

Outcome and Reproductive Function After Conservative Surgery for Borderline Ovarian Tumors

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Objective: To study reproductive function and disease outcome in women with borderline ovarian tumors who were treated with conservative surgery.

Methods: Patients with borderline ovarian tumors were identified from institutional databases. Patients were eligible if they had pathologically confirmed borderline ovarian tumors, no prior sterilization, no history of radiation therapy, retained their uterus and ovarian tissue, and were younger than age 45. Information was acquired by retrospective medical record review and patient interview.

Results: Forty-three patients met the eligibility criteria. The median age was 25 years, with a range of 15–39 years. Twenty-six patients had serous tumors, and 17 had mucinous tumors. Fifteen had stage I disease, three had stage III, and 25 were unstaged. Follow-up was available for all patients (median, 5.7 years). Twenty-nine remained disease-free, and 14 developed a new primary lesion/recurrence, with a median time to recurrence of 39.3 months. Recurrence was more frequent in patients treated with ovarian cystectomy than in those treated with oophorectomy alone (58% compared with 23%) ($P < .04$). After treatment, 29 of 36 patients (81%) retained normal menstrual cycles, and 12 of 24 patients attempting pregnancy conceived 25 pregnancies. Most patients were highly satisfied with conservative surgery.

Conclusion: Conservative surgery remains a therapeutic option in selected patients with borderline ovarian tumors. Although the rate of new lesion/recurrence is relatively high, especially in those treated with ovarian cystectomy, mortality from cancer remains low. Many patients who desire pregnancy are able to conceive and deliver healthy offspring after conservative surgery. (Obstet Gynecol 2000;95:541–7. © 2000 by The American College of Obstetricians and Gynecologists.)

Borderline ovarian tumors were first described by Taylor in 1929.¹ In 1971, the International Federation of Gynecology and Obstetrics (FIGO) officially recognized borderline tumors as a separate pathologic and clinical entity² and was followed in this by the World Health Organization (WHO) in 1973.³ Borderline tumors comprise 15–20% of all ovarian malignancies.^{4,5}

The majority of borderline tumors are of either the serous or mucinous histologic type. Clinically, borderline tumors behave more indolently than frankly invasive ovarian cancers. Patients with borderline tumors are characterized by a younger age at diagnosis, an earlier stage at presentation, longer survival, and late recurrences.^{6–11} For patients with stage I borderline tumors, surgery alone is curative in approximately 90% of cases of mucinous tumors^{12,13} and in almost 100% of cases of serous tumors.¹⁴ On the other hand, for patients with advanced stage borderline tumors, postoperative treatment remains controversial.^{9–11,15}

Borderline tumors are indolent, and a high proportion occur in young women; therefore, conservative surgery with retention of reproductive potential assumes great importance. Although conservative, fertility-sparing surgery has been practiced for several years, relatively little information exists regarding the outcome. Our study identified young women with borderline ovarian tumors treated with conservative surgery at our institution and examined their subsequent outcomes.

Materials and Methods

Five hundred eighteen patients with a diagnosis of borderline ovarian tumor who were seen at the University of Texas M.D. Anderson Cancer Center from 1956 to 1996 were identified using the databases of the institution and of the departments of Gynecologic On-

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Table 1. Primary Surgical Procedure by Stage in 43 Patients With Borderline Ovarian Tumors

Procedure	FIGO stage						Total
	IA	IB	IC	IIIA	IIIB	Unstaged	
Ovarian cystectomy							
Unilateral	0	0	1	0	0	4	5
Bilateral	0	0	0	0	0	2	2
Plus C/L ovarian biopsy	0	0	1	0	0	0	1
Unilateral oophorectomy							
Alone	7	0	2	1	0	13	23
Plus C/L ovarian cystectomy	0	1	0	0	1	2	4
Plus C/L ovarian biopsy	2	0	1	1	0	4	8
Total	9	1	5	2	1	25	43

FIGO = International Federation of Gynecology and Obstetrics; C/L = contralateral.

cology and Pathology. Upon review of the medical records, those who met the following criteria were included in this study: pathologically confirmed borderline ovarian tumor, no history of sterilization before diagnosis, no prior history of pelvic or abdominal radiation therapy either pre- or postoperatively, younger than age 45, and primary treatment consisting of conservative surgery with or without postoperative chemotherapy. For the purpose of this study, conservative surgery was defined as any surgery that preserved the uterus and one or both ovaries. Forty-three such patients were identified and constituted the study population.

Histologic typing and grading of the primary lesion in all 43 cases were performed by one of the authors (EGS). The histopathologic criteria outlined in the WHO classification of ovarian tumors were used for the diagnosis of borderline ovarian tumors.³ These tumors were staged according to FIGO criteria.¹⁶

Detailed information regarding patient characteristics, treatment, and follow-up was abstracted from the medical record. In addition, all patients signed an informed consent and were sent an Institutional Review Board–approved questionnaire regarding the psychological impact of the disease and treatment and their reproductive performance. Those who failed to return their questionnaires were contacted by telephone.

Descriptive statistics were calculated using the Statview 4.5 program (Abacus Concepts, Berkeley, CA). Differences in variables were tested using the Fisher exact test.

Results

We identified 43 patients with borderline ovarian tumors who met the eligibility criteria for the study. At diagnosis, their median age was 25 years, with a range of 15 to 39 years. Their median gravidity was 0, with a range of 0–5, and their median parity was 0, with a

range of 0–3. Thirty-two patients were white, seven were Hispanic, and four were black. Six patients had a prior history of infertility, and five had prior pelvic surgery (one diagnostic laparoscopy and four cesarean deliveries).

Thirty-two patients had their primary surgery at outside hospitals before referral, and 11 underwent primary surgery at M.D. Anderson Cancer Center. The types of primary surgical procedures by stage are shown in Table 1. As noted, all patients underwent conservative surgery, with 35 patients (81%) undergoing unilateral oophorectomy with or without other procedures and eight patients (19%) undergoing ovarian cystectomy with or without other procedures. Fifteen patients had stage I disease, three had stage III, and 25 patients had incomplete surgical staging (all had their primary surgery at an outside hospital).

All 43 patients had either serous or mucinous borderline tumors of the ovary. Table 2 shows the stage distribution by histologic subtype. Twenty-five patients had insufficient surgicopathologic information to assign a stage. Thirteen of 17 patients (76%) with mucinous histology were inadequately staged compared with 12 of 26 (46%) with serous histology ($P = .06$). Nine of 11 patients (82%) were completely staged, compared with nine of 32 patients (28%) who underwent primary surgery at an outside institution ($P < .01$). Of the 25 incompletely staged patients, 18 appeared to have dis-

Table 2. Histologic Type by Stage in 43 Patients With Borderline Ovarian Tumors

Stage	Histologic type	
	Serous	Mucinous
I	11	4
II	0	0
III	3	0
Unstaged	12	13
Total	26	17

Table 3. Fourteen Patients With Borderline Ovarian Tumors Who Developed New Primary Lesion or Recurrence

Pt	FIGO stage	Histology	Procedure	Interval (mo)	Site	Status
1	Unknown	Serous	B/L cystectomy	5.0	Ipsilateral	NED
2	Unknown	Serous	B/L cystectomy	39.1	Ipsilateral	NED
3	Unknown	Mucinous	Cystectomy & C/L oophorectomy	3.4	Ipsilateral	NED
4	IIIA	Serous	Oophorectomy	14.6	Contralateral	NED
5	Unknown	Mucinous	Oophorectomy	109.4	Contralateral	NED
6	IA	Serous	Oophorectomy	39.6	Contralateral	NED
7	Unknown	Serous	Oophorectomy	24.4	Contralateral	NED
8	Unknown	Serous	Oophorectomy	42.3	Contralateral	NED
9	Unknown	Mucinous	Cystectomy	17.3	Contralateral	AWD
10	Unknown	Serous	Cystectomy	102.3	Lung	AWD
11	Unknown	Serous	Oophorectomy	138.8	Contralateral	AWD
12	IIIB	Serous	Cystectomy & C/L oophorectomy	58.4	Ipsilateral	AWD
13	IC	Serous	Oophorectomy	4.8	Upper abdomen	DID
14	Unknown	Serous	Cystectomy & C/L oophorectomy	147.3	Ipsilateral	DOD

Pt = patient; B/L = bilateral; NED = no evidence of disease; AWD = alive with disease; DID = dead of intercurrent disease; DOD = dead of disease; all other abbreviations as in Table 1.

ease confined to the ovary(ies) as indicated by operative descriptions; however, lack of omental, peritoneal, and nodal biopsies precluded complete staging.

Four of the 43 patients (9%) received 27 cycles of postoperative chemotherapy. The mean number of chemotherapy cycles was 6.8, with a range of 3–12 cycles. Two of these patients had stage IC disease, and two had stage III. Seven patients (16%) received salvage chemotherapy after disease recurrence; three of these patients were disease-free at last follow-up, two were alive with disease, one died of disease, and one died of intercurrent disease.

Nineteen of the 43 patients (44%) underwent 22 secondary operations for pelvic abnormality or suspected recurrence. These surgical procedures included hysterectomy and salpingo-oophorectomy in 11 instances, salpingo-oophorectomy in four, ovarian cystectomy in three, exploratory laparotomy in two, and diagnostic laparoscopy in one. Five of the eight patients previously treated with ovarian cystectomy (63%) required additional surgery, and 14 of 35 initially treated with oophorectomy (40%) required additional surgery. The median time to reoperation was 31.7 months, with a range of 3–147 months. In addition, five patients underwent six subsequent operations for other indications—second-look surgery in two patients, diagnostic laparoscopy for infertility in two patients, and two laparotomies for ectopic pregnancies in one patient.

Median follow-up time was 5.7 years, with a range of 1.4–25 years. Fourteen patients (33%) developed a new primary borderline tumor or recurrence; in 12 of these patients, the new lesion was local (in the ipsilateral or contralateral ovary), and in two it was distant. None of the 11 patients who underwent primary surgery at our institution developed new or recurrent disease, whereas 14 of 32 patients (44%) who underwent surgery

elsewhere did ($P < .008$). This difference most likely reflects the presence of more extensive disease than was initially appreciated at the initial operation. Median time to new primary lesion/recurrence was 39.3 months, with a range of 3–147 months. The details of these new lesions are presented in Table 3.

Seven of 31 patients treated with unilateral oophorectomy (23%) had a recurrence—six in the contralateral ovary and one in the upper abdomen. Seven of the 12 patients treated with ovarian cystectomy (including three of four who also had contralateral oophorectomy) (58%) had a recurrence. This difference was statistically significant ($P < .04$). When only stage I patients were considered, there was no statistically significant difference in the rate of recurrence between those treated with ovarian cystectomy (unilateral, bilateral, or unilateral plus contralateral oophorectomy) (zero of three) and those treated with oophorectomy (two of 12). In unstaged patients, six of eight (75%) who underwent cystectomy developed a new primary lesion compared with four of 17 (24%) who underwent oophorectomy ($P < .03$).

Fourteen ovaries were treated with ovarian cystectomy; five (36%) of these ovaries developed a recurrent or new primary lesion. No occult disease was detected in the nine patients in this study who underwent wedge biopsy of a normal-appearing contralateral ovary. However, one patient with stage IIIA disease who underwent wedge biopsy subsequently developed a 6-cm recurrent borderline tumor in the same ovary, and a small upper abdominal tumor 14 months later.

Forty-one of the 43 patients completed the questionnaire; of the two who did not, one had died of recurrent borderline tumor, and the other had died of an unrelated cause. Thirty-six of the 41 surviving patients (88%) provided menstrual histories. Twenty-nine of the 36

Table 4. Pregnancy Outcome in 12 Women Who Conceived Following Treatment of Borderline Ovarian Tumor

Pt	FIGO stage	Histology	Procedure	Pregnancy event	Interval from diagnosis (mo)	Status
1	Unstaged	Serous	B/L cystectomy	Term SVD	33	NED
				Term SVD	65	
2	Unstaged	Serous	B/L cystectomy	Ectopic	10	NED
				Ectopic	16	
				Ectopic	23	
				Term SVD	39	
				SAB	72	
3	IIIB	Serous	Cystectomy + C/L oophorectomy	Ongoing	86	AWD
				Term CD	59	
4	Unstaged	Serous	Cystectomy + C/L oophorectomy	Term SVD	60	DOD
5	IB	Serous	Cystectomy + C/L oophorectomy	SAB	15	NED
6	Unstaged	Mucinous	Oophorectomy	Term SVD	15	NED
7	IA	Serous	Oophorectomy	Term SVD	11	NED
8	Unstaged	Mucinous	Oophorectomy	Term SVD	57	NED
9	Unstaged	Serous	Oophorectomy	SAB	11	NED
				Ongoing	22	
10	IC	Serous	Oophorectomy	Term SVD	63	NED
				Term SVD	90	
11	Unstaged	Mucinous	Oophorectomy	Term SVD	30	NED
				Term SVD	54	
				Term SVD	78	
12	Unstaged	Mucinous	Oophorectomy	Term CD	10	NED
				Term SVD	23	
				Term SVD	55	
				SAB	72	

SVD = spontaneous vaginal delivery; SAB = spontaneous abortion; CD = cesarean delivery; all other abbreviations as in Tables 1 and 3.

women (81%) were experiencing regular menstrual cycles. Seven were having irregular cycles (three with hypermenorrhea and four with oligomenorrhea or amenorrhea); four of the seven had had oligomenorrhea before diagnosis of borderline ovarian tumor.

Of 41 surviving patients, 24 (59%) attempted pregnancy during the follow-up period. The remaining 17 patients either did not desire pregnancy or were not sexually active over that period. Twelve of the 24 patients attempting pregnancy (50%) conceived 25 times. Pregnancy outcomes included 16 viable births from ten women, four spontaneous abortions, three ectopic pregnancies, and two ongoing pregnancies in the second trimester at the time of last follow-up. No fetal abnormalities in the offspring of these women have been reported. The details of the 12 women who conceived are presented in Table 4.

Of the 43 patients in this study, 14 (33%) reported or experienced infertility. Infertility was defined as 1 year or more of unprotected coitus without conception in a woman attempting pregnancy. Five patients reported infertility before diagnosis of borderline ovarian tumor, and nine reported infertility after treatment for borderline ovarian tumor. Eight of the 14 patients underwent formal infertility evaluations; four received ovulation induction agents, and two underwent in vitro fertilization. Twelve of the 14 patients with a history of infer-

tility attempted pregnancy after treatment for borderline ovarian tumor; four (33%) conceived 11 times after treatment—three gestations followed in vitro fertilization, one followed administration of ovulation induction agents, and the remaining seven were spontaneous.

Patients were asked in the questionnaire whether having a remaining uterus and one or both ovaries caused anxiety about possible disease recurrence. Each patient was provided multiple choices to describe her anxiety level. Twenty-three of the 29 patients who did not have a recurrence (79%) reported having no or very little anxiety, whereas the other six reported frequently worrying about recurrence. Three of those six have consulted a physician regarding their anxiety; however, none has requested additional surgery. When asked to rate their levels of anxiety on a scale of 0 to 10 (with 0 representing no anxiety and 10 representing the most severe), all 29 patients who had not had a recurrence rated theirs between 0 and 4, with a median of 1.

Thirty-seven of the 41 surviving patients (90%) indicated that they would have chosen the same conservative treatment that they received. Two patients who remained without disease recurrence and who experienced infertility indicated that they would have preferred an even more conservative approach that preserved both ovaries. Two patients who developed recurrent tumor stated that they would have preferred

abdominal hysterectomy and bilateral salpingo-oophorectomy at their initial surgery; one of these two is alive with disease, and the other is disease-free but required subsequent hysterectomy.

Discussion

Borderline ovarian tumors are frequently diagnosed in women of reproductive age. Approximately half of such diagnoses are made in women younger than age 40.¹⁷⁻¹⁹ The youth of our patients is consistent with that in other series of conservatively managed patients.^{20,21} Because the prognosis for patients with borderline ovarian tumors is excellent, particularly in patients with the most common stage—stage I—there has been a trend over the past several years toward fertility-sparing surgery in women of reproductive age who have not completed childbearing. However, the efficacy of conservative surgical management and its reproductive and psychologic sequelae have not been conclusively established.^{11,20,22-25} The few studies that have specifically examined fertility-sparing surgery have reported acceptable disease outcomes and sporadic post-treatment pregnancies.^{11,14,17,21}

Although some series have reported no local persistent or recurrent tumor after conservative surgery, most indicate that the rates of local recurrence after such surgery are higher than after hysterectomy and bilateral adnexectomy.^{14,17-20,24-26} Nevertheless, death attributable to disease appears to be equally rare in both patient groups.^{17,21,24-26} Therefore, conservative surgical management of women with borderline ovarian tumors who wish to preserve fertility is a common and acceptable practice.

The rate of recurrence or new primary lesion in our series (33%) exceeds the rates in other published reports of conservatively managed patients (0-17%).^{14,17,19-26} However, most of these other series exclusively or predominantly included patients with stage I disease and reported no deaths attributable to disease among conservatively treated patients. Of the 28 patients in our study with stage III or unstaged disease, 12 (43%) had persistent or recurrent disease. If only stage I patients are considered, our recurrence rate of 13% is similar to the recurrence rates of 15% and 17% in the studies of Tazelaar et al²⁰ and Lim-Tan et al,²¹ respectively.

The risk of recurrence and survival probability for patients with borderline ovarian tumors is directly related to stage. For patients with mucinous borderline tumors, the finding of extraovarian disease is quite unusual. Relapse is rare for patients with stage I mucinous borderline tumors, and the 5-year survival rate is 95% or better.^{12,18,27} For patients with stage I serous borderline tumors, the relapse rate is 1% or less, and the

5-year survival rate approaches 100%.¹⁴ However, patients with stages II-IV serous borderline tumors have a quite different outcome. For women with serous borderline tumors with noninvasive peritoneal implants, relapse rates range from 8% to 33%, with a mean of 20%; death rates range from 0% to 17%, with a mean of 7% in reported series.²⁸ For patients with invasive peritoneal implants, relapse rates range from 0% to 83%, with a mean of 39%; death rates range from 0% to 67%, with a mean of 28% in reported series.²⁹

Unfortunately, incomplete surgical staging remains a problem that compromises decision-making in caring for women with borderline ovarian tumors. In our series, 25 of the 43 patients (58%) had incomplete surgical staging; all incompletely staged patients underwent their primary surgery at an outside hospital, and all recurrences were observed in this cohort. In a recent study of 255 cases of serous borderline ovarian tumors referred to our institution for pathology consultation during the 1990s, 66% had at least one staging biopsy performed, and only 12% had comprehensive surgical staging, as defined by having biopsy samples taken from pelvic and abdominal peritoneum, omentum, and retroperitoneal lymph nodes.³⁰ General surgeons performed complete staging in 0% of patients, obstetrician-gynecologists in 9%, and gynecologic oncologists in 50%.

Although the benefits of postoperative therapy for patients with stages II-IV serous borderline tumors are inconclusive, comprehensive surgical staging will provide the patient and her family with realistic prognostic information.²⁸⁻³⁰ On the other hand, because the overall prognosis for women with borderline ovarian tumors is excellent, the probability of having stage I disease is approximately 60%, and the use of postoperative treatment is controversial, one cannot too strongly advise reoperation and surgical staging for a woman who has been referred after incomplete staging of a borderline ovarian tumor. Our current practice is to discuss options for further management, including observation and reoperation with surgical staging, and to allow the patient to arrive at an informed decision based on the risks and benefits of each option. The key to improving the current status is to heighten awareness among obstetrician-gynecologists and the public regarding the potential benefits of comprehensive surgical staging of borderline ovarian tumors.

The decision for or against conservative surgery in a young patient with an adnexal mass is based on several characteristics. If the ovarian mass is unilateral, judged to be benign, and adjacent to normal ovarian tissue, ovarian cystectomy may be preferable. Before resection, the ovarian capsule should be inspected for any evidence of rupture, adherence, or excrescences. If no

normal adjacent tissue is evident, oophorectomy or salpingo-oophorectomy is appropriate. The specimen should then be sent for frozen-section examination and the contralateral normal-appearing ovary should be carefully inspected. Although some would recommend routine biopsy of a normal-appearing contralateral ovary, leaving it undisturbed is preferable because unnecessary biopsy or wedge resection may result in peritoneal adhesions or ovarian failure. Our findings of no evidence of occult tumor on wedge biopsies of nine normal-appearing contralateral ovaries support this treatment strategy. If the frozen-section examination indicates a borderline or invasive malignancy, then comprehensive surgical staging is recommended for treatment planning and prognostic purposes, as discussed extensively in one of our prior reports.³⁰

If bilateral adnexal masses are present in a young patient desirous of preserving fertility, intraoperative decision making is more difficult. Before any resection, the ovarian masses should be carefully inspected and assessed for adjacent normal ovarian tissue. In general, the more suspicious ovary should be removed using the most conservative means (ovarian cystectomy, if possible) and the specimen sent for frozen-section analysis. If a borderline tumor is diagnosed, then either ovarian cystectomy or oophorectomy should be performed on the contralateral side. In addition, surgical staging biopsies should be performed in this setting. Whenever possible, treatment options for each possible operative finding—benign ovarian tumor, borderline ovarian tumor, or invasive ovarian tumor—should be discussed thoroughly with the patient and her family, including the advantages and disadvantages of each treatment approach.

Even for patients with stage II, III, or IV borderline ovarian tumors who have not completed childbearing, conservative surgery may be indicated. Treatment of the ovaries should be considered separately from treatment of extraovarian disease. Metastatic disease in borderline ovarian tumors is usually of small macroscopic volume or microscopic, and, most commonly, all gross disease can be totally resected.^{28,29} Furthermore, as discussed above, even with peritoneal implants, the prognosis is quite good. Although the incidence of bilateral ovarian involvement is higher with higher stage disease, at least a portion of normal ovary can be left intact in many young patients.

The posttreatment reproductive performance of women who have undergone conservative surgery for borderline ovarian tumors has not been adequately studied. The issue of fertility is particularly germane because there appears to be a relationship between infertility and epithelial ovarian malignancies.³¹ A survey of the literature reveals that 36 patients have

conceived after conservative surgery for borderline ovarian tumors.^{14,17–19,21,32} Our study adds another 12 patients to that number. Lim-Tan et al²¹ reported that eight of 16 patients with stage I tumors who underwent conservative surgery subsequently conceived. Gotlieb et al¹⁷ described 15 patients treated with conservative surgery (12 with stage I disease, one with stage II, and two with stage III) who delivered 19 healthy children, with three ongoing pregnancies at the time of last follow-up.

In addition to fertility, other long-term effects of conservative surgery for borderline ovarian tumors that are of interest include quality-of-life issues. The psychologic impact of less aggressive surgery with associated anxiety over potential disease recurrence has not been studied previously. In response to our questionnaire, 79% of patients who did not have a recurrence reported having little or no anxiety, and 90% of surviving patients stated that they would choose the same conservative treatment again. Although the combined interview and questionnaire were not designed to be an exhaustive psychologic assessment tool, these data suggest that less aggressive surgical therapy and the fear of recurrence are not problems for most patients once they are treated.

Finally, should women who have undergone conservative surgery for borderline ovarian tumors consider resection of the uterus and residual ovary(ies) after completion of childbearing? There is no scientific basis for such a recommendation, and no standard practice exists. In fact, it is difficult to make a compelling argument for this practice. For women with either stage I or more extensive disease, there is no known benefit for subsequent resection for those who have undergone comprehensive surgical staging and complete resection of all gross disease. On the other hand, for women who did not have comprehensive surgical staging at the primary surgery, one could theorize that further surgery might provide the potential for both prognostic and therapeutic benefits. At present, the ultimate decision regarding such a practice should rest with the patient after a careful discussion of the risk–benefit ratio with her physician.

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