitive procedures included abdominal hysterectomy with bilateral oophorectomy in the laparotomic group and laparoscopic hysterectomy in the laparoscopy group.

A second look laparoscopy was performed 6 months after initial surgery in those cases which underwent conservative treatment (laparoscopic or laparotomic) to evaluate the efficacy of the treatment and exclude eventual persistence of the disease.

Table 2 – *Borderline ovarian tumors: prognostic factors*

• Invasive extraovarian implants- stage *(Casey, 1993)*
• Pseudomyxoma peritonei *(Bell, Nakashima)*
• Involvement of the resection margins of the cystectomy *(Lim Tan, 1988)*
• Multifocality *(Lim Tan, 1988)*
• Histologic type *(Tropé, 1992)*
• High grade *(Norris)*
• DNA ploidy *(Dresher, 1992)*

Table 3 – *Preoperative CA125 levels distribution*



Results

The stage distribution of the patients is shown in *Table 4* while the histological findings are illustrated in *Table 5*.

The laparotomy group (n=32) included 15 stage IA (46.8%), 1 stage IB and 10 stage IC (31.25%) patients – a total of 81.25% of the cases approached by laparotomy were in initial stages. Thirteen patients (40.62%) underwent conservative treatment in the laparotomy group *(Table 6)*.

The laparoscopy group (n=26) included 17 stage IA (65.3%), 2 stage IB (7.6%), and 6 stage IC (23.07%) patients – the prevalence of initial stages was 96.15% and conservative treatment was carried out in 73.07% of the cases *(Table 7)*. Our data reveal that in the laparoscopy group the conservative approach was more frequent but this was due to the higher incidence of initial stages in these patients.

Table 4 – *Borderline ovarian tumors: case series (n=58)*

Stage distribution	
• IA - 31 (55%)	• IIB - 1 (2%)
• IB - 4 (5%)	• IIC - 2 (4%)
• IC - 16 (27%)	• IIIA - 4 (7%)
TOTAL 51	TOTAL 7

Table 5 – *Borderline ovarian tumors: case - series (n=58)*

Histology	N. cases	%
Serous	42	72
Mucinous	11	19
Mixed	3	5
Endometrioid	1	2
Clear Cell	1	2

Microinvasion foci in 6 cases (10.34%)

Table 6 – *Borderline ovarian tumors. Type of surgery: laparotomy (n=32)*

Stage	Conservative	Non conservative
IA	8	7
IB	1	–
IC	3	7
IIB	–	1
IIC	–	1
IIIA	1	3
TOTAL	13	19

Table 7 – *Borderline ovarian tumors. Type of surgery: laparoscopy (n=26)*

Stage	Conservative	Non conservative
IA	10	7
IB	2	–
IC	6	–
IIC	1	–
TOTAL	19	7

Considering only stage IA patients, 10 out of 17 (58.8%) in the laparoscopy group and 8 out of 15 (53.3%) in the laparotomy one had conservative surgery, therefore the two groups may be considered homogeneous with regard to the type of surgical approach. The mean follow up was 48 months (range 62-66). Fifty-seven patients are alive with no evidence of disease, one NED patient died for other reasons Eighteen patients out of 32 who had had conservative surgery underwent a second look laparoscopy; in 4 cases (15.6%) persistance or recurrence of the disease was found and subsequently treated conservatively in 3 cases. *(Table 8).*

Discussion and Conclusion

Borderline ovarian tumors have peculiar clinical and histological characteristics, therefore more than 70% of the patients are diagnosed in initial stages and have a good prognosis. Data in the literature show that no patients with a borderline serous ovarian tumor at stage IA, IB or IIA died of disease. Recurrences may present with a frequency of 10-30% even 10 years after initial surgery. In a previous study we reported the optimal prognosis of 21 cases of borderline tumors in fertile woman treated by conservative surgery [24]. At 10 year follow up, all the patients were alive, with no evidence of disease. The high incidence of these tumors in fertile patients as well as the frequent diagnosis in early stages suggest a conservative surgical approach. Some Authors reported the excellent results of a conservative surgical treatment even of frank malignant tumors in young women and stressed the importance of preserving a good quality of life [25]. Encouraged by our personal experience and by the reported case series in the literature we consider conservative laparoscopic treatment (monolateral adnexectomy) the gold standard in the management of early stage borderline ovarian tumors in young patients. Enucleation of the cyst might be considered appropriate in stage I tumors, with free resection

margins in patients desiring a pregnancy and accurately informed about the need of a long follow up. Complete staging by peritoneal washing, multiple target biopsies, during conservative surgery is mandatory. Contralateral ovarian resection is considered overtreatment in fertile patients as it may cause infertility in 14% of the cases. Lymphadenectomy is not suggested for borderline ovarian tumors but may be performed in selected cases with peritoneal implants (stage III) as positive nodes are more likely associated to a high risk of recurrence and a closer follow up is needed in these cases. An early laparoscopic second look is useful in order to evaluate persistent disease after conservative treatment, but a late second look in correctly staged patients seems excessive.

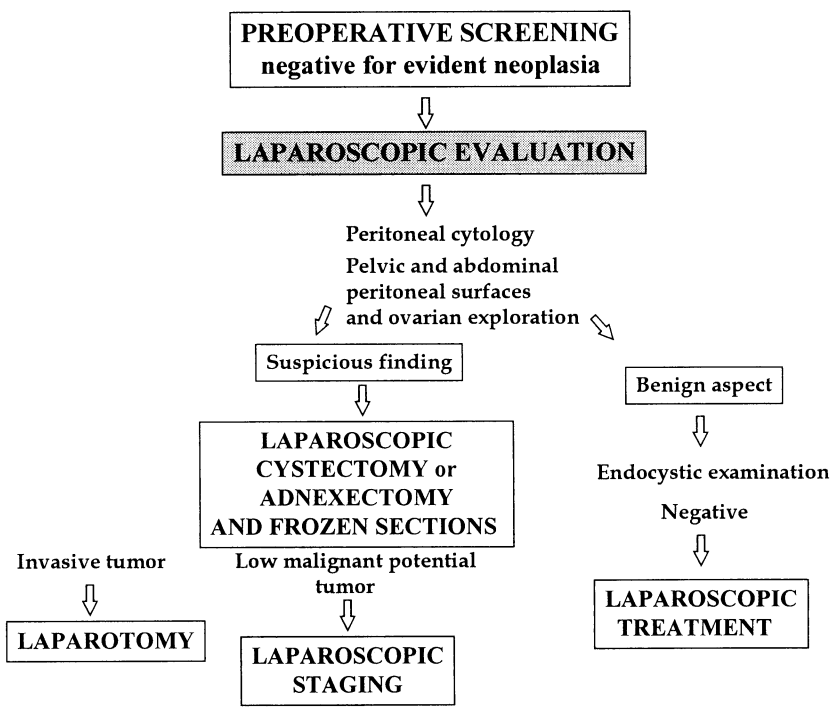
Table 8 – *Recurrences after laparoscopic conservative treatment*

N.	Initial surgery	Histology	Recurrences	Second surgery
1.	LPS right adnexectomy	serous LMP stage IA	ovarian contralateral LMP cysts (LPS II look after 6 months)	LPS left adnexectomy
2.	LPS bilateral ovarian cystectomy	serous LMP stage IB	peritoneal implants (LPS II look after 11 months)	LPS excision of peritoneal implants
3.	LPS resection of ovarian superficial bilateral excrescenses	serous LMP stage IB	minimal ovarian implants (LPS II look after 8 months)	LPS bilateral ovarian biopsies and peritoneal biopsies
4.	LPS right adnexectomy in pregnancy - 14 weeks of gestation	serous LMP stage IA	left ovarian cyst and peritoneal implants (cesarean section after 6 months)	LPS left ovarian cystectomy and peritoneal biopsies

LPS - laparoscopy LMP - low malignant potential tumors

NOTES
Case 1 and case 2 - classic recurrences for LMP ovarian tumors
Case 3 - calculated risk of recurrence as superficial ovarian excrescenses are difficult to remove radically
Case 4 - not a "real" recurrence but a persistance as during initial surgery a left ovarian implant mimicked endometriosis

Table 9 – *Laparoscopic management of borderline ovarian tumors (flow-chart)*



The controversies and challenges of the laparoscopic treatment of ovarian borderline tumors include tumor spillage and dissemination and the use of intraoperatory frozen sections. Recent studies [26, 27] suggested that the tumor intrasurgical spill does not affect prognosis, while laparoscopic management of a malignant ovarian tumor may worsen prognosis with respect to laparotomy according to Volz [28] because of the influence of CO_2 on malignant cell dissemination. At the time of laparoscopic surgery, even if the reported specificity of frozen section for borderline tumors is low [29], if high quality intraoperatory diagnosis is available, it should be used.

In conclusion, we consider conservative laparoscopic treatment (monolateral adnexectomy or even cystectomy in selected cases) in the management of early stage ovarian borderline tumors in young patients, an appropriate and reasonable surgical option. Randomized prospective trials with a long follow-up are still needed to evaluate the recurrence rate in laparoscopically treated patients.

The laparoscopic approach of adnexal masses offers the opportunity of a mininvasive treatment in many cases, but only preoperatory rigid criteria, intraoperatory strict protocols and the use of surgical guidelines minimize the risk of misleading and undertreating an ovarian malignancy.

References

[1] Canis M., Mage G., Pouly J. L. *et al.*: "Laparoscopic diagnosis of adnexal cystic masses: a 12 years experience with log term follow up". *Obstet. Gynecol.*, 1994, *83*, 707.
[2] Canis M., Pouly J. L., Wattiez A. *et al.*: "Laparoscopic management of adnexal masses suspicious at ultrasound". *Obstet. Gynecol.*, 1997, *89*, 679.
[3] Russell P.: "Borderline epithelial tumors of the ovary: a conceptual dilemma". *Clin. Obstet. Gynecol.*, 1984, *11*, 259.
[4] Tasker M., Langley F. A.: "The outlook for women with borderline epithelial tumors of the ovary". *Br. J. Obstet. Gynaecol.*, 1985, *92*, 969.
[5] Nikrui N.: "Survey of clinical behaviour of patients with borderline epithelial tumors of the ovary". *Gynecol. Oncol.*, 1981, *12*, 107.
[6] Leake J. F., Currie J. L., Rosenshein N. B. *et al.*: "Long term follow up of serous ovarian tumors of low malignant potential". *Gynecol. Oncol.*, 1992, *47*, 150.
[7] Casey A. C., Bell D. A., Lage J. M. *et al.*: "Epithelial ovarian tumors of borderline malignancy: long term follow up". *Gynecol. Oncol.*, 1993, *50*, 316.
[8] Lim Tan S. K., Cajigas H. B., Scully R. E.: "Ovarian cystectomy for serous borderline tumors: a follow up study of 35 cases". *Obstet. Gynecol.*, 1988, *72*, 775.
[9] Rice L. W., Berkowitz R. S., Mark S. D. *et al.*: "Epithelial ovarian tumors of borderline malignancy". *Gynecol. Oncol.*, 1990, *39*, 195.
[10] Tazelaar H. D., Bostwick D. G., Ballon S. C., Hnedrickson M. R. *et al.*: "Conservative treatment of borderline ovarian tumors". *Obstet. Gynecol.*, 1985, *66*, 417.
[11] Bell D. A., Weinstock M. A., Scully R. E.: "Peritoneal implants of ovarian serous borderline tumors of the ovary. Histologic features and prognosis". *Cancer*, 1988, *62*, 2212.
[12] Barnhill D. R., Kurman R. J., Brady M. F. *et al.*: "Preliminary analysis of the behaviour of stage I ovarian serous tumors of low malignant potential: a Gynecologic Oncology Group Study". *J. Clin. Oncol.*, 1995, *13*, 2752.
[13] Tropé C., Kaern J., Vergote J. B. *et al.*: "Are borderline tumors of the ovary overtreated both surgically and systemically? A review of four prospective randomized trials including 253 patients with borderline tumors". *Gynecol. Oncol.*, 1993, *51*, 236.
[14] Kliman L., Rome R. M., Fortune D. W.: "Low malignant potential tumors of the ovary: A study of 76 cases". *Obstet. Gynecol.*, 1988, *68*, 338.
[15] Nakashima N., Nagasaka T., Oiwa N. *et al.*: "Ovarian epithelial tumors of borderline malignancy in Japan". *Gynecol. Oncol.*, 1990, *38 (1)*, 90.
[16] Bell D. A., Scully R. E.: "Ovarian serous borderline tumors with stromal microinvasion: a report of 21 cases". *Hum. Pathol.*, 1990, *21*, 397.
[17] Tavassoli F. A.: "Serous tumor of low malignant potential with early stromal invasion (serous LMP with microinvasion)". *Mod. Pathol.*, 1988, *1*, 407.
[18] Leake J. F., Rader J. S., Woodruff J. D. *et al.*: "Retroperitoneal lymphatic involvement with epithelial ovarian tumors of loe malignant potential". *Gynecol. Oncol.*, 1991, *42*, 124.
[19] Kurman R. J., Trimble C. L.: "The behaviour of serous tumors of low malignant potential are they ever malignant?". *Int. J. Gynecol. Pathol.*, 1993, *12*, 120.
[20] Link Cj jr., Kohn E., Reed E.: "Review: The relationship between borderline ovarian tumors and epithelial ovarian carcinoma: epidemiologic, pathologic and molecular aspects". *Gynecol. Oncol.*, 1996, *60*, 347.
[21] Nezhat F., Nezhat C., Welander C. E. *et al.*: "Four ovarian cancers diagnosed during laparoscopic management of 1011 women with adnexal masses". *Am. J. Obstet. Gynecol.*, 1992, *167*, 790.
[22] Darai E., Teboul J., Fauconnier A. *et al.*: "Management and outcome of borderline ovarian tumors incidentally discovered at or after laparoscopy". *Acta Obstet. Gynecol. Scand.*, 1998, *77*, 451.
[23] Candiani M., Maggi R., Natale A., Giambelli F. *et al.*: "Masse annessiali borderline: trattamento laparoscopico", negli Atti della SIGO, Congresso Firenze, 1996, 855.
[24] Candiani M.: "Trattamento laparoscopico delle masse annessiali borderline in età fertile". In: "Trattamento laparoscopico delle cisti ovariche". Atti della Riunione GLEG, Senago, marzo 1997.
[25] Marchetti M., Padovan P., Fracas M.: "Malignant ovarian tumors: conservative surgery and quality of life in young patients". *Eur. J. Gynaec. Oncol.*, XIX, 1998, *3*, 297.
[26] Katzenstein A. A., Mazur M. T., Morgan T. E. *et al.*: "Priliferative serous tumors of the ovary". *Am. J. Surg. Pathol.*, 1978, *2*, 339.
[27] Sjovall K., Nilsson B., Einhorn N.: "Different types of rupture of the tumor capsule and impact on survival in early ovarian carcinoma". *Int. J. Gynecol. Cancer*, 1994, *4*, 333.
[28] Volz J., Kostners S., Melchert F.: "The effects of penumoperitoneum on intraperitoneal tumour implantation in nude mice". *Gynaec. Endoscopy*, 1996, *5*, 193.
[29] Chapron C., Dubuisson J. B., Kadoch O. *et al.*: "Laparoscopic management of organizc ovarian cysts: is there a place for frozen section diagnosis?" *Hum. Reprod.*, 1998, *13 (2)*, 324.

Address reprint requests to:
MASSIMO CANDIANI, MD
2nd Clinic of Obstetrics and Gynaecology
"L. Mangiagalli"
Via della Commenda, 12 - Milano (Italy)