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Diagnosis and Management of Borderline Ovarian Tumor Based on the Iranian Guidelines

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Abstract

Borderline ovarian tumors (BOT) consist of epithelial ovarian lesions that express cytological features of malignancy, but unlike malignant ovarian tumors, do not show obvious stromal invasion. The tumor incidence is between 1.8 and 4.8 per 100,000 females per year. The two major groups of BOT include serous BOT (S-BOT) and mucinous BOT (M-BOT). S-BOTs are divided into two categories: tumors limited to ovary and tumors spreading outside the ovary. M-BOTs are divided into two categories. The more common type is intestinal that constitutes 85% of cases and the second type is endocervical or Mullerian. Mullerian M-BOTs is bilateral in 40% of cases, while it is accompanied by pelvic endometriosis in 20-30% of patients. Microscopic examination by intraoperative frozen section is necessary because macroscopic view of ovarian tumors alone is not reliable. It is better to perform conservative surgery until the final report is ready in patients who wish to preserve their fertility. It is hard to differentiate them based on clinical characteristics. Values of tumor markers including CA125, CA19-9 and CEA in diagnosis of BOT are confirmed. Standard treatment of BOT is surgery as is the case with invasive epithelial ovarian cancer. In the majority of patients referred for BOT, since there is no suspicion of malignancy, staging is not performed. In these cases, making decision to repeat surgery and staging depend on factors such as the type of histology, abdominal exploration results in the previous surgery and probability of the presence of residual tumor.

Keywords: Borderline Ovarian Tumor, Serous BOT, Mucinous BOT, Treatment

1. Context

Borderline ovarian tumor (BOT), that is also known as atypical proliferative tumor and low malignant potential tumor (1), consists of epithelial ovarian lesions that express cytological features of malignancy, but unlike malignant ovarian tumors do not show obvious stromal invasion. BOTs, clinically and histologically, express a behavior between those of benign and malignant ovarian tumors; therefore they have a slow clinical course and prognosis (2) and a five-year survival rate is over 90% (3).

2. Epidemiology

The tumor incidence is between 1.8 and 4.8 per 100,000 females per year. Compared with patients with epithelial ovarian cancer, patients with BOT are younger, with prevalence of the disease by age being 10 years younger. BRCA gene mutations are rarely found in these patients and most of the patients are in the early stages of the disease at the time of diagnosis (stage I in 75% of patients) (4). Primary infertility, ovulation-induction drugs, family history of ovarian cancer, nulliparity and smoking increase the risk of BOT, while birth control pills, pregnancy and breastfeeding have protective effects (5).

3. Histology

Histologically, ovarian tumors are divided into three groups: benign, borderline (BOT) and malignant. The two major groups of BOT include serous BOT (S-BOT) and mucinous BOT (M-BOT).

4. Serous Borderline Ovarian Tumors (S-BOT)

S-BOTs are divided into two categories: tumors limited to ovary and tumors spreading outside the ovary. Tumors spread into the peritoneum occur in implant form and are different from metastasis. Extra-ovarian implant has a non-invasive nature in 85% of the cases, but sometimes aggressive changes (invasive implant) are found. To diagnose the invasion by the pathologist, the surgeon must remove a sufficient amount of healthy tissue surrounding the lesion.

Micro papillary pattern is a specific pathological characteristic occasionally found in S-BOT. In these cases, the bilateral involvement, ovarian surface involvement and presence of invasive or non-invasive implants are more commonly found. Gene expressions in S-BOT have a micropapillary appearance similar to those of low grade invasive ovarian cancer and in both cases genes involved in mitogen-activated protein kinase (MAPK) pathway are involved. It seems that both BOT and invasive cancer are caused by mutation in KRAS, BRAF and sometimes HER-2 genes (6-11).

Stromal microinvasion is defined as invasion up to 10 cubic millimeters and is more frequently found in S-BOT, compared with M-BOT.

5. Mucinous borderline tumor (M-BOT)

M-BOTs are divided into two categories. The more common type is intestinal type that constitute 85% of cases and the second is endocervical-type (Mullerian).

Mullerian M-BOTs are bilateral in 40% of the cases, while it is accompanied by pelvic endometriosis in 20-30% of patients. It is possible that all of the three pathologies are simultaneously found in a tumor (12). In 60% of the cases, the tumor occurs due to mutations in the KRAS gene. Stromal microinvasion is less observed in M-BOT and makes no contribution to prognosis.

The term intraepithelial carcinoma refers to a pathological finding in mucinous tumors. Given the possibility of simultaneous presence of benign, borderline and malignant elements in a sample, this finding in mucinous tumors must alert pathologist to more carefully examine the sample by making more sections to find possible malignant part of the sample.

6. Role of Frozen Section in Diagnosis of Borderline Tumors

Macroscopic view of ovarian tumors alone is not reliable to differentiate benign, borderline and malignant ovarian tumors. Therefore, microscopic examination by intraoperative frozen section is necessary. Sensitivity and specificity of frozen section is lower in case of BOT, compared with benign and malignant cases. In 20 to 30% of the S-BOT cases and to a greater extent in the M-BOT cases, it is possible to provide final pathological report of malignancy only after a better examination of the sample using more sections. However, it is better to perform conservative surgery in the patients who wish to preserve their fertility, until the final report is ready.

7. Diagnosis

BOT shares some clinical characteristics with benign and malignant ovarian tumors. Therefore, it is hard to differentiate them based on clinical characteristics (13).

Ultrasound findings are the most important criterion to diagnose malignancy in pelvic tumors. Combination of trans-abdominal and transvaginal ultrasound is a good method to examine adnexal masses if performed by a person skilled in the field of females' imaging; however, it should be accompanied by color Doppler sonography to increase precision of diagnosis.

Currently, there is no reliable diagnostic characteristic to differentiate borderline from malignant tumors and the objective of examining images is to identify patients with borderline and malignant tumors in order to refer them to gynecologist oncologist to ensure more accurate staging and consequently providing the patient with a better prognosis.

8. Ultrasonography

If ultrasound is performed by a person skilled in females' imaging, observation of the following characteristics indicates tumor's malignancy and accordingly the patient should be referred to gynecologist oncologist:

- Tumor with irregular solid parts.
- Ascites.
- At least four papillary projections.
- Significant arterial flow in solid part of tumor.
-Irregular multilocular tumor measuring greater than 10 cm.

At present, the routine use of magnetic resonance imaging (MRI) and computed tomography (CT) scan to differentiate malignant and benign ovarian tumors does not provide higher sensitivity and specificity greater than transvaginal ultrasound. However, in some cases of complex ovarian lesions, MRI of pelvis with a contrast agent can be helpful (14).

Overall, it can be said that preoperative diagnosis mostly depends on clinical judgment, suspicious ultrasound findings, and assessment of tumor markers.

Standard treatment for BOT is surgery as is the case with invasive epithelial ovarian cancer. This surgery includes hysterectomy, bilateral salpingo-oophorectomy, and removal of the whole tumor along with complete staging, i.e. peritoneal cytology, biopsy of different areas of the peritoneum and omentectomy.

Even if lymphadenectomy shifts the tumor to higher stage, it has no effect on survival of patient, and therefore, pelvic and para-aortic lymphadenectomy can be excluded,

unless lymph nodes are so large that their removal reduces the size of residual tumor (15).

Standard surgery is performed in the following stages:

- Making an abdominal longitudinal incision.
- Providing a sample of ascitic fluid or peritoneal washing.
- Examining inside of the abdomen and pelvis, and taking samples from all metastasis-suspected areas.
- In the absence of suspected areas, random biopsy of the pelvic and abdominal peritoneal surfaces, and surfaces below the diaphragm and paracolic spaces.
- Sending ovarian mass to pathology lab for frozen section examination.
- Hysterectomy along with bilateral oophorectomy while ensuring that the tumor is not torn apart.
- Omentectomy.
- Appendectomy (in mucinous tumors).
- Para-aortic lymphadenectomy, up to the inferior mesenteric artery and preferably renal vein.
- Pelvic lymphadenectomy, including the common iliac, external iliac, internal iliac and obturator cavity (in BOT lymphadenectomy did not affect the prognosis).

In cases where the tumor spreads fast, the following measures can be taken to ensure an ideal surgery and reduce the size of residual tumor by less than 1 cm, and preferably ensure that no microscopic tumor has remained in place.

- Radical pelvic surgery.
- Bowel resection.
- Stripping of diaphragm.
- Splenectomy.
- Removing the tail of the pancreas.
- Appendectomy (appendectomy is necessary for mucinous tumors).
- Partial removal of liver.
- Partial removal of bladder.

9. Prognostic Factors

BOT often shows a benign prognosis; however, in 10-15% of patients, tumor can have an invasive behavior, spreading beyond ovary or recur like malignant tumor (16). Identifying the prognostic factors that can predict such behaviors is very important, because knowledge of such factors can significantly contribute to deciding the extent of surgery in the first treatment or after recurrence of the disease.

Stages of the disease are especially predictors of recurrence likelihood and survival rate of BOT patients when invasive implants are present. Micropapillary appearance in BOT is recognized as a risk factor.

However, it is not proven as an independent factor and poor prognosis is only found in cases where micropapillary appearance is accompanied by invasive implants (17). The presence of microinvasion is more prevalent in serous tumors and is among their prognostic factors (9, 18). Microinvasion is not considered as a prognostic factor in mucinous tumors. If laparoscopy is performed by a person skilled in this field, it will not negatively affect prognosis. However, it is sometimes required to make sure that cyst is not ruptured during surgery and to prevent metastasis, endobag is used when removing the cyst. Other factors affecting prognosis are age, histological type of tumor and DNA ploidy. Age of over 75 years, mucinous tumors and DNA aneuploidy are negative factors.

10. Role of Restaging

In majority of patients referred for BOT, staging is not performed due to failure to suspect malignancy. In these cases, making decision to reoperate and restage depends on factors such as the type of histology, abdominal exploration in the previous surgery and probability of the presence of residual tumor (5, 19-21). When M-BOT is clearly limited to the ovary, it is unlikely that reoperation deteriorates the disease. In the case that there is suspicion for extraovarian spread, it is necessary to reoperate for staging (22, 23). Briefly, the second time surgery is recommended in the following cases:

- Cystectomy in M-BOT.
- Micropapillary appearance.
- Microinvasion.
- Not complete resection of intraperitoneal implants.
- Unknown nature of intraperitoneal implants.

11. Fertility-Preserving Conservative Surgery

BOT has excellent prognosis and recurrence occurs late; therefore, given prevalence of this disease among young females, conservative surgery (conserving uterus and at least part of ovary with complete staging of surgery) can be used in all stages of the disease in patients who wish to preserve their fertility (21, 24).

Although the recurrence rate increases after conservative surgery, compared with standard surgery (10-20% vs. 5%) (20), fortunately a recurrence has a borderline (rather than invasive) histology; therefore survival of patients with conservative surgery does not decrease. The following points should be considered before conservative surgery:

- Counsel the patient about the type of surgery, recurrence rate after conservative surgery, and the follow-up period.

Box 1. Stages of the Disease

Stages Description
Stage I
In stage I, the tumor is found in one or both ovaries. Stage I is divided into IA, IB and stage IC.
- Stage IA: The tumor is found inside a single ovary.
- Stage IB: The tumor is found inside both ovaries.
- Stage IC: The tumor is found inside one or both ovaries and one of the Following is true
Tumor cells are found on the outside surface of one or both ovaries; or
The capsule of the ovary has ruptured or tumor cells are found in the fluid of the peritoneal cavity or in washings of the peritoneum
Stage II
In this stage, the tumor is found in one or both ovaries and has spread into other areas of the pelvis. Stage II is divided into IIA, stage IIB and stage IIC.
- Stage IIA: The tumor has spread to the uterus and/or fallopian tubes
- Stage IIB: The tumor has spread to other tissue within the pelvis.
- Stage IIC: The tumor is found inside one or both ovaries and has spread to the uterus and/or fallopian tubes, or to other tissue within the pelvis. Also, one of the following is true
Tumor cells are found on the outside surface of one or both ovaries; or
The capsule of the ovary has ruptured or
Tumor cells are found in the fluid of the peritoneal cavity or in washings of the peritoneum.
Stage III
The tumor is found in one or both ovaries and has spread outside the pelvis to other parts of the abdomen and/or nearby lymph nodes. Stage III is divided into stage IIIA, stage IIIB and stage IIIC.
- Stage IIIA: The tumor is found in the pelvis only, but tumor cells that can be observed only with a microscope have spread to the surface of the peritoneum, the small intestines, or the tissue that connects the small intestines to the wall of the abdomen.
- Stage IIIB: The tumor has spread to the peritoneum and the tumor in the peritoneum is 2 cm or smaller.
- Stage IIIC: The tumor has spread to the peritoneum and the tumor in the peritoneum is larger than 2 cm and/or has spread to lymph nodes in the abdomen. The spread of tumor cells to the surface of the liver is also considered stage III disease.
Stage IV
In this stage, tumor cells have spread beyond the abdomen to other parts of the body, such as the lungs or the tissue inside the liver. Tumor cells in the fluid around the lungs are also considered stage IV disease. Ovarian low malignant potential tumors almost never reach stage IV.

- It is recommended to counsel patients over 40 years who wish to preserve their fertility.

-Whereas such patients should undergo complete staging, it is better that this surgery is performed by gynecologist oncologist.

- In advanced stages of the disease, conservative surgery should be limited to patients whose peritoneal implants are fully removed and are of non-invasive type.

If the tumor is unilateral, treatment of choice is salpingo-oophorectomy of the ipsilateral ovary, if the contralateral ovary is apparently normal (25-28). In case of bilateral involvement, initially both ovaries should be examined to identify the normal ovarian tissue in both ovaries, and accordingly, the ovary with more normal tissue will undergo cystectomy, while the other ovary will undergo salpingo-oophorectomy (26).

Cystectomy is recommended for patients who have only one ovary and are very young to ensure maximum preservation of ovarian tissue (29).

Cystectomy is not recommended for M-BOT due to increased risk of recurrence (30).

12. Role of Assisted Reproductive Technology in Preserving Fertility

In Iran, embryo-freeze method is currently more common and there is not much experience with oocyte-freeze method. Minimum time required for induction ovulation is two weeks. Therefore, it is recommended to use antagonist protocol. If the patient is on day two or three of menstruation, standard antagonist protocol will be applied, and if she is on other days, antagonist cycle is started, and at the same time induction ovulation is also performed (31).

13. Treatment of Infertility After Fertility-Preserving Surgery

About half of BOT patients who have conservative surgery become pregnant automatically (32); 10-35% of patients were infertile before diagnosis of BOT (33, 34). Stimulation of ovulation and high estrogen levels in patients with BOT do not increase the risk of recurrence; furthermore, pregnancy has no negative impact on the survival of these patients (33, 35).

14. Role of Laparoscopy in BOT Surgery

BOT is mostly diagnosed in young females and in early stages of the disease. There is no certain criterion to diagnose the disease before surgery, and these tumors are almost always diagnosed in frozen section or in pathology after surgery. Therefore, in many cases, laparoscopic approach is already started (36). If BOT is apparently in the early stages, it is necessary to perform a comprehensive staging. This can be achieved through continuing to perform laparoscopy by gynaecologist oncologists or by converting the surgery to laparotomy (37, 38). The evidence overall suggests that laparoscopy as a primary approach in BOT is effective and safe (34, 38).

15. Postoperative Adjuvant Therapy (Chemotherapy, Radiation)

Based on strong evidence, chemotherapy has no role in stage I of BOT. In more advanced stages, where invasive implant is absent, lymph nodes are involved or rupture of the cyst has occurred, further studies have shown that chemotherapy has no effect on improving survival and reducing recurrence rate and/or improving the prognosis (39-42).

The only important concern is presence of invasive implants, which are present only in few cases of BOT. In other words, only 15% of all implants are invasive. Treatment and prognosis of these patients are different. In presence of invasive implant, survival reduces from 34 to 4.7%, (43) and recurrence of tumor in invasive form increases from 8.3 to 29% (44). Overall, factors affecting the survival of patients with invasive implant are optimal surgery and residual tumor after surgery (45). There is currently no evidence suggesting that using adjuvant postoperative radiotherapy in patients with BOT can increase survival rate (46). In addition, patients who received adjuvant radiotherapy showed high recurrence rate (up to 40%) (47). Radiotherapy can only have palliative effect in cases as suffer from bleeding or pain (48).

16. Hormone Replacement Therapy

In patients with gynecologic cancers such as BOT, if bilateral oophorectomy is performed, sudden and severe menopausal symptoms will occur. According to the recent studies by Cochrane and women's health initiative (WHI), the risk of cardiovascular disease, stroke and cancer was associated with long-term use of hormone replacement therapy (HRT) both before and after menopause. The studies also found that the use of estrogen alone in patients who had hysterectomy did not increase the risk of breast cancer and cardiac disease (49). HRT is very important to prevent osteoporosis and cardiovascular complications and improve the quality of life of such patients. Given that many of these patients are young and in the early stages of the disease, HRT should be recommended in the patients (50).

17. Follow-Up

Recommendations for follow-up are as follows:

Patients should be informed about recurrence. Symptoms such as pelvic pain, bloating, bowel obstruction, weight loss and fatigue are important. If there were high levels of CA125 and other tumor markers, they should be measured at every visit (47). In case of clinical suspicion of recurrence, imaging techniques such as ultrasound, CT scan of the abdomen, pelvis and chest, or MRI are recommended (48, 49). The preferred diagnostic method for follow-up of patients with BOT who have undergone fertility-preserving surgery is ultrasound (preferably transvaginal) and it is necessary to perform such ultrasound every three months for two years, then, every six months for five years, and then annually.

Summary follow-up of patients with BOT:

- Visit a doctor every three to six months for the first five years and once a year.

The measures that should be taken at each visit:

- Physical examination including pelvic examination.
- Measurement of CA125 level or other tumor markers in case their levels were originally high.
- Ultrasound at each visit in case of patients with fertility-preserving surgery.
- Recommendation of complete surgery after completion of family.

18. Recurrence of Disease

In such patients, overall recurrence rate is 11%. Recurrence rate is 5% after radical surgery, 10-20% after fertility-preserving surgery, and about 31% after cystectomy (20,

51). Most of reoccurrences are in form of borderline tumor; however, in 20-30% of cases, recurrence is in invasive form. Mucinous tumors are more likely to recur in invasive form than serous tumors. Therefore, in case of patients with mucinous tumor who wish to preserve fertility, unilateral salpingo-oophorectomy is preferred, and cystectomy is not recommended (31). In most cases, recurrence occurs after five years as invasive form (51). These tumors are usually low grade and are rarely high grade. Recurrence almost always occurs inside ovary (52); extraovarian recurrence occurs in 2% of patients at stage I and in about 20% of patients in the higher stages (51). In the recurrence as borderline form in the ovary that previously received cystectomy, and the patient wishes to preserve her fertility, choice of treatment method depends on the status of the contralateral ovary. If contralateral ovary is normal, salpingo-oophorectomy of the ovary is recommended, and if her contralateral ovary was removed in a previous surgery, cystectomy is recommended. Conservative surgery is recommended only when invasive implants are absent, and patient is younger than 40 and also long-term and careful follow-up is possible (53, 54).

Questions not sufficiently covered by literature, but covered by expert opinion as follows:

When can the patients who have undergone fertility-preserving surgery become pregnant?

- If the patient is in stage I of the disease and does not have poor prognostic factors, she does not need to delay pregnancy and can immediately become pregnant.

Patients at a more advanced stage of the disease, that is, stage II - IV, without invasive implant should be examined after conservative treatment by gynecological oncologist and infertility specialist, in order to decide pregnancy strategy, including oocyte or embryo cryopreservation. In case of patients who wish to have physiological pregnancy, or ovulation induction, it is required to wait for 6 - 24 months after remission of the disease to ensure that disease will not recur. It is required to treat invasive implant like invasive epithelial ovarian cancer.

Is it required to perform definitive surgery after completion of family in patients who had conservative surgery?

- If the patient was in stage I of the disease and does not have poor prognostic factors, it is not required.

In patients with poor prognostic factors, or patients in higher stages of the disease, definitive surgery is performed after completion of family.

Is it allowed to preserve one ovary to prevent early menopause in patients under 45 whose family is complete?

- In a patient who is in early stages of the disease and does not have poor prognostic factors, healthy ovary can be preserved when tumor is unilateral. Otherwise, it is not allowed to preserve the ovary.

Is it allowed to preserve part of ovary to prevent early menopause in case the patient has only one ovary, and recurrence has occurred in that ovary, and the family is complete?

- If the patient does not have invasive implant, and is very young, part of ovary can be preserved if possible.

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