

Conservative surgery for borderline ovarian tumors – emphasis on fertility preservation. A review

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Rezumat

Chirurgia conservatoare pentru tumori ovariene borderline - impactul asupra păstrării fertilității. Trecere în revistă

Istoric: Tumorile Ovariene Borderline (TOB) reprezintă 15-20% din totalul tumorilor epiteliale ovariene. Au fost descrise din 1929, dar cunoștințele despre evoluția lor și privind patologia lor moleculară au avansat semnificativ în ultimele 2 decenii. Astfel a fost permisă reducerea amplitudinii tratamentului chirurgical al acestor tumori.

Metoda: Am studiat literatura dedicată atitudinii chirurgicale față de TOB, accentuând aspectele cele mai importante ale prezentării consacrate comparației terapiilor radicale cu cele conservatoare în ideea păstrării fertilității.

Rezultate: Deși există raportări contradictorii privind unele dintre aspectele tratamentului chirurgical al acestor tumori, întrucât TOB afectează femeile în perioada lor reproductivă punând în discuție planurile lor familiale, ele au un prognostic global excelent și sunt depistate în mare majoritate (50 până la

85%) în stadiul I, chirurgia conservatoare (anexectomie sau chiar chistectomie) poate fi indicată în condiții de siguranță după stadializarea intraoperatorie exactă, în scopul menținerii fertilității. Este prezentat cazul unei paciente de 26 ani cu tumori ovariene borderline bilaterale.

Concluzie: Chirurgia conservatoare a TOB la paciente tinere se dovedește a fi sigură, cu condiția unei urmăriri atente.

Cuvinte cheie: tumori ovariene borderline, tratament conservator, fertilitate, recurență, supraviețuire

Abstract

Background: Borderline ovarian tumors account for 15-20% of all ovarian epithelial tumors. Since their original description in 1929, our knowledge of their natural history and molecular pathology has advanced most dramatically over the last two decades. This improved knowledge of BOT has permitted to drastically decrease the therapeutics of these tumors, which remains mostly surgical.

Method: We studied the available literature on surgical management of BOT accentuating the most important aspects on this topic: radical vs. conservative treatment, fertility preservation.

Results: Although there are conflicting reports about some of the aspects of surgical management of these tumors, since BOTs commonly affect women of reproductive age, who have not completed childbearing, have an excellent overall prognosis and the majority of them (approximately 50% to 85%) are stage I at diagnosis, conservative surgery (unilateral salpingo-

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oophorectomy or cystectomy) can be safely performed after comprehensive surgical staging, in order to preserve fertility.

Conclusion: Conservative surgery could be safely performed in young patients treated for BOT, provided that they are carefully followed-up.

Key words: borderline ovarian tumors, conservative treatment, fertility, recurrence, survival

Introduction

Epithelial ovarian tumors with histopathologic features and biologic behavior intermediate between clearly benign and frankly malignant have been identified as a separate group since 1929 (1). In 1973 this group of tumors was accepted by the World Health Organization (WHO) as borderline tumors (2). It is questionable whether a small fraction of these tumors are truly malignant, with the ability to invade and set metastases, while the majority are benign tumors (3).

They affect a younger group of women than do malignant epithelial ovarian tumors, frequently during reproductive age who want to preserve their childbearing potential. Concerning the risk factors of developing a borderline ovarian tumor, it seems that women with a history of infertility and who are nulliparous have an increased risk, while pregnancies, breast-feeding, and use of oral contraceptives have a protective effect. Hypotheses concerning incessant ovulation and ovulatory age have been proposed (4,5). An endocrine disorder may be the basic cause of borderline tumors (6) and it is also unknown whether some women have a genetic predisposition to the disease.

The imagistic and intraoperative findings are often strongly suggesting an ovarian cancer (Fig. 1-4).

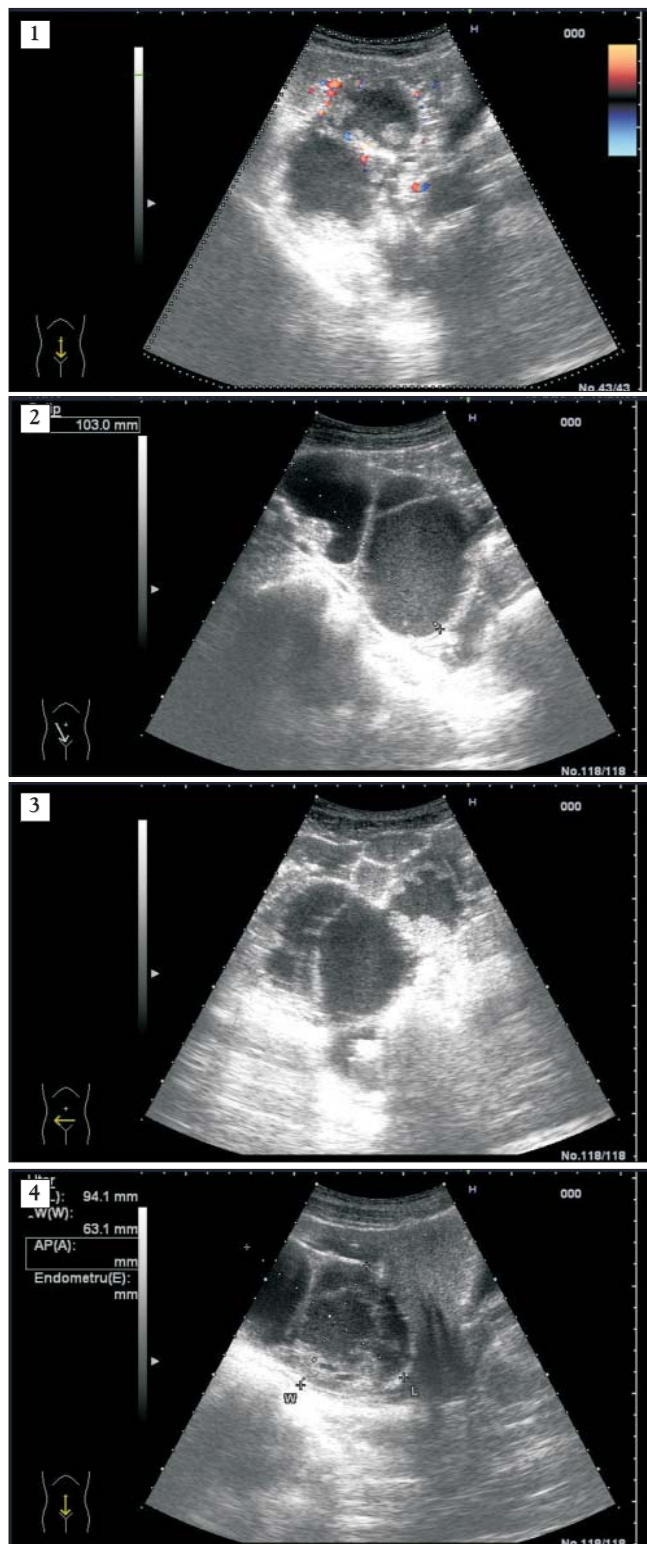
Borderline ovarian tumors are staged using the FIGO criteria, developed and applied to invasive ovarian carcinomas.

Most borderline ovarian tumors present as Stage I lesions (50% to 80%) and stage III lesions occur in 8% to 35% of cases (7, 8).

Although the prognosis of BOT is excellent, late recurrence (after 5 or 10 years) has been observed (9, 10). A review of 1001 cases by Massad et al. showed recurrence or persistence in patients with stage I disease as 2.1%, 7.1% in stage II and 14.4% in stage III/IV (8).

Stage for stage, patients with borderline tumors have better survival rates than their counterparts with frank cancer. Survival for Stage I tumors is excellent, with a 15-year survival of 99% (10). In Stage III, however, the 15-year reported mortality rate varies from 0% to 50%. The survival rate seems to be related only to extra-ovarian spread, not to bilaterality (11, 12). Extra-ovarian spread and peritoneal implants at the time of diagnosis have been reported in about 35% of the cases (9).

For over 50 years, BOTs was considered in the natural history of ovarian cancer as a premalignant disease. The treatment of this tumor, as in malignant ovarian diseases,



Figures 1-4. Ultrasonographic features of bilateral borderline ovarian tumors mimicking ovarian carcinoma (large irregular cysts with thick wall, cauly-flower endoluminal proliferations, septa, hypervascularity)

was based on radical surgery (hysterectomy with bilateral salpingo- oophorectomy) to reduce the risk of recurrence in the form of invasive carcinoma. But over these last two

decades, as the prognosis of BOT is excellent (99% of long-term in stage I disease) (2), this dogma has been abandoned and several teams chose a more conservative surgery in order to favor subsequent fertility of young patients treated for BOTs.

Histologic subtypes

The histologic diagnosis of borderline tumors is based on the following criteria: 1. an unusual degree of epithelial cellular proliferation (stratification of the epithelial lining of the papillae, multi-layering of the epithelium, mitotic activity, and nuclear atypia) (3). (Fig. 5 and 6); 2. absence of destructive invasion of the stromal component of the neoplasm (13).

The most common hystotypes are the serous (60%) followed by the mucinous (35%) (endometrioid 1%, clear cell < 1, other 5%) (8).

Serous borderline tumors are unilateral in 50% of cases and bilateral in 41% (range, 28% to 66%) (3). Information about the frequency of microscopic or macroscopic bilaterality disease is currently lacking. There is a frequent extraovarian diffusion (35%) in the form of peritoneal implants (40% benign, 35% non-invasive, 25% invasive) (7,14). Reports suggest that mucinous tumors have 8% rate of bilaterality (range, 0% to 13%) (3,15) and can reveal all grades of malignity from the benign to the invasive in just one tumor (14,16). These are characterized by a frequent extraovarian diffusion (10%) in the form of pseudomixoma peritonei (8).

Peritoneal implants

According to their cytohistologic characteristics, peritoneal “implants” are classified into benign implants (simple tubular structures, covered by tube-like epithelium), non-invasive implants (papillary structure, characteristics analogous with ovarian borderline tumor), invasive implants (structure similar to infiltrating adenocarcinoma, well differentiated) (8).

Peritoneal implants and extra-ovarian spread at the time of diagnosis have been reported in about 35% of the serous tumors. Some controversy remains about these implants. Are they true implantation metastases or manifestations of multifocal in situ lesions of the peritoneum? Both conditions seem to occur, but according to the literature the latter occur most frequently (11,12). Some of these implants will progress to infiltrating cancer, while the majority will remain either stationary or regress after removal of the main ovarian tumor. Examination of the nuclear DNA content of the implant and the ovarian tumor might contribute to the differential diagnosis between metastatic lesions and in situ lesions.

Lymph node involmment

Spread to lymph nodes is not uncommon in patients with borderline ovarian tumors. In one study of 171 patients with borderline ovarian tumors, the incidence of retroperitoneal, pelvic and para-aortic lymph node positivity was 21%, 17% and 18%, respectively. However the nodal status did not

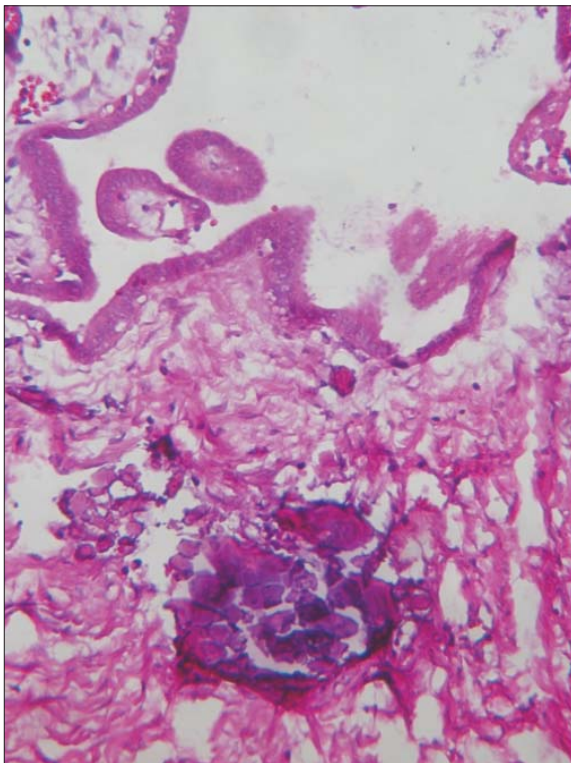


Figure 5. Calcifications/psamoma body HE, 40X

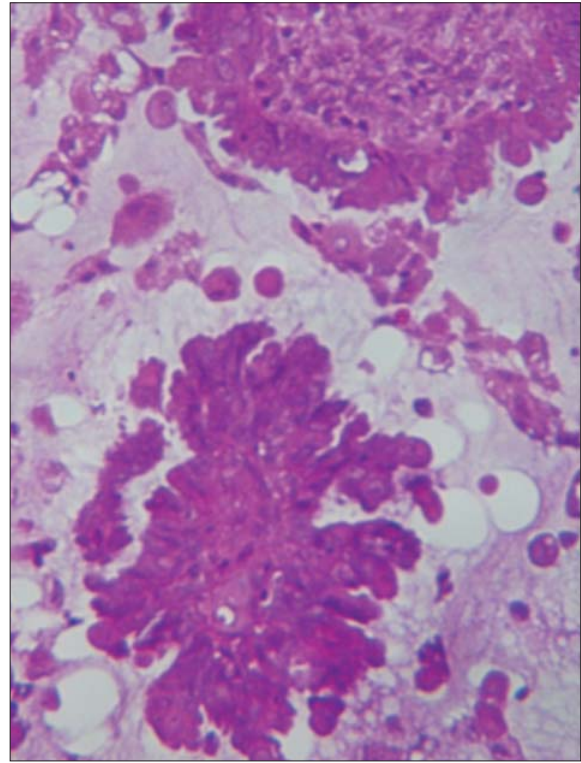


Figure 6. Cell groups detached from papillae HE, 40X

seem to affect survival (8).

According to the sum of the evidence from the studies, lymph node involvement does not appear to worsen the prognosis (17,18).

Microinvasion of the stroma

The authors, who have studied serous borderline ovarian tumors (19) with evidence of microinvasion of the stroma (microinvasion was defined as foci less than 0.3 cm in diameter with infiltration into the stroma as single cells, nests of cells or papillae), demonstrated that the presence of microinvasion was associated with a similar prognosis to common serous borderline ovarian tumors. Of note, this type of stromal microinvasion is not associated with significant stromal edema, desmoplasia or cellular response typically seen in early invasion by carcinoma.

Basic principles of treatment

The basic and in the most cases the exclusive treatment for borderline tumors is surgery. Adjuvant treatment in borderline tumors is questionable since the majority of the patients have Stage I disease and a very low risk of recurrence (3, 17). Indications of adjuvant therapy are flow cytometry findings suggesting malignancy, invasive peritoneal implants or nodal spread located near the nodal sinus although no randomized studies have demonstrated the advantage of adjuvant therapy on survival in these rare indications.

The standard primary surgery strategy for borderline ovarian tumors follows the guidelines used for invasive ovarian malignancies and consists of hysterectomy, bilateral salpingo-oophorectomy, omentectomy and careful debulking. However, no studies have demonstrated the interest of the addition of a systematic hysterectomy in borderline tumors.

In addition, it is important to point out that lymph node sampling is not part of the standard surgical treatment for borderline tumors and complete systematic lymphadenectomy should not be systematically performed in early stage disease (20). Some studies support that lymphadenectomy or selective adenectomy should be performed in case of adenomegaly (20, 21).

Frozen section analysis may be useful for discrimination between borderline ovarian tumor-ovarian carcinoma and benign tumor but not for discrimination between borderline ovarian tumor and invasive ovarian carcinoma (3). The accuracy of this exam is lower in BOTs and it depends on several factors: the size of the tumour, the histologic subtype and the experience of the pathologist himself (20,21).

Staging surgery (peritoneal cytology, infracolic omentectomy or large omental biopsies and random peritoneal biopsies, appendectomy, palpation of pelvic and para-aortic node areas) is a crucial point in order to ensure the exact stage of the disease and should be associated with the treatment of the ovarian tumour. Currently, due to the nonspecific clinical, biologic, and imaging features of borderline ovarian tumors and the relatively poor diagnostic accuracy of intra-operative histology, a restaging operation [can be carried out

laparoscopically (9)] sometimes is performed to complete treatment and to determine the disease stage precisely (3, 22). Also a second operation should be performed in case of serous tumors since lymph node involvement has been reported in about 20% of cases with apparent Stage I tumors, and even higher in more advanced stages (3). Restaging surgery should not be discussed if the following criteria are fulfilled (1) if the BOT is of serous or mucinous subtype and without micropapillary patterns (2) peritoneum explored and reported as normal on the surgical report of the initial surgery and (3) the patient agrees with a careful follow-up (20).

The staging surgery upstaged 13–22% of patients with apparent stage I disease, because microscopic implants were discovered on surgical specimens (20,23). Additionally, only 12–29% of patients were adequately staged even in cases where frozen section analysis confirmed the diagnosis of borderline malignancy, in two recent studies. It is worthy of note that recent studies demonstrate that, even if such staging procedures are beneficial (microscopic implants were discovered whereas macroscopic exploration was normal), these procedures have no impact on the patients' survival (3,24).

Conservative surgery

In accordance with the International Federation of Gynecology and Obstetrics classification (FIGO), approximately 50 to 85% of borderline tumors have stage I disease (Fig. 7 and 8). This is the reason that, recently, some reports recommended a conservative approach for patients with early-stage disease (8) (Fig. 9 and 10). Moreover, although standard treatment for all the patients includes at least bilateral salpingo-oophorectomy, recent studies have shown that the preservation of reproductive organs is feasible (25). Many young patients, who have not completed childbearing, can be safely treated with unilateral salpingo-oophorectomy or cystectomy after comprehensive surgical staging, thereby preserving fertility.

Conservative surgery - Cystectomy

In the case of cystectomy it is recommended that a complete pathological analysis of the margins should be carried out in order to rule out any microscopic invasion, although pathological interpretation of section margins in case of cystectomy is very difficult, especially if morcellation or fractionation of the tumor occurs during surgery (9,26).

The presence of persistent or recurrent disease is correlated with multifocality and involvement of resection margins. The authors who have studied the possibility of relapse after cystectomy have reported conflicting data. Some of them demonstrated that no recurrence of disease was seen in ovaries from which a single cyst had been removed with negative resection margins. In contrast in other studies, even though a completed excision at the time of microscopic examination had been performed, there was a rate of recurrence about 39% (20). This high rate of recurrences after cystectomy is the marker of frequent multifocal

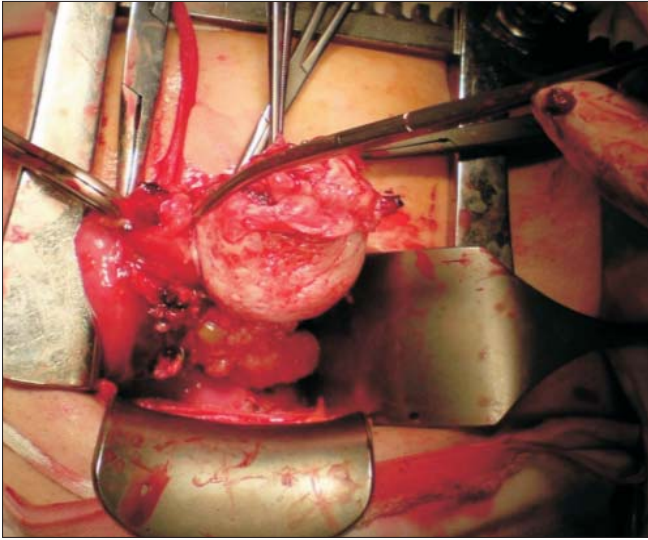


Figure 7. Intraoperative aspect of BOT

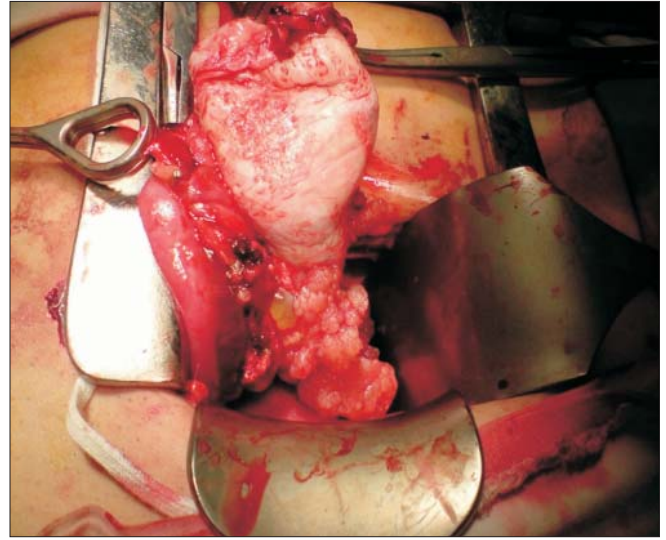


Figure 8. Macroscopic details of previous BOT

lesion in the same ovary, particularly in patients with serous BOTs. Subsequently, multifocality may be a strong predictor of the failure of cystectomy to control the disease.

Another point of debate is the performance of salpingo-oophorectomy compared to oophorectomy alone in patients with unilateral tumour. There are no published studies providing preliminary comparison of salpingo-oophorectomy and oophorectomy alone. It seems that in patients with bulky unilateral tumour and with a large development in the mesovarium, salpingo-oophorectomy should be preferred (if the contralateral tube is present and macroscopically normal).

Conservative surgery - Biopsy of contralateral ovary

In order to reduce the rate of relapse in the remaining ovary, some authors suggest the performance of ovarian biopsies in the spared ovary(10). Nevertheless, in nonserous tumors, wedge biopsy of a normally looking contralateral ovary is not necessary and the same procedure is safe in stage IA diploid serous tumors, especially in young women who wish to remain fertile. However, if a serous tumor is found, a wedge biopsy of the contralateral ovary is recommended because of the risk of occult disease in the contralateral ovary. In contrast, other authors demonstrate that this is not a harmless procedure, as it

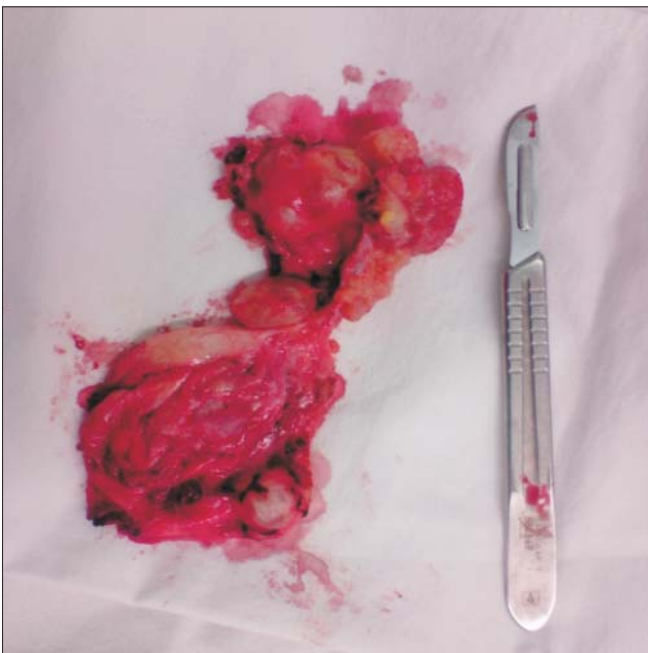


Figure 9. Salpingo-oophorectomy specimen in a BOT



Figure 10. Partial oophorectomy specimen in a BOT

may induce infertility due to postoperative ovarian adhesions. The results of the above studies indicate that macroscopic inspection is sufficient, and biopsies should be performed only when a macroscopically or ultrasonographically suspicious lesion is identified (9). Furthermore, it is worthy of note that the incidence of infertility after this type of procedure is about 10% to 20%. In conclusion, it appears that the low diagnostic rate negates the value of the procedure (3,27).

Conservative surgery - Re-laparotomy

Some authors evaluated the impact of the performance of a re-operation in order to remove the remaining ovary in patients where fertility is no longer an issue and who have conceived after conservative treatment of BOT. It seems that systematic removal of the spared ovary is not mandatory because of the small rate of recurrence and the easy cure of recurrent disease (simple surgical procedure) on condition that patients undergo regular follow-up examinations. However, some patients prefer to undergo oophorectomy after pregnancy, for psychological reasons or because the patient wished to simplify the modality of follow-up procedures. Although there are long-term studies which confirm an extremely low risk of malignant recurrence, there are no studies which have shown a survival benefit of additional "prophylactic" surgery for these women. Oophorectomy is proposed only in case of relapse.

The combination of routine US & markers (CA 125 in serous tumour and 19.9 in mucinous tumour) has been suggested to follow-up patients (the benefits of CA 125 level determination remain doubtful according some authors). Such follow-up should be continued after 5 years, because very late recurrence could be observed.

Conservative surgery - The risk of relapse

The risk of relapse after unilateral salpingo-oophorectomy, which is increased after this type of surgery, is estimated at between 0 and 25% but is less than that after cystectomy (from 12 to 58%) (25,27-28). Some of these recurrences were observed long after treatment of the initial tumour, (72-240 months)(28). It is important to point out that it is more likely that some of these lesions are in fact new primary tumors rather than recurrences of the initial BOT. Subsequently, the high rate of relapse implies that the optimal treatment in patients with intraoperative diagnosis of BOT is unilateral adnexectomy. Cystectomy should be performed only in cases of bilateral tumour (with oophorectomy in the contralateral tumour) and/or in patients with only one ovary (previous history of adnexectomy) and in case of relapse on the remaining ovary. Survival is not affected if the patients are re-operated at recurrence. The corresponding recurrence rate is below 5% for patients with borderline serous tumors, who have received relapse treatment (15,26).

Conservative surgery - Peritoneal implants

Two major series have been published, and each has concluded

that conservative management should be proposed for patients with peritoneal implants, with the proviso that these implants were to be entirely removed, with a reliable pathological interpretation (9). A question is whether it is possible to propose such surgical management in patients with invasive peritoneal implants. Considering the aggressiveness and bad prognosis of BOT with invasive peritoneal implants, it seems logical to propose conservative therapy only to BOT patients with no invasive implants.

Conservative surgery - Limits

There are technical limits and limits concerning the indications of conservative treatment.

In patients with initial bulky bilateral tumor with massive involvement of both ovaries (or the last ovary in patients with previous history of unilateral oophorectomy), preservation of at least a part of one ovary is not feasible because no part of an apparent healthy ovary could be preserved. In such patients, bilateral oophorectomy should be performed but with the preservation of the uterus.

The sum of the evidence from the studies suggests that the use of conservative surgery in patients with invasive peritoneal implants is debatable, and that conservative treatment is not a good indication in patients with mucinous BOTs and peritoneal spread.

Another point of debate is whether conservative surgery is safe for patients with early stage mucinous subtype and whether conservative surgery could be safely proposed to patients with micropapillary patterns. Further clinical studies are required in order to achieve confident conclusions. Controversial also remains the removal of the ovary after child-births (9) and the discussion of this option depends on several factors (histologic subtype, stage, type of conservative surgery, patient's own wish).

Conservative surgery - Pregnancy

The spontaneous fertility rate reported in the literature varies between 32% and 65% after conservative treatment. Recently was published one of the most important series specifically dealing with the pregnancy rate after conservative surgery. The conception rate was 42% in patients aged under 35 compared to 22% in patients aged between 35 and 40. No pregnancies were observed in patients aged >40 and treated conservatively (20).

Conflicting results have been reported about whether ovarian stimulation or IVF should be proposed to patients treated. According to some studies hyperstimulation has been incriminated in the genesis of BOT and ovarian cancer (9). In contrast two recent experimental studies on in vitro cell culture suggest that estradiol or follicle stimulating hormone (FSH) had no deleterious impact on cell proliferation (29, 30). Moreover, one of the studies showed that human chorionic gonadotropin (HCG) reduces the proliferation of cell line (30). These important results seem to suggest that ovarian induction could be used in patients with stage I BOT, without affecting

the patients' prognosis (31) but it is likely that the number of stimulation cycles should be limited, so as not to increase the potential risk of recurrence(20). Literature data concerning the safety of hyperstimulation in patients with peritoneal implants concern series involving only a small number of patients. Therefore guidelines concerning hyperstimulation and IVF in these patients is not yet possible to be given. Also, it should be mentioned that pregnancies have been reported in patients who underwent a bilateral salpingo-oophorectomy (with uterine preservation) for BOT, with an oocyte donor or successful transfer of frozen embryos, obtained before bilateral salpingo-oophorectomy was carried out (a cryo-conservation of ovarian tissue is also possible to be proposed) (32,33).

Conclusions

Conservative surgery could be safely performed in young patients treated for BOT, and then carefully followed-up.

In case of relapse on the remaining ovary under borderline form, another conservative management (cystectomy) may be proposed, in order to preserve fertility.

Even for patients with stage II, III or IV borderline ovarian tumors who have not completed childbearing, conservative surgery may be indicated.

Few published data exist relating to conservative management in BOT with peritoneal implants.

The spontaneous pregnancy rate, after conservative treatment, is nearly 50%.

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