Frozen section as a guide in intra operative decision making in management of adnexal mass lesions

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Abstract
Ovarian tumours present with vague pelvic, abdominal and menstrual symptoms. Lack of histological diagnosis before hand with no definite evidence of malignancy intra operatively may put the surgeon at the cross roads, whether to proceed with a complete surgical staging or conservative approaches like a fertility sparing procedures or a simple ovariectomy. Frozen section done intra operatively in the above setting may help in differentiating benign and invasive ovarian tumours and help in proceeding with optimal surgical procedure. But the reliability of frozen is limited in borderline and mucinous ovarian tumours.

Keywords: Frozen section, Concordance, Discordance, Accuracy, Borderline tumours of ovary (BTO), Mucinous ovarian tumors.

Introduction

Ovarian tumors may present with vague pelvic, abdominal and menstrual symptoms. Pre-operative assessment is usually based on Trans Vaginal Ultrasound and serum markers CA 125, He 4. Ultrasonogram fails to confirm diagnostic suspicions even when applying the "pattern recognition" criteria to differentiate benign and malignant adnexal masses. Ca 125 lacks specificity, He 4 and Risk of Malignancy Index (RMI) enhances the specificity of CA 125. A preoperative definite diagnosis of an atypical adnexal mass is currently impossible to achieve with reasonable accuracy. Without a histological diagnosis before hand and no definite evidence of malignancy intra operatively may put the surgeon at cross roads, on whether to proceed with a complete surgical staging or conservative approaches like a fertility sparing procedures by simple ovariectomy. Frozen section done intra operatively may help in classifying tumours into benign, borderline and invasive ovarian tumours and help in deciding with optimal surgical procedure. Frozen section has overall high accuracy for the diagnosis of ovarian malignancy but its value in detecting BTOs is limited. In this article we come up with our experience in frozen section in our institution and possible ways of improving the accuracy of frozen section.

Patients and Methods

Patients diagnosed with ovarian tumours clinically and by imaging, with equivocal CA 125, without a pre-operative histopathological diagnosis of malignancy were included in the study. These patients underwent excision of adnexal lesions which were then subjected for frozen examination. The objective of this study is to assess the accuracy, reliability and limitations of frozen section in the diagnosis of adnexal mass lesions by comparing it with final histopathological diagnosis. The concordance and discordance of frozen section with final histopathological diagnosis of 46 adnexal mass lesions were studied. Sensitivity, specificity and accuracy rates were determined and results analysed.

Results

Totally 46 patients were included in the study, of which 17 patients were benign, 7 patients were borderline and 22 patients were malignant as per frozen section diagnosis (Table 1). Among the 17 patients diagnosed as benign by frozen section, 16 cases were confirmed to be benign by final histopathology and one turned out to be functional ovarian cyst. (Table 1)

Of the 7 borderline tumours, 4 patients had discordance with the final pathology. Among the four patients with discordance 2 were misinterpreted as benign and 2 patients diagnosed as BTO by frozen were ultimately malignant on final histopathology. Among the 22 malignant patients only 2 patients had discordance and the turned out to be benign on final histopathology. Overall accuracy rate of frozen was 84%. The sensitivity of frozen in diagnosing benign tumours was 100%, borderline was 40% and malignant tumours was 94%, specificity was 75%, 50% and 80% and accuracy rates 94%, 42% and 90% respectively (Table 2).

Discussion

Ovarian cancer accounts for 4% of cancers occurring in women. It accounts for most of the gynaecological cancer mortality next only to cancer cervix in India.[1] Majority of women with epithelial ovarian cancer have vague and nonspecific pelvic, abdominal and menstrual symptoms. Ovarian epithelial cancers must be differentiated from benign, borderline tumour of ovary (BTO) and functional cyst of ovaries.

Ultrasonographic signs of malignancy include a pelvic mass with areas of complexity and multiple echogenic patterns. An elevated CA 125 is not specific to ovarian cancer and is seen in diverse group of condition. The accepted cut off value is 35 U/dl. A number of benign gynaecological conditions such as endometriosis, fibroids, infections, and pelvic inflammatory disease may increase CA 125 levels.

Risk of malignancy Index (RMI) incorporates the menopausal status, an ultrasonic score, and the serum CA 125 level.[2] With a RMI score of more than 200, laparotomy and frozen section analysis should be done. For benign pathology treatment should be individualized, limited staging for BTO and full surgical staging for invasive ovarian cancers.

Borderline Ovarian Tumors: Borderline ovarian tumours are distinguished from ovarian carcinoma by the absence of stromal invasion. BTO have indolent natural history and are of low malignant potential. It is often said that even though BTOs don't have stromal invasion, cells from the primary tumour can be shed into the peritoneal cavity and eventually form serosal implants that involve bowel, omentum and upper abdomen. Similar to epithelial cancer, BTOsmay exhibit serous and mucinous features. Serous BTOs are more common and may be bilateral in 10 to 20% of patients. Mucinous BTOs are tend to be larger than serous counterparts, rarely bilateral and at times associated with pseudomyxoma peritonei. Pseudomyxoma peritonei may be associated with mucinous borderline tumors, mucinous ovarian carcinoma, appendiceal mucinous cystadenocarcinoma. Mucinous borderline tumors are characterized by multi loculated cystic masses, with smooth outer surfaces and areas of solid thickening on the inner surface. All the above features help only to a little extent in the diagnosis of borderline ovarian tumours intra operatively.

Borderline tumours with low malignant potential are distinguished from benign cystadenomas histologically by the presence of epithelial budding, multilayering of the epithelium, increased mitotic activity and nuclear atypia. They are distinguished from epithelial carcinomas by the absence of stromal invasion. Because absence of stromal invasion is a criterion for making diagnosis of BTOs, careful examination of tissue blocks is necessary to exclude a component of invasive carcinoma. Mucinous borderline tumours consists of tall, columnar, mucin secreting cells. Mucinous BTOs also lack stromal invasion and they are difficult to distinguish from their invasive mucinous carcinoma counterparts. Mucinous BTOs have fewer than four layers of stratified mucinous cells lack invasion whereas mucinous carcinomas demonsrate an infiltrative or expansile pattern of stromal involvement. This makes histological examination vital in the diagnosis of BTOs and to differentiate this from benign and malignant ovarian tumours. Histological diagnosis can be established either by frozen section or definitive histopathological examination. Frozen section diagnosis of BTO helps in intra operative decision making as younger patients with early stage borderline tumour who wish to preserve fertility, conservative surgery with preservation of uterus, the contralateral ovary and fallopian tube, and in some cases the ipsilateral ovary (i.e. cystectomy) may be appropriate treatment.

Thus frozen section study plays an important role as a guide in intra operative decision making in adnexal mass lesions. But the real question is how far frozen section can be relied upon in decision making. The diagnostic accuracy varied from 86 – 100%.[3] Approximately 20% of tumours diagnosed as borderline on frozen-section analysis prove to be carcinomas on review of the permanent section. The overall accuracy in our setting was 84%. The accuracy rates were more than 90% for benign and malignant lesions but accuracy rates drastically fell to 42 % for BTO.

Also as per other series the majority of the discordance was for mucinous and borderline tumors.[3] The diagnostic accuracy of frozen section in borderline ovarian tumours has been less well characterized with reported rates ranging from 56 to 89%.[4] A diagnosis of BTO cannot be made prior to surgery and histopathological examination. Intra operative decision regarding surgical management is thus based on frozen section. Benign tumour reported as BTO may result in unnecessary surgery also BTO reported as malignant may result in an unnecessary staging procedure.

Over a period of time a lot had been tried to improve the accuracy of frozen section in BTO. A combined preoperative assessment through serum markers and ultrasonographic features may potentially reduce the risk of under diagnosis of BTOs on frozen section while likely increasing the concomitant incidence of false-positive events.[5] The common explanation for decreased accuracy given is inadequate sampling. It is also said that mucinous tumors contains benign, borderline and malignant components in different areas in the same tumor. Adequate sampling of representative areas and proper communication with the pathologist may improve the results of frozen section.[6] The accuracy of frozen section in the diagnosis of BTOs are influenced by certain clinical and pathological features. Certain predictors of misdiagnosis are histology different from serous histology, tumour size more than 20 cm, and tumor confined to ovaries according to Houck et al. Brun et al. reported as significant predictive factors for FS misdiagnosis mucinous histology tumor size larger than 10 cm, a borderline component greater than 10%, and even the pathologist's experience.

Combined pre-operative assessment through ultrasound and tumour markers like CA 125, He 4 potentially reduce the risk of under diagnosis of BTOs on frozen section while concomitantly increasing the false positive events.[7]

From clinical perspective the important question is whether or not to abort the surgical procedure after a frozen diagnosis of BTO and wait for a definitive pathological diagnosis. But it is prudent to postpone the definitive surgical management of BTO until a final histopathology is available.[6] Postponement of surgical staging after definitive pathology results in increasing rate of reintervention, post-surgical tumour spread, delay in initiating adjuvant treatment and increased psychological stress in young women desiring fertility.

High Risk Borderline Ovarian Tumour: High risk BTOs are those which are likely to evolve in to invasive disease. Serum tumour markers like CA125, CA19-9, CEA are not useful in the diagnosis of high risk Borderline tumours. Pelvic ultrasonogram is an important tool for detection and assessment of ovarian tumours. Till date, no ultrasound criterion can identify high risk group of borderline ovarian tumours. Recent radiological studies have underlined the role of diffusion weighted MRI in differentiating benign, BTOs and ovarian cancer. Early tumour enhancement on dynamic contrast enhanced MRI images were helpful in differentiating these lesions. MRI findings correlated with the angiogenic status of the tumour ascertained by expression of VEGF receptors in the paraffin embedded specimen. Correlation of such radiohistologic findings may help in identification of high risk BTO pre operatively. Histologically invasive peritoneal implants and residual disease after surgery are two important factors associated with high risk BTOs. Other histological features which are controversial are micropapillary patterns in serous borderline ovarian tumour, intraepithelial carcinoma in mucinous lesions, stromal microinvasion in serous lesions, and use of cystectomy in mucinous borderline ovarian tumours.[8]

Table 1: Comparing Frozen section with final histopathology

S. No.	Type of Tumor	Total Number (Frozen section)	Concordance (With Final HPE)	Discordance (with Final HPE)
1	Benign	17	16	1
2	Borderline	7	3	4
3	Malignant	22	20	2

Table 2: Showing sensitivity, specificity and accuracy of frozen section in various ovarian tumors

S. No.	Type of Tumor	Sensitivity	Specificity	Accuracy
1	Benign	100 %	75 %	94 %
2	Borderline	40 %	50 %	42 %
3	Malignant	94 %	80 %	90 %

Conclusion

Frozen section is reliable in diagnosing benign and malignant ovarian tumours but not so in diagnosing borderline ovarian tumours. It is a guide to decide the extent of surgical management in benign and malignant tumours intra operatively. Surgeon has to keep in mind the possibility of invasive component when a diagnosis of borderline ovarian tumour is given by frozen section and it may be prudent to postpone the definitive procedure until final histopathology is available. Combining Ultrasound and tumour markers with frozen section have reduced under diagnosis by frozen section. Also after a diagnosis of BTO, high risk features like peritoneal implants and residual disease after surgery are to be noted by histopathological examination as this may evolve into invasive disease.

References

1. http://cancerindia.org.in/cp/index.php/know-about-cancer/statistics
2. Jacobs I, Oram D, Fairbanks J, 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.
3. da Silva RD[1], Souto LR, Matsushita Gde M, Matsushita Mde M., Diagnostic accuracy of frozen section tests for surgical diseases. *Rev Col Bras Cir.* 2011 May-Jun;38(3):149-54.
4. C. B. Tempfer, S. Polterauer, E.-K. Bentz, et al. "Accuracy of intraoperative frozen section analysis in borderline tumors of the ovary: a retrospective analysis of 96 cases and review of the literature," *Gynecologic Oncology,* vol. 107, no. 2, pp.248–252, 2007.
5. Salvatore Gizzo, Roberto Berretta et al., Borderline Ovarian Tumors and Diagnostic Dilemma of Intraoperative Diagnosis: Could Preoperative He4 Assay and ROMA Score Assessment Increase the Frozen Section Accuracy? A Multicenter Case-Control Study, *BioMed Research International,* Volume 2014. doi.org/10.1155/2014/803598
6. Clemens B. Tempfer et al., Accuracy of intraoperative frozen section analysis in borderline tumors of the ovary: A retrospective analysis of 96 cases and review of the literature, November 2007, Volume 107, Issue 2, pp.248–252.
7. Salvatore Gizzo, Roberto Berretta et al. Borderline Ovarian Tumors and Diagnostic Dilemma of Intraoperative Diagnosis: Could Preoperative He4 Assay and ROMA Score Assessment Increase the Frozen Section Accuracy? A Multicenter Case-Control Study, *Biomed Res Int.* 2014;2014:803598.
8. Philippe Morice, Catherine Uzan, Raffaele Fauvet, et al. Borderline ovarian tumour: pathological diagnostic dilemma and risk factors for invasive or lethal recurrence, Volume 13, No. 3, March 2012, e103–e115.