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Original Research Article

Existing challenges and histopathological review of borderline ovarian epithelial tumors

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ABSTRACT

Background: The borderline tumour seen in the ovary can be with or without stromal invasion. Diagnosis and application of the correct criteria are of utmost importance to avoid over or undertreatment of these. We analyzed the borderline tumors reported in 2 years with respect to clinical outcome based on the morphological diagnosis and points that needed reconsideration.
Methods: Cases reported as borderline tumors in ovary were retrieved from records reviewed and follow up was recorded. Additionally, we performed a morphometric analysis to confirm the maximum size of the invasive front.
Results: A total of 467 resected ovarian tumor specimens were received, of which 266 (266/467 *100=56.9%) were epithelial tumors; out of them 54.88% were benign, 4.88% were borderline and 40.22% were malignant. The mean age at the time of borderline diagnosis was 38.66 years. On follow-up two cases among them developed further disease. One was reported from our center and one from outside, both were mucinous-type tumors. On critical review we found that there was minimal nuclear atypia in both, there was no evidence of convincing stromal invasion except few irregular well formed glands were seen infiltrating the stroma in one case.
Conclusions: A large multicenter, interdisciplinary collaboration and data-driven study is needed to reconfirm and reconsider the cut-off of 5mm especially in mucinous tumors.

Keywords: Borderline ovarian tumours, Diagnostic criteria, Mucinous ovarian tumour, Morphometry, Serous ovarian tumour

INTRODUCTION

Borderline tumors (BTs) are subtypes of epithelial tumors in ovary lying on the verge of benign and malignant. These are common in women of the the reproductive age group and represent 10-15% of all epithelial neoplasms. The diagnosis of BTs plays a significant role in the treatment plan and overall survival of the patient. The diagnosis of borderline tumours is primarily a histomorphological diagnosis. Therefore, it is very crucial to follow the protocols strictly while diagnosing borderline tumours. Few markers like CA125 have been investigated to identify or segregate carcinoma from borderline tumors; however, the results are contradictory in literature and till yet only histology is decisive for diagnosis.[1,2] Therefore, the morphological assessment is the only tool.

Serous borderline tumours are bilateral in 15-25% of patients, while mucinous borderline tumours are

unilateral and large. These patients present with vague abdominal symptoms and abdominal mass or urological disturbances. Relapse is more common in serous borderline tumours, and in the case of relapse in mucinous borderline tumours, the risk of invasive disease is higher. Serum levels of CA125 and CA19-9 may increase. The levels of CA125 and CA19-9 have been found to be comparable in the case of borderline and malignant epithelial tumours in the ovary, with few reports also contrasting.[3] Few radiological features like irregularity of wall and complexity of cysts have been suggested to indicate risk of malignancy on ultrasonography.[1]

BT can be managed through oophorectomy or fertility-sparing surgeries if it affects women of reproductive age. Unilateral/ bilateral cystectomy, unilateral or bilateral salpingo-oophorectomy or radical treatment involving bilateral salpingo-oophorectomy with hysterectomy and omentectomy are also performed; radical procedures are more likely when there is clinical suspicion of malignancy. Borderline ovarian tumours have a good prognosis with an overall 5- and 10- year survival rate of 95-97% and 90%, respectively, for FIGO stages I- III, while for stage IV the overall survival decreases to 77%.[4] It is most important to know that chemotherapy is not required and is said to be more detrimental in borderline tumours.[5]

Recurrence rates after radical surgery are lower, but it does not affect overall survival. Recurrence is most likely to occur within the first two years after surgery, but it can occur up to 15 years after surgery. Therefore, follow-up after surgery is necessary, with regular monitoring of tumour markers and ultrasound is recommended in BT.

With the above we know that the morphological distinction between BTs and invasive carcinoma of ovary is primarily a morphological diagnosis, the treatment of both the entities differs in terms of post operative chemotherapy along with prognosis. Hence, we conducted this audit to analyze the borderline neoplasms in ovary reported in 2 years to find out the outcome based on morphological diagnosis. The detailed morphological assessment led to highlight the points that need to be reconsidered in diagnosing borderline neoplasms in ovary.

The main objective was to be very strict in reporting borderline neoplasms, as overdiagnosis and underdiagnosis are detrimental to the well-being of the patient.

METHODS

The study was a lab-based observational retrospective and prospective study where a dataset of borderline neoplasms in ovary reported at our laboratory was subjected to objective review. The study was approved by institutional ethical committee via letter number 1949/ethics/2023 (Ref code: XIV-PGTSC-IIA/P61). All the cases that were diagnosed as BT between 2021-2023 were retrieved from the record. All the slides were independently reviewed by two pathologists, morphometric analysis to confirm the maximum size of invasive front was performed and the patients were followed up for treatment provided, disease outcome, and current status. These findings were recorded in an Excel sheet. Primary diagnosis, review diagnosis and outcome were stringently compared according to the set WHO criteria for reporting BT. Observations were recorded where all these did not match up, and reasons for this discrepancy were investigated.

RESULTS

During 2 years, a total of 467 oophorectomy specimens were received. Of these, 27.40% (128/467) were reported as benign cysts and 72.60% (333/467) as ovarian neoplasms. Of all ovarian neoplasms 56.9% were epithelial (266/467), while the rest were reported as mesenchymal neoplasm (n=3), 6 as metastatic carcinomas, 13 cases were reported as Sex cord stromal tumour, and 51 as germ cell neoplasm (Table 1).

Table 1: Distribution of cases according to diagnosis in study population.

Diagnosis	Number	Percentage
Benign cyst	128/461	27.76
Follicular cyst	43/128	33.6
Simple inclusion cyst	21	16.40
Luteal cyst	53	41.40
Endometriotic cysts	11	8.60
Epithelial neoplasm	266/461	57.70
Serous	164	61.65
Mucinous	53	19.92
Endometroid	23	8.65
Clear cell	03	1.12
Brenner	01	0.37
Undifferentiated	22	8.27
Germ cell	51/461	11.06
Dysgerminoma	07	13.72
Yolk sac	03	5.88
Embryonal	01	1.96
Teratoma	36	70.59
Immature teratoma	00	00
Mixed germ cell tumor	04	7.84
Sex cord stromal	13/461	2.82
Granulosa cell tumor	07	53.85
Fibroma	06	46.15
Thecoma	00	00
Others	3/461	0.65
Mesenchymal neoplasm	03	100
Metastatic carcinoma	00	00

Among epithelial neoplasms, 146 were benign (54.88%: 146/266),13 belonged to the borderline category (4.88%:

13/266) and 107 were malignant (40.22%:107/266) (Figure 1).

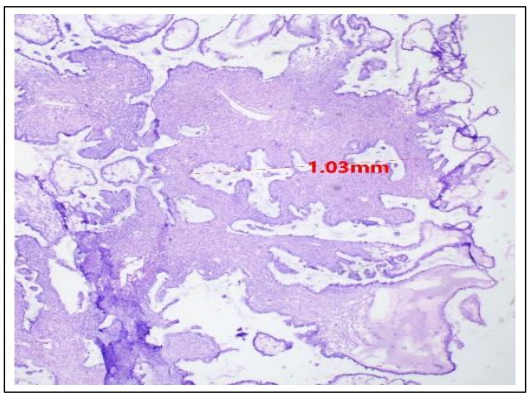

Figure 1: Section shows a serous papillary neoplasm displaying borderline features (H&E x40).

The incidence of borderline neoplasms was 4.88%, according to our data, with a mean age of diagnosis of 38.66 years (17-53 years). 10 of these cases were reported as Serous borderline neoplasm, 4/10 were bilateral. Two among these had papillary architecture (Figure 1). 2 cases were reported as mucinous borderline neoplasms and 1 case was signed as senoromucinous borderline neoplasms. The mean duration of follow-up was 18.2 months. We lost the follow up of 1/13 patients reported as Serous borderline neoplasm.

In all cases, the primary diagnosis was concurrent with the review diagnosis and morphometric analysis. These patients underwent surgery only.

Total 12 of these cases were available for follow-up and 10 women were apparently asymptomatic and had no complaints related to the female genital tract of lower abdominal pain or fullness. Two females complained i.e., 15.4% of abdominal discomfort. One soon after surgery and another after 1-2 months of surgery and both of them developed further disease. One was reported from our center and one from outside, both were mucinous-type tumors. On critical review we found that there was minimal nuclear atypia in both, there was no evidence of convincing stromal invasion except few irregular well-formed glands were seen infiltrating the stroma in one case. Both of these patients later presented abdominal metastases and malignant neoplasm in the opposite ovary.

Both were borderline mucinous tumours. One of them succumbed to disease 16 months after surgery, as per telephonic communication she had refused any further treatment due to personal issues. In the second case, the patient was under close follow-up and underwent radical surgery, where the diagnosis of well differentiated mucinous carcinoma was given after 20 months of the first surgery (Table 2).

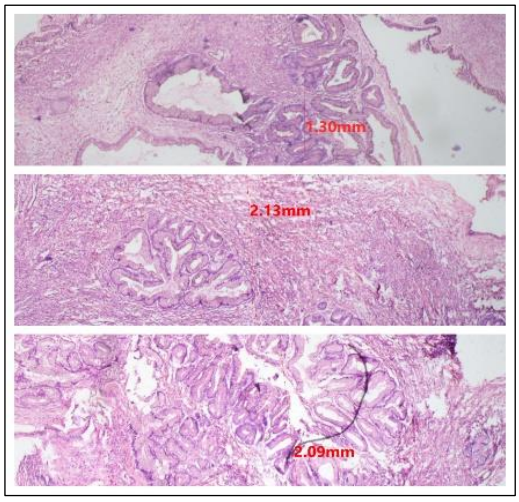

Figure 2: Section shows a mucinous borderline neoplasm with minimal nuclear atypia and few irregular glands identified in stroma. Morphometric overlay data also included in the images. (H&E x 40; measurements by calibrated MagVision ™ software).

Table 2: Details of cases diagnosed as borderline ovarian tumors.

Age (years)	Morphological diagnosis	Treatment given	Post operative lower abdominal pain	Review notes
25	Borderline mucinous tumor	Oophorectomy	Continuously symptomatic	Recurrence after 20 months
24	Serous borderline tumor	Salpingo-oophorectomy	Asymptomatic	
45	Borderline mucinous cystadenoma	Oophorectomy	Continuously symptomatic	Reoccurrence after 4 months.
26	Serous borderline tumor with microinvasion	TAH with BSO	Asymptomatic	Depth of invasion 2mm on morphometry
46	Serous borderline tumor	Oophorectomy	Asymptomatic	
17	Borderline seromucinous cystadenoma	Oophorectomy	Asymptomatic	
37	Serous borderline tumor	Oophorectomy	Asymptomatic	
37	Borderline mucinous tumor	Oophorectomy	Asymptomatic	
53	Borderline serous cystadenoma	TAH with BSO	Asymptomatic	

Continued.

Age (years)	Morphological diagnosis	Treatment given	Post operative lower abdominal pain	Review notes
28	Serous borderline tumor	Oophorectomy	Asymptomatic	
40	Serous papillary borderline tumor	TAH with BSO	Asymptomatic	
53	Borderline serous cystadenoma	TAH- BSO with omentectomy	Asymptomatic	
36	Bilateral serous papillary borderline tumor	TAH with BSO	Asymptomatic	

DISCUSSION

Borderline tumours have been reported to account for 10-15% of all ovarian epithelial neoplasms according to published Western literature.[1] In our study, the percentage prevalence of borderline tumors was 4.88% which is comparable to reported Indian datasets by multiple authors.[8,9] This may be due to geographical and cultural variation and increased prevalence of hypoestrogenic states and obesity in the Western world compared to the Indian population. Both are risk factors for ovarian cancer.[11,12]

The median age of borderline ovarian neoplasm in our study was 38 years (range: 17-53 years), which is lower than the published literature of 42 years.[2] As the Indian population tends to present at a younger age, fertility-sparing treatment is often considered for nulliparous females with FIGO stage I disease. However, managing invasive borderline neoplasms in nulliparous women can be challenging for obstetricians and surgical oncologists, due to the high risk of recurrence and the need to balance fertility preservation with the potential loss of follow-up in hospitals with high patient-to-low doctor ratios.[4]

Our research indicates that there was a recurrence rate of 15.4% (2 out of 13 cases) for borderline ovarian neoplasms and 66% (2 out of 3 cases) for borderline mucinous neoplasms. However, no recurrence was observed in serous borderline neoplasms. According to the literature, mucinous borderline neoplasms have a recurrence rate of 57.1% and serous borderline neoplasms have a recurrence rate of 42.8%.

Fitori et al in their study highlighted that mucinous borderline tumours tend to reoccur; they saw contralateral reoccurrence in one of their cases after 3 years. Mucinous borderline tumors are large ranging from 4 to 32 cm. Grossly, these are multilocular cystic masses filled with mucoid material. The thorough examination and careful sampling are crucial in the diagnosis of borderline ovarian tumours. At least one section per centimeter of the largest tumor diameter should be sampled to ensure accurate diagnosis and avoid misclassification. This is particularly important in cases with stromal invasion, as the extent of invasion can affect treatment decisions and patient outcomes. In general, attention to detail and adherence to established protocols are the key to ensuring the best possible outcomes for patients with borderline ovarian tumours.[6]

Borderline ovarian tumours are a challenging morphological diagnosis where stringent following of criteria is needed; they may be aided with digital tools such as morphometry and to avoid misinterpretation in few cases. The current audit highlights that post operative symptoms even minor like lower abdominal discomfort are important in females diagnosed as borderline neoplasm. Secondly, mucinous neoplasm is prone for reoccurrences. Metastasis from gastrointestinal tract has also been listed as a cause of recurrence in ovarian mucinous neoplasm. Immunohistochemistry to rule out the likely intestinal origin must be applied in all cases of ovarian neoplasm especially mucinous.[13]

In our cases, it was not applied. Retrospectively, we performed IHC on the available blocks in filing and tumour cells displayed PAX8 expression with faint focal CDX2 expression. Cytokeratin expression does provide much help in mucinous tumors in ovary as cytokeratin 20 is seen to be expressed in tumors of gastrointestinal origin and mucinous ovarian tumors.[13,14]

According to Sahraoui et al in borderline tumours especially mucinous microscopic examination reveals cysts lined with intestinal-like epithelium containing goblet cells. Nuclear atypia is generally mild to moderate, and microinvasion (<5mm in the greatest dimension) may be observed.[6] Sometimes cysts and mild atypia can also become a concern, as the fine line between borderline and malignant dims in this type of morphology. The variability in clinical behavior observed among borderline mucinous tumors highlights the necessity for precise histopathological examination to assess their aggressiveness and potential for progression. Hence, based on this audit, we recommend that in regions like ours where follow-up is a challenging task and morphometry is not every time possible, first immunohistochemistry must be performed to rule out metastatic lesion and even after applying the criteria of 5 mm invasion, these patients must be properly advised for high recurrent rates. This also highlights that interdisciplinary collaboration is of prime importance in these cases.

The short follow-up period was a limitation of this study. Data on the level of tumour markers of all patients were not compared.

CONCLUSION

Stringent and extensive follow-up studies must be carried out to separate mucinous BT from others as they behave differently and have greater chances of reoccurrence. Multidimensional approach, with histopathological review, IHC to rule out metastasis serving as a cornerstone for accurate diagnosis of ovarian borderline neoplasms, incorporating the minimum number of sections to be sampled, and the case to be reviewed by at least 2 pathologists, incorporating morphometry before signing out can also be added to the workup of these cases.

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