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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/16141
DOI URL: http://dx.doi.org/10.21474/IJAR01/16141

RESEARCH ARTICLE

BORDERLINE OVARIAN TUMORS

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Manuscript Info

Manuscript History
Received: 30 November 2022
Final Accepted: 31 December 2022
Published: January 2023

Key words:
Borderline Ovarian Tumor, Serous Tumor, Mucinous Tumor

Abstract

"Borderline" tumors of the ovary are lesions that have certain abnormalities, particularly microscopic, common with cancers, nevertheless they are not "cancer" in the strict sense of the term. The diagnosis of this pathology requires a good expertise in anatomo-pathology because there are several histological "variants" that can modulate the therapeutic management. They can be located only on one or two ovaries but can also extend to the lymph nodes and/or the peritoneum. These tumors have a very good prognosis overall. The most important prognostic factors are: the stage, the type of peritoneal implants (less good prognosis in case of invasive implants in serous tumors) and the existence of a tumor remnant (in stages II or III). Treatment is primarily surgical. The reference surgery for ovarian tumours (in a patient no longer of childbearing age) is bilateral adnexectomy. However, this surgery must be conservative in a young woman in the case of a stage I or stage II/III tumour but without invasive implants. In case of tumor with peritoneal implants, surgical resection of peritoneal locations is the rule. In macroscopically limited ovarian stages, there is an indication to perform a peritoneal staging (cytology, multiple biopsies and omentectomy) in serous micropapillary forms. Treatment is in the vast majority of cases exclusively surgical (most often conservative in order to preserve future fertility in young patients). Indications for chemotherapy are rare; the only indications for chemotherapy are the presence of invasive peritoneal implants and certain forms of lymph node involvement. Follow-up is done on a regular basis, especially in the case of conservative treatment, and is based on a clinical examination, markers and imaging by abdomino-pelvic ultrasound (in patients who have had conservative treatment). Recurrences are not life-threatening since they usually occur in a borderline mode and therefore have a good prognosis. Surveillance beyond 10 years is required (especially after conservative treatment). This surveillance is then based on clinical examination, marker assay and imaging.

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Introduction:

Borderline tumors of the ovary are an intermediate category between benign and malignant lesions of the ovary. They generally occur in young women and their prognosis is often favorable. The modalities of management remain controversial.

The definition of borderline ovarian tumor is anatomopathologic. It combines the presence of four histological criteria: multi-stratification and epithelial budding, increased mitotic activity, cyto-nuclear atypia and absence of stromal invasion. The long-term prognosis is very good with a risk of late recurrence (more than 20 years) [1].

The incidence of this type of tumor is poorly documented and is estimated at approximately 1.8 to 4.8 per 100,000 women per year [1]. It is considered to represent 10-20% of ovarian tumors [2,3] and the average age of onset is 10 years younger than that of cancers.

Borderline tumors of the ovary are rare tumors and characterized, compared to ovarian adenocarcinomas, by:

- An average age of onset of 10 years lower than that of malignant tumors,
- In 1/3 of cases, occurrence in "young" patients for whom fertility preservation must be considered as an important factor
- A very good overall prognosis
- And the possibility of late recurrence (after 20 years).

Diagnostic strategy

The preoperative diagnosis of borderline ovarian tumours remains difficult and is based essentially on clinical examination, assisted by ultrasound and the determination of serum tumour markers. Very often, these complementary examinations do not allow a distinction to be made between a benign, malignant or borderline ovarian tumour, and the diagnosis will only really be established per- or post-operatively

In any patient presenting with a pelvic mass, pelvic ultrasound is the first-line examination, via the abdominal and/or vaginal route. Currently, few data are available regarding their sonographic characteristics. Darai [17] does not find specific sonographic criteria although the majority of these tumors were multilocular. It is important to remember that both the benign sonographic appearance and the tumor size should not be reassuring and that even thin-walled anechoic unilocular lesions do not formally eliminate a borderline tumor of the ovary.

In the case of complex masses or masses considered as "indeterminate" on ultrasound, pelvic MRI completes the work-up [4], although it is not possible to confirm a preoperative diagnosis.

Relevance of tumor markers: No recommendation can be made regarding the use of tumor markers (CA 125, CA 19-9, CEA, CA 72-4, HE4) or specific scores for the preoperative differential diagnosis between presumed benign ovarian tumors / borderline ovarian tumor / malignant ovarian tumors because of the low level of evidence of the identified works regarding their discriminative value. Nevertheless, in case of suspicion of mucinous borderline ovarian tumor on imaging, CA 19-9 assay may be proposed.

Borderline tumors are tumors with a histological diagnosis. It is extremely difficult to make a diagnosis preoperatively and it will therefore most often be made postoperatively. In case of suspicion of a borderline tumor, it will be necessary to give priority to a 2-step treatment. First of all, diagnosis by carrying out a cystectomy or adnexectomy depending on feasibility, with additional surgical treatment being proposed at a second stage if the borderline nature is confirmed and depending on the staging carried out. Moreover, the sensitivity of the extemporaneous examination in the diagnosis of ovarian tumors with attenuated malignancy is low [5].

There are several types of borderline tumors:

- Serous tumors, the most common and often bilateral, and account for approximately 55% of borderline tumors (Fig. 1). This histological type is more often associated with extra-ovarian locations, since peritoneal implants, invasive or not, are found in an average of 30% of cases, the prognostic value of their invasiveness being controversial. One particular subtype, micropapillary tumors, falls into the category of serous borderline tumors. For some, this type of lesion could be a transitional form between borderline serous tumor and low-grade invasive serous cancer.
- Mucinous tumors, often voluminous but usually unilateral with a high risk of recurrence in the invasive mode, represent about 40% of borderline tumors. These tumors are subdivided into two subtypes: the intestinal or enteroid type (75% of cases), which is often diagnosed early and has a very good prognosis [6]. When the diagnosis is made at a more advanced stage, the mortality rate is much higher, related to an association in 85% of cases with a peritoneal pseudomyxoma, considered as a primary digestive tumor. The second subtype is called endocervical or Mullerian. This group is not associated with peritoneal pseudomyxoma, but may be associated with peritoneal implants or lymph node metastases [7]. Despite this, their prognosis also remains excellent.

- The rarer non-serous, non-mucinous tumors: clear cell tumors, endometrioid tumors and Brenner's tumors occurring at a later age, represent about 5% of borderline tumors of the ovary.

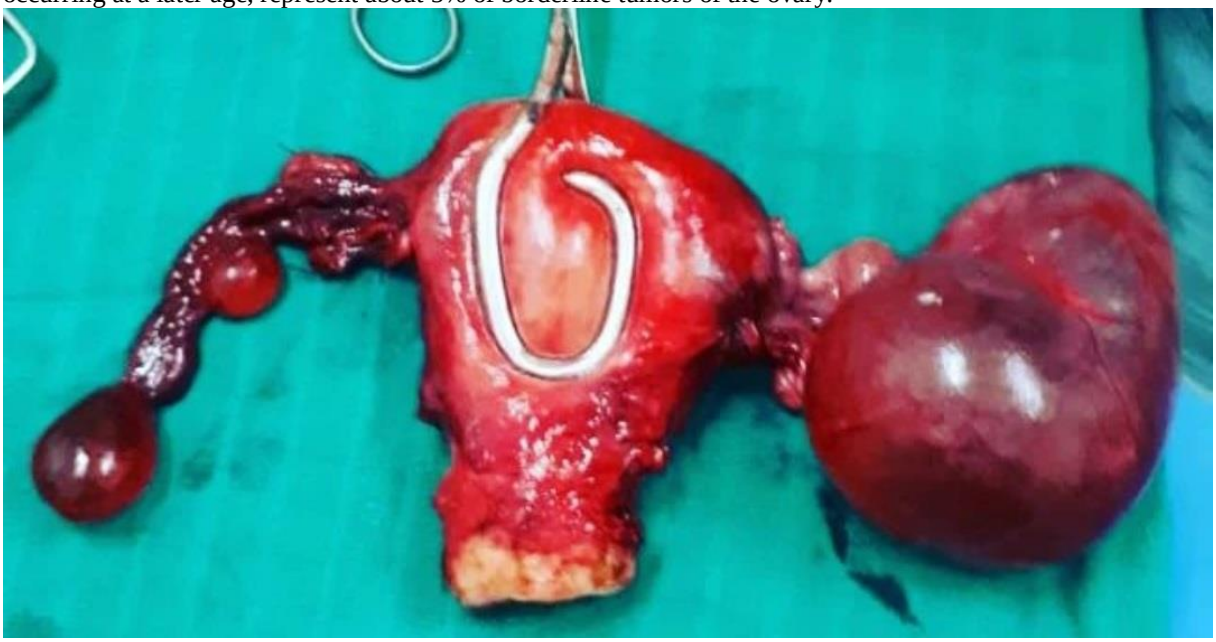

Figure 1: bilateral serous borderline tumor of the ovary

Treatment strategy

The surgical intervention must always start with a precise staging: sampling of peritoneal fluid or lavage fluid, and various biopsy samples, such as vesico-uterine peritoneum, douglas cul-de-sac, parieto-colonic gutter and diaphragmatic dome.

Classification of borderline tumors of the ovary: This staging is performed at the time of the initial surgery

STAGE 1: tumors limited to the ovaries
- **IA**: unilateral intra ovarian tumor, without ascites
- **IIB**: bilateral intra-ovarian tumor, without ascites
- **IC:** single or bilateral tumor with external vegetations and or capsular rupture and or positive peritoneal cytology.

STAGE 2: single or bilateral tumor with pelvic extension
- **IIA:** extension to the uterus and fallopian tubes, without ascites
- **IIB**: extension to other pelvic organs, without ascites
- **IIC:** IIA or IIB with positive peritoneal cytology

STAGE 3: single or bilateral tumor with abdominal or lymph node extension
- **IIIA**: microscopic peritoneal involvement
- **IIIB:** macroscopic peritoneal involvement less than 2 cm
- **IIIC:** macroscopic peritoneal involvement greater than 2 cm and or retroperitoneal lymph node metastasis.

Conservative treatment is questionable in almost all situations of borderline tumours when there is conservable tissue (cystectomy possible) and in the absence of invasive peritoneal implants if the patient has a desire to preserve her fertility. In the Koskas study published in 2010 [8], comparing unilateral adnexectomy versus cystectomy for the management of borderline tumors in patients of childbearing age, the 5-year recurrence-free survival rate was higher in the adnexectomy group (94.7% versus 49.1%, $p < 0.041$). Furthermore, the 5-year pregnancy rate was comparable between the 2 groups (41.8% versus 45.9%, $p = 0.66$). In 2011, Song [9] published a series of patients managed for borderline tumor and compared recurrence rates and fertility in adnexectomy group ($n = 117$) versus cystectomy ($n = 39$). The recurrence rate was lower in the adnexectomy group (5.9% versus 13.2%). Regarding fertility, the delivery rate was similar between the 2 groups (89.2% versus 87.5%). In the meta-analysis by Darai published in 2012 [3], the conclusions drawn are in favor of conservative treatment being possible even in advanced stages as long as uterine preservation is possible. Very recently in 2016, Vancraeynest published a series where the recurrence rate after conservative treatment is higher than with radical treatment but without impact on long-term survival [10].

Today, it is possible to adopt a minimally aggressive and conservative strategy for young patients wishing to become pregnant and presenting a lesion diagnosed at an early stage. In any case, the intervention should start with an accurate staging, followed by a therapeutic procedure.
Adnexectomy should now be considered as the reference treatment for a young patient wishing to become pregnant. Indeed, even if conservative treatment is associated with a higher recurrence rate, it has no influence on the overall survival of patients, even in the presence of invasive implants. Cystectomy, whose recurrence rate varies between 12 and 58% according to the studies [12], should be preferred to adnexectomy in specific situations: in the case of a single ovary or in the case of bilateral tumours, for which adnexectomy is performed on the side with the largest tumour and cystectomy on the side with the least affected ovary.
In the case of extra-ovarian implants, the results of conservative treatment are less well documented. There are two cases: if they are non-invasive, conservative treatment is possible provided that complete surgery is performed to remove the lesions. If the implants are invasive or if there is a peritoneal pseudomyxoma, it does not seem justified to propose conservative treatment, in view of the risk of evolution towards an invasive disease, estimated at 30%: surgery must then be radical and associated with the most complete resection of the peritoneal lesions possible.
For these young patients, the question of secondary totalization surgery is not settled after the fertility period.
For some, it is necessary [11] because it allows a significant reduction in the risk of recurrence, estimated at 15.2% in stage I when the treatment is conservative and 2.5% when it is radical. Hysterectomy would not be of interest, but contralateral adnexectomy would be necessary.
For others [13], it is not necessary if the initial procedure has allowed a complete staging and if the patient is compliant for surveillance. For postmenopausal patients or those who do not wish to become pregnant, a total hysterectomy with bilateral adnexectomyis recommended, even if the literature rarely reports cases of uterine tumor invasion. The results of radical treatment are excellent: in an analysis of 846 cases, the prognosis of stage I is very favorable with an overall recurrence rate of 8.5% [14].

Place and techniques of fertility preservation

Because of the double particularity of borderline tumors compared to ovarian cancers, younger age and better prognosis, prevention of recurrence but also preservation of fertility are major issues in the management. It is currently possible to adopt a conservative attitude with minimally aggressive surgery in young patients who wish to preserve fertility. In these patients, surgical treatment will involve an initial peritoneal staging with cytology, followed by an adapted surgical procedure that is as conservative as possible: cystectomy if possible, unilateral adnexectomy if necessary. This first step will provide histological evidence. In a second phase, restaging surgery will be performed with peritoneal exploration ± resection of peritoneal implants, infra colic omentectomy and ± appendectomy for mucinous contingents. Patients may therefore be offered fertility preservation at both stages of this management: preoperatively when the diagnosis has been suspected, and postoperatively when the diagnosis has been made by histological analysis. In the particular case of borderline tumours, and particularly in the advanced stages, the possibility of uterine conservation must also be taken into consideration. Indications for hysterectomy have become rare in this context. However, the current problem of the prohibition of surrogate motherhood in France raises the question of the interest of conserving ovarian tissue or vitrified oocytes in patients for whom a hysterectomy would be necessary. When conservative (ovarian) treatment is possible, the patient may be offered priority for oocyte or embryo conservation with or without stimulation [15]. The particular subgroup of borderline tumours with a papillary component raises the question of a higher risk of recurrence and the problem of the existence of hormone receptors for estrogens and progesterone [16]. In this sub-group, given the high risk of recurrence and therefore of bilateral oophorectomy, the decision to carry out ovarian stimulation with a view to oocyte vitrification may be considered after cystectomy. There is little experience in this context and a multidisciplinary discussion with the patient must be carried out. In the case of stimulation, it would be interesting to collate the cases in order to carry out an observational study.

Adjuvant therapy:

The role of adjuvant treatment in the management of borderline ovarian tumors remains complex and controversial at present. Its impact on patient survival is difficult to assess, firstly because of the need for a very long follow-up period, and secondly because there are currently no randomized studies comparing adjuvant treatment to simple monitoring after surgery. Today, the chemotherapies proposed for borderline ovarian tumors are the same as those for invasive carcinomas. The indication of adjuvant chemotherapy is currently discussed, even in the case of

invasive implants. In this particular situation, however, it is proposed in the majority of specialized centers and must be discussed on a case-by-case basis.

Therapeutic protocols

For tumors identified during surgery:
- In all cases: complete staging: cytology, peritoneal samples, omentectomy, appendectomy if mucinous form.
- No desire for pregnancy: bilateral adnexectomy, optional hysterectomy
- Desire for pregnancy: unilateral adnexectomy if contralateral adnexa present or cystectomy if single adnexa.

Secondary histological finding:
- Ideal initial surgery: re-staging not systematic
- Non ideal initial surgery (rupture, incomplete samples, cystectomy in a patient who no longer wishes to become pregnant, absence of duly performed peritoneal exploration): re-stadification with possible complementary excisional surgery

Macroscopic per operative doubt:
- Unilateral adnexectomy remains the rule except in the case of a single ovary in a young woman wishing to become pregnant
- Avoid rupture of the tumour and contamination of the trocar tracts
- Extemporaneous examination is useful but has its limits
- The question of staging arises and must be performed

Treatment of recurrences: The treatment of recurrences is essentially the same as for the primary tumor at the same stage:

- In case of homolateral recurrence after conservative treatment: adnexectomy is indicated if the contralateral ovary is present. If the contralateral ovary is absent and there is a desire for fertility, conservative treatment can still be considered, but with reservations.
- In case of contralateral recurrence after conservative treatment: if the patient no longer wishes to become pregnant, radical treatment is indicated. Otherwise, conservative treatment can be applied iteratively.
- In case of peritoneal recurrence: the treatment is surgical, often radical, but sometimes chemotherapeutic (presence of invasive implants).

The prognosis of borderline ovarian tumours is generally favourable, the average recurrence rate varies between 2 and 14% depending on the series. The main prognostic factors are: advanced age, bilaterality, histological type (serous borderline tumors have the most favorable prognosis) and above all the presence of invasive or non-invasive peritoneal implants.

Surveillance methods

Surveillance of treated borderline tumours must continue beyond 5 years, combining a systematic clinical examination and endovaginal or suprapubic ultrasound, particularly in the case of conservative treatment (ovarian parenchyma and uterus). Nevertheless, the data in the literature are insufficient to specify the frequency of these examinations.

Conclusion:

Borderline tumors of the ovary, or "tumors of low malignant potential," are defined by histo-pathologic features intermediate between benign and malignant tumors. They are rare, representing 15 to 20% of epithelial tumors of the ovary, and differ from ovarian cancers in two main ways: first, their average age of onset, which is on average 10 years earlier, and second, their prognosis, which is much better than that of ovarian cancers, with a survival rate, all stages combined, of 95% at 5 years and 90% at 10 years. Consequently, the stakes in the management of this pathology will be, of course, to avoid recurrence, but also to preserve the fertility of patients who are often young and wish to have subsequent pregnancies.

Declarations
Funding: None.
Conflict of interest: The authors declare no competing interest.
Ethical Approval**:** Not required.

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