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SHORT COMMUNICATION

Management of ovarian tumors

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Abstract

Border line ovarian tumors are one of the common asymptomatic tumors in young women. They are mostly diagnosed at the time of routine examination. The management of tumor is crucial, since fertility preservation is a challenge in this age group. A fine balance needs to be drawn between maximal removal of tumour and preserving fertility till her reproductive needs are fulfilled. Therefore a clear idea for management will help in individual management. Surgery is the treatment of choice, but fertility preservation with close 3-6 monthly follow up is appropriate till woman completes her family.

Keywords: Border line ovarian tumor; Molecular genetics; Staging of ovarian tumor

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Introduction

Borderline ovarian tumors (BOT) are epithelial tumors constituting for approximately 10-20% of all ovarian neoplasias [1]. The mean age of presentation of borderline ovarian tumors is approximately 20 years earlier than that of invasive ovarian carcinomas [2]. Therefore preserving fertility is a consideration. Completion of surgical staging and the type of operative approach (laparoscopy vs. laparotomy) often remain the topics of debate. A literature research shows that there is a recent trend in last 10 years reported from various parts of world towards the availability of a variety of management options for better patient care.

Borderline Tumors (BOT)

A group of tumors distinguished as tumor of low malignant potential are called Border line tumors (Figure 1). These are lesions that tend to remain confined to the ovary for a long time. The criteria for diagnosis of border line serous tumors are as follows: 1) Epithelial hyperplasia in the form

of pseudostratification, tufting, cribriform and micropapillary architecture. These tumors are frequently bilateral, exophytic and high stage. 2) Mild nuclear atypia and mild increased mitotic activity. 3) Detached cell clusters. 4) Absence of destructive stromal invasion (i.e. without tissue destruction). BOTs harbour foci of stromal micro-invasion.

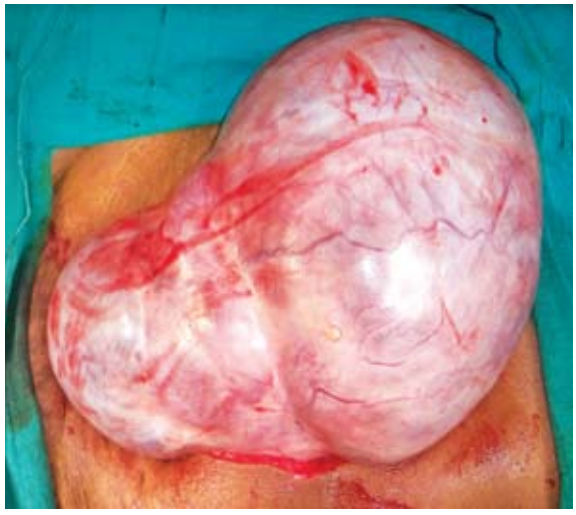

Figure 1: Intra operative border line tumor

Case 1

A 35 year old infertile woman underwent ovulation induction (5 cycles) followed by three cycles of Intra Uterine Insemination(IUI) presented with complaint of pain in right lower abdomen. After primary evaluation a 3 x 3 cm ovarian mass with variable consistency was noticed with possibility of torsion. The patient underwent laparoscopic right salpingo ophorectomy and it was reported as serous borderline ovarian tumor. The status of other ovary was not known and hence she underwent completion staging laparotomy which did not show any other sites of spread and she was kept on observation. She was disease free till her last visit 6 months ago.

Case 2

A 25 year old para 2 after 6 month of second delivery presented with abdominal pain and distension of abdomen. On evaluation there was a huge 15 x 10 cm solid cystic mass with possibility of ovarian origin, Patient underwent staging laparotomy with frozen biopsy and was diagnosed a serous borderline ovarian tumor. Hysterectomy was not performed. Patient is under follow up and she was disease free till her last visit.

Here we need to think, a 25 year with two children has her uterus and ovaries while a 35 year old woman desirous for children lost her uterus and both the ovaries, both the cases disease was the same but management plan differed a lot and created a big difference. We will discuss about it again.

Epidemiology

The recent trend shows BOT comprises 15-20 % of epithelial ovarian tumors [3]. The age of presentation of BOT ranges from 16-70 year, although high age in BOT cannot be neglected [4, 5].

Parity: Souki DZ et al. in study of 10 case sequel found 40% patients to be nulliparous [8]. But higher age group women were either nullipara or with single pregnancy and willing to conceive again in various prospective fertility sparing surgery with BOT.

Signs and symptoms: Approximately 16% of patients are asymptomatic at the time of diagnosis [6]. Vine et al. evaluated the symptoms and their duration before the diagnosis of invasive cancer or BOT [7]. Sometimes nonspecific symptoms such as abdomino-pelvic pain or mass were seen. The duration of symptoms are prolonged as compared to ovarian cancer (six versus four months). These aspects of the clinical presentation of BOT are probably a reflection of the more indolent nature of these tumors [8].

Tumor markers: The CA 125 is a useful tool most of the time. In selected mucinous tumors where CA 125 is not elevated, Ca19.9 is used [9, 10].

Molecular genetics and classifications

As the term borderline implies it behaves intermediate between benign and malignant tumors. Histologically this is expressed by cellular proliferation and nuclear atypia without destructive stromal invasion [9]. In 1929, Taylor described BOT as “semi-malignant” serous tumors of the ovary [11]. According to the grade of differentiation, nuclear atypia and stromal invasion the ovarian cancer is distinguished into three groups: benign, borderline, and malignant tumors [12]. According to heterogeneity Kurman and Shih divided ovarian carcinomas into two categories, type I and type II (Table 1) [13].

Table 1: Kurman and Shih classification.

Features	Type I	Type II
Grade and type	low-grade serous, low-grade endometrioid, clear cell, and mucinous carcinomas	high-grade serous, high-grade endometrioid, and undifferentiated carcinomas
Overall percentage of ovarian cancer	25%	75%
Mortality	10%	90%
Behavior of tumor	Indolent , slow growth	rapid growth
Genetic association	KRAS, BRAF, PTEN, PIK3CA, and ERBB2 mutation	p53 mutation , inactivation of BRCA1/2 , and CCNE1 amplification.
Genetic stability	Genetic stability present	Genetic instability present
Prognosis	Good	Poor

As per clinical variants Prat classified ovarian cancer in five groups: high-grade serous (HGSC), endometrioid (ECs), clear cell (CCCs), mucinous (MCs), and low-grade serous (LGSC) [14]. Among these LGSCs account for <5% of all cases of EOC [18], WHO 2003 classified border line tumors in five categories as per histologic features, these are serous, mucinous, endometroid, clear cell and brenner cell tumor [17]. In mucinous epithelial ovarian cancer (EOC) due to significant correlation between HER2 gene, IHC is recommended [15].

Investigation and diagnosis

Ultrasound is broadly accepted as a highly accurate preoperative method in discriminating between benign and malignant adnexal masses if performed by experienced ultrasound examiner [16-18]. Pýnar Yörük et al. from turkey in a prospective study compared morphologic characters of tumor with addition of doppler study and Risk Malignancy Index (RMI) score and strongly recommended doppler study as a better tool with high predictive value [19].

The RMI is calculated as originally described by Jacobs et al. as follows: RMI = U (ultrasound score) × M (menopausal score) × serum CA-125 level (units per liter) [20]. A cutoff value of 200 is accepted as indicator of malignant tumor [24]. Rice LW et al. in a prospective study evaluated the pre-op CA125 levels and concluded that the progressive correlation between pre-op CA125 and stage of the disease [20].

As a large number of cases are diagnosed incidentally, intra operative biopsy is recommended for proponents of fertility sparing surgery. A research carried out by Prapaporn Suprasert et al. in this query and claimed sensitivity in the diagnosis of benign, borderline and malignant tumors to be 100%, 84%, and 92 %, respectively, with specificities of 92.7%, 97.9%, and 100%, respectively. The overall accuracy with frozen sections was 94% [22]. But trend of hysterectomy with no peritoneal implants on the surface of the uterine serosa are present [2, 23]. Menczer et al. showed a low rate (2%) of uterine involvement among patients with BOTs who underwent hysterectomy in addition to bilateral adnexectomy [24].

Staging of BOT

Worldwide FIGO staging is considered as clinical tool for staging of various cancers. Though Borderline tumors are not malignant they are staged as per FIGO staging (Table 2) only.

Management

An interesting result from multi-center survey in Germany was the high grade of unsureness in the clinical management of BOT among clinicians which resulted in under or over treatment. Therefore higher centers perform surgical evaluation to avoid restaging and continued medical education is important to deliver proper evidence based treatment [24].

Treatment of BOT depends on age of the patient, histologic and clinical characteristics and stage of

Table 2: FIGO 2014 staging of ovarian cancer.

Stage	*Findings*
STAGE I:	Tumor confined to ovaries
IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings.
IB	Tumor involves both ovaries otherwise like IA.
IC	Tumor limited to 1 or both ovaries.
IC1	Surgical spill.
IC2	Capsule rupture before surgery or tumor on ovarian surface.
IC3	Malignant cells in the ascites or peritoneal washings.
STAGE II:	Tumor involves 1 or both ovaries with pelvic extension (below the pelvic) or primary peritoneal cancer
IIA	Extension and/or implant on uterus and/or fallopian tubes.
IIB	Extension to other pelvic intraperitoneal tissues.
STAGE III:	Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA	IIIA (Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis).
IIIA1	Positive retroperitoneal lymph nodes only IIIA1 (i) Metastasis = 10 mm IIIA1 (ii) Metastasis > 10 mm.
III A2	Microscopic, extrapelvic (above the brim), peritoneal involvement ± positive, retroperitoneal lymph nodes.
IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
IIIC	Macroscopic, extrapelvic, peritoneal metastasis >2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
STAGE IV:	Distant metastasis excluding peritoneal metastasis
IVA	A Pleural effusion with positive cytology.
IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extraabdominal organs (including Inguinal lymph nodes and lymph nodes outside of the abdominal cavity).

the disease at the time of diagnosis. In BRCA1 and BRCA2 mutation carriers prophylactic salpingo-oophorectomy is currently recommended as strategy to reduce ovarian cancer risk [27]. The recent NCCN guidelines version 2.2014 states that stage of the disease should be evaluated by a gynecologic oncologist [28]. BOT should be confirmed from institutional pathology review. The staging if done in primary surgery and no invasion/implant reported, only observation and follow up 3-6 monthly for five year minimum is enough. Physical examination, including pelvic examination, CA 125 levels (if raised previously) and ultra sonogram is ideal in fertility sparing surgery cases. Radical surgery is advisable but with invasive implants. Residual disease can be managed in a similar way or with chemotherapy (category 2B) [29].

In case of primary inadequate surgery, close follow up is advised. Once clinical relapse is suspected surgical evaluation with debulking surgery is needed. If invasion is found, further treatment will be similar to that of primary epithelial ovarian cancer barring those who underwent unilateral salpingo-oophorectomy till their child bearing is completed [29].

Route of surgery

The surgical option for BOT is strongly recommended as diagnostic laparoscopy followed by surgical staging. Statistically the staging of laparoscopy and laparotomy are similar, even laparoscopy is feasible if meticulously approached [9, 29, 30]. To avoid surgical site metastasis protected specimen retrieval is used [30]. In view of future fertility, frozen biopsy of contra lateral ovary in suspicious case is advisable. The advantage of laparoscopy in this aspect is to avoid undue hospital stay and less adhesion formation, which are known to decrease fecundity [31-33].

Steps of surgical staging

Surgical staging for ovarian cancer originally necessitated an exploratory laparotomy to perform the various procedures advised by FIGO: hysterectomy and salpingo-oophorectomy, pelvic and para aortic lymph node dissections, omentectomy, peritoneal washings, and peritoneal biopsies [34]. The meticulous approach to ovarian tumour includes certain principals: a) A thorough examination of whole abdomen is compulsory, b) The tumor should

be removed intact, if possible, frozen histologic section obtained, c) The minimal residual disease less than 0.5 mm has shown superior survival [36]. The survival rate improves by 90-100% if patients are staged properly [35, 36].

Adjuvant treatment after primary surgery

The role of adjuvant chemo-radiation is controversial. A multicenter survey reflected that after primary surgery 30% health centres did not advice adjuvant treatment. Around 64% centres suggested chemotherapy only in the high-risk situation: tumour residuals, microinvasion with evidence for invasive implants or in mucinous or clear cell histological subtype. Thus, a high grade of insecurity in diagnostic and therapeutic approach of BOT exists in some gynaecological departments and underlines the need for more educational and study activities [34]. Strong association of HER2 in mucinous tumours has been found, target therapy with trastuzumab or pertuzumab can be beneficial in these cases [37].

Follow up

The follow up is very important not only to control the disease but to evaluate any additional disease and recurrence. The investigations during followup must be very meticulously chosen. In a prospective study Zanetta et al. concluded that the vaginal ultrasound is the most effective diagnostic technique. Three follow-ups per year are recommended for the first two years, then one follow-up every six months during the next three to five years, and thereafter annually [38]. Follow-up of patients must be done up to 15 years following the initial diagnosis as recently Maria et al. concluded from a Meta analysis [13, 29].

Survival and prognosis

The survival in any cancer disease is very unpredictable and mostly a question asked by relatives of the patient. The 5-year survival for women with Stage-I borderline tumors is favourable, about 95-97%, but the 10-year survival is only between 70 and 95%, caused by late recurrence. The survival data for 10 years for advanced mucinous BOTs are limited: at 5 years, it reached 85.5% ± 9.0% [39].

Relapse

Relapse is another challenge if a plan of extensive surgery already done, followed by chemotherapy. Pateint may come with same disease years later. Uzan et al. concluded young age, tumor bilaterality and the use of a cystectomy were identified as risk factors for recurrence [40]. Though Margarita et al. in their series noticed relapse risk was significantly higher in patients who had not undergone lymphadenectomy.

Summary

Thus the whole research work justifies the management of above two cases. The elderly lady with incomplete staging and young woman with preservation of uterus and ovary with close follow up is justified. A comprehensive surgical staging procedure is clearly indicated in cases of early ovarian cancer and oncologic guidelines should be respected. The laparoscopic approach could be a valid alternative to laparotomy but in limited hands. The survival and recurrence improves if primary surgical approach is meticulous. The fertility sparing surgery is optional but once child bearing is completed, radical surgery is a judicial option. Five year recurrence rate is high therefore minimum of five year routine follow up at 3-6 monthly intervals is advisable in borderline ovarian tumor.

Conflict of interest

The authors wish to express that they have no conflict of interest.

References

1. Sutton GP. Ovarian tumors of low malignant potential. In: Rubin SC, Sutton GP, editors. Ovarian Cancer. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. pp. 399–417.
2. du Bois A, Ewald-Riegler N, du Bois O, et al. Borderline tumors of the ovary: A systematic review. Geburtsh Frauenheilk. 2009;69:807–833.
3. Lenhard MS, Mitterer S, Kümper C, Stieber P, Mayr D et al. Long-term follow-up after ovarian borderline tumor: relapse and survival in a large patient cohort. Eur J Obstet Gynecol Reprod Biol. 2009; 145(2):189-194.
4. Auranen A, Grénman S, Mäkinen J, Pukkala E, Sankila R, et al. Borderline ovarian tumors in Finland: epidemiology and familial occurrence. Am J Epidemiol. 1996; 144(6):548-553.
5. Harlow BL, Weiss NS, Lofton S. Epidemiology of borderline ovarian tumors. J Natl Cancer Inst 1987; 78:71-74.
6. Sherman ME, Mink PJ, Curtis R, Cote TR, Brooks S, et al. Survival among women with borderline ovarian tumors and ovarian carcinoma: a population-based analysis. Cancer 2004; 100(5):1045-1052.
7. Vine MF, Ness RB, Calingaert B. Types and duration of symptoms prior to diagnosis of invasive or borderline ovarian tumor. Gynecol Oncol. 2001; 83(3):466–471.

8. Patrono MG, Minig L, Diaz-Padilla I, Romero N, Rodriguez Moreno JF, et al. Borderline tumours of the ovary, current controversies regarding their diagnosis and treatment. Ecancermedicalscience 2013; 7:379.
9. Schorge JO, en Williams Ginecología. 1a edición. México: McGraw-Hill Interamericana; 2009. Cáncer epitelial de ovario pp. 719–721.
10. Berek JS, Crum C, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet. 2012; 119 Suppl 2:S118-29.
11. Taylor HC Jr. Malignant and semimalignant tumors of the ovary. Surg Gynecol Obstet 1929; 48:204-230.
12. Lee KR, Tavassoli FA, Prat J, et al. Tumours of the ovary and peritoneum: surface epithelial-stromal tumours. In: Tavassoli FA, Devilee P, editors. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. chapter 2. Lyon, France: IARC Press; 2003. p. 117–145.
13. Kurman RJ, Shih IeM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm. Hum Pathol. 2011; 42(7):918-931.
14. Prat J. Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. Virchows Arch. 2012; 460(3):237-249.
15. Chao WR, Lee MY, Lin WL, Chen CK, Lin JC, et al. HER2 amplification and overexpression are significantly correlated in mucinous epithelial ovarian cancer. Hum Pathol. 2014; 45(4):810-816.
16. Valentin L. Prospective cross-validation of Doppler ultrasound examination and gray-scale ultrasound imaging for discrimination of benign and malignant pelvic masses. Ultrasound Obstet Gynecol. 1999; 14(4):273-283.
17. Valentin L, Hagen B, Tingulstad S, Eik-Nes S. Comparison of 'pattern recognition' and logistic regression models for discrimination between benign and malignant pelvic masses: a prospective cross validation. Ultrasound Obstet Gynecol. 2001; 18(4):357-365.
18. Timmerman D, Schwärzler P, Collins WP, Claerhout F, Coenen M, et al. Subjective assessment of adnexal masses with the use of ultrasonography: an analysis of interobserver variability and experience. Ultrasound Obstet Gynecol. 1999; 13(1):11-16.
19. Yörük P, Dündar O, Yildizhan B, Tütüncü L, Pekin T. Comparison of the risk of malignancy index and self-constructed logistic regression models in preoperative evaluation of adnexal masses. J Ultrasound Med. 2008; 27(10):1469-1477.
20. Jacobs I, Oram D, Fairbanks J, Turner J, Frost C et al. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol. 1990; 97(10):922-929.
21. Rice LW, Lage JM, Berkowitz RS, Goodman A, Muto MG, et al. Preoperative serum CA-125 levels in borderline tumors of the ovary. Gynecol Oncol. 1992; 46(2):226-229.
22. Suprasert P, Khunamornpong S, Phusong A, Settakorn J, Siriaungkul S. Accuracy of intra-operative frozen sections in the diagnosis of ovarian masses. Asian Pac J Cancer Prev. 2008; 9(4):737-740.
23. Morice P. Borderline tumours of the ovary and fertility. Eur J Cancer. 2006; 42:149–158.
24. Menczer J, Chetrit A, Sadetzki S; National Israel Ovarian Cancer Group. The effect of hysterectomy on survival of patients with borderline ovarian tumors. Gynecol Oncol. 2012; 125(2):372-375.
25. FIGO Ovarian Cancer Staging. (Available on 1 January 2014 at www.sgo.org/clinical-practice/guidelines/new-figo-ovarian-cancer-staging-guidelines/Effective).
26. Coumbos A, Sehouli J, Chekerov R, Schaedel D, Oskay-Oezcelik G, et al. North-Eastern German Society of Gynecological Oncology (NOGGO). Clinical management of borderline tumours of the ovary: results of a multicentre survey of 323 clinics in Germany. Br J Cancer. 2009; 100(11):1731-1738.
27. Schwartz GF, Hughes KS, Lynch HT, Fabian CJ, Fentiman IS, et al. Consensus Conference Committee The International Consensus Conference Committee. Proceedings of the international consensus conference on breast cancer risk, genetics, & risk management, April, 2007. Cancer. 2008; 113(10):2627-2637.
28. NCCN Guidelines Version 2. 2014. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer 2014.
29. Huang KG, Wang CJ, Chang TC, Liou JD, Hsueh S et al. Management of port-site metastasis after laparoscopic surgery for ovarian cancer. Am J Obstet Gynecol. 2003; 189(1):16-21.
30. Wenzl R, Lehner R, Husslein P, Sevelda P. Laparoscopic surgery in cases of ovarian malignancies: an Austria-wide survey. Gynecol Oncol. 1996; 63(1):57-61.
31. Nezhat FR, Ezzati M, Chuang L, Shamshirsaz AA, Rahaman J, et al. Laparoscopic management of early ovarian and fallopian tube cancers: surgical and survival outcome. Am J Obstet Gynecol. 2009; 200(1):83.e1-86.
32. Colomer AT, Jiménez AM, Bover Barceló MI. Laparoscopic treatment and staging of early ovarian cancer. J Minim Invasive Gynecol. 2008; 15:414–419.
33. Muzii L, Palaia I, Sansone M, Calcagno M, Plotti F et al. Laparoscopic fertility-sparing staging in unexpected early stage ovarian malignancies. Fertil Steril. 2009; 91(6):2632-2637.
34. Shepherd JH. Revised FIGO staging for gynaecological cancer. Br J Obstet Gynaecol. 1989; 96(8):889-892.
35. Young RC, Decker DG, Wharton JT, Piver MS, Sindelar WF, et al. Staging laparotomy in early ovarian cancer. JAMA. 1983; 250(22):3072-3076.
36. Schueler JA, Cornelisse CJ, Hermans J, Trimbos JB, van der Burg ME, et al. Prognostic factors in well-differentiated early-stage epithelial ovarian cancer. Cancer 1993; 71(3):787-795.
37. Hillig T, Thode J, Breinholt MF, Franzmann MB, Pedersen C, et al. Assessing HER2 amplification by IHC, FISH, and real-time polymerase chain reaction analysis (real-time PCR) following LCM in formalin-fixed paraffin embedded tissue from 40 women with ovarian cancer. APMIS. 2012; 120(12):1000-1007.
38. Zanetta G, Rota S, Lissoni A, Meni A, Brancatelli G, et al. Ultrasound, physical examination, and CA 125 measurement for the detection of recurrence after conservative surgery for early borderline ovarian tumors. Gynecol Oncol. 2001; 81(1):63-66.
39. Sherman ME, Mink PJ, Curtis R, Cote TR, Brooks S, et al. Survival among women with borderline ovarian tumors and ovarian carcinoma: a population-based analysis. Cancer 2004; 100(5):1045-1052.
40. Uzan C, Muller E, Kane A, Rey A, Gouy S, et al. Prognostic factors for recurrence after conservative treatment in a series of 119 patients with stage I serous borderline tumors of the ovary. Ann Oncol. 2014; 25(1):166-171.