ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 02 | February - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

OVARIAN MASQUERADES: A COMPARATIVE STUDY OF FROZEN SECTION REPORTING OF OVARIAN MASSES WITH FINAL HISTOPATHOLOGICAL DIAGNOSIS AT A TERTIARY CANCER CENTRE: A TWO YEAR STUDY.

Pathology

Champaka G	Associate Professor of Pathology, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore – 560029, Karnataka, India.
Akkamahadevi S Patil*	Associate Professor of Pathology, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore – 560029, Karnataka, India.*Corresponding Author
Geeta V. Patil Okaly	Associate Professor of Pathology, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore – 560029, Karnataka, India.
Suma M N	Associate Professor of Pathology, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore – 560029, Karnataka, India.
Usha Amirtham	Associate Professor of Pathology, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore – 560029, Karnataka, India.
Premalata C S	Professor and HOD of Pathology, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore – 560029, Karnataka, India.

ABSTRACT

Introduction: Intraoperative assessment of ovarian neoplasms on Frozen section (FS) as epithelial and non-epithelial types is crucial for appropriate surgical management. Accurate categorization is important as treatment plan includes cystectomy for benign tumors, extensive staging procedures for ovarian carcinomas and oophorectomy or limited surgical staging for borderline tumors especially in younger patients to preserve fertility.

Objectives: To study the accuracy of ovarian FS interpretation with reference to final histopathological (HPE) diagnosis on paraffin embedded sections after analyzing by morphology and immunohistochemistry (IHC) wherever necessary.

Materials and Methods: A retrospective analysis of 170 cases of FS study on ovarian masses during the period of two years (2017, 2018) was done at a tertiary oncology center.

Results: Of the total 170 cases on frozen, 74 cases were benign, 27 cases borderline and 69 cases malignant. On final HPE 73 cases were benign, 20 cases borderline and 77 cases malignant neoplasms. The sensitivity and specificity were 95.89%, 95.87% in benign tumors, 80%, 92.66% in borderline and 88.3%, 98.92% in malignant tumors respectively. The positive and negative predictive values were 94.59%, 96.87% in benign lesions, 59.25%, 97.20% in borderline, 98.55%, and 91.08% in malignant neoplasms respectively.

Conclusions: In our study there was a good concordance between frozen and final histopathology in the diagnosis of benign and malignant ovarian neoplasms. Ovarian FS study is a reliable tool for intraoperative decision making regarding the extent of surgery.

KEYWORDS

Ovary, Frozen, Intraoperative.

INTRODUCTION:

Ovarian cancer is the sixth most common cancer in women with a high mortality rate. Estimation of serum markers and image analysis is mandatory for a preoperative diagnosis; however, it lacks specificity and sensitivity[1-4]. Ovarian epithelial tumors of mucinous and borderline categories in general have high false negative FS diagnosis, as heterogeneity in these tumors is well-known and tissue sampling on frozen sections is limited[5,6]. Intraoperative FS evaluation is crucial in determining the extent of surgery in benign, borderline and malignant neoplasms particularly in patients requiring fertility preservation[4]. In addition, the ovaries being a common site for metastasis (accounting for up to 15% of ovarian malignancies in Western countries) and categorizing ovarian mucinous neoplasms as primary or metastatic is of paramount importance[7,8]. Whenever possible, the frozen section diagnosis should be specific as for the favored primary tumor site, Mullerian or metastatic, especially in patients with a clinical history of or suspicion for another primary.

MATERIALS AND METHODS:

one hundred and seventy cases of ovarian frozen sections during the period of 2017 and 2018 were retrospectively analyzed at our institute. The FS diagnosis was compared with final HPE diagnosis to evaluate the accuracy, sensitivity, specificity and positive and negative predictive values. The specimens were grossly examined for size, colour, laterality and capsular integrity after noting the age and clinical findings. On cutting open the proportion of solid, papillary and cystic areas were identified and the contents noted. Imprint /scrape smears were taken from representative areas. Two to three bits for frozen analysis were taken routinely and additional bits in tumors showing variegated appearence and extensive necrosis. Tissue sections of 0.5 to 1mm thickness were freeze dried in a cryostat using optimal cutting temperature compound (OCT). 1-2 microns thick sections were taken at -20 degree, stained using toluidine blue and rapid Haematoxylin and Eosin (around 10 minutes for the entire procedure). The specimen was then placed in 10% buffered neutral formalin for routine processing. The results of frozen sections were compared with paraffin tissue sections.

RESULTS:

The epithelial neoplasms of serous and mucinous type were classified as benign, borderline and malignant. Mucinous neoplasms were further classified as primary or metastatic. The non-epithelial benign and malignant group of neoplasms included germ cell and sex cord stromal tumors. The non-neoplastic entities included inflammatory lesions, endometriosis and those masses which had undergone torsion without discernible lining.

Of the 170 cases of ovarian neoplasms sent for frozen, 74 cases (43.52%) were reported as benign which composed of 56 cases of neoplastic and 18 cases of non-neoplastic lesions like torsion, inflammation and endometriosis (Table1). There were 27 cases (15.88%) of borderline and 69 cases (40.58%) of malignant ovarian neoplasms.

Final histopathology diagnosis on paraffin sections revealed 73 cases (42.94%) of benign neoplasms and non-neoplastic lesions. Of the non-neoplastic lesions three were endometriosis, and the remaining 9 showed torsion with inflammation including two cases of granulomatous inflammation (Table 1). The borderline category included 20 cases (11.76%) of serous and mucinous neoplasms (Table 2). Total malignant neoplasms reported on final histopathology was 77(45.29%) (Table 3).

Table I : Benign Neoplasms/ non neoplastic lesions

	FROZEN	HISTOPATHOLOGY
Serous	34	36
Mucinous	08	11
Teratoma	08	08
Sex cord Stromal tumor	06	06
Endometriosis	02	03
Torsion and Inflammatory	16	9
Total	74	73

Table -2 : Borderline neoplasms

	FROZEN	Histopathology
Serous	13	12
Mucinous	14	8
Total	27	20

Table 3 : Malignant Neoplasms

	Frozen	Histopathology
Serous and non-mucinous	25	30
Mucinous	19	23
Mullerian carcinosarcoma	0	02
Germ cell tumors	09	10
Granulosa cell tumor	09	11
Metastatic melanoma	0	01
Poorly differentiated malignant tumors	07	0
Total	69	77

The sensitivity and specificity were 95.89%, 95.87% in benign ovarian neoplasms, 80%, 92.66% in borderline neoplasms, 88.3%, 98.92% in malignant neoplasms respectively. The positive and negative predictive values were 94.59%, 96.87% in benign neoplasms/lesions, 59.25%, 97.20% in borderline neoplasms, 98.55%, 91.08% in malignant ovarian neoplasms respectively (Table4).

Table 4: Results

Type	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Benign neoplasms and lesions	95.89%	95.87%	94.59%	96.87%
Borderline neoplasms	80%	92.66%	59.25%	97.20%
Malignant neoplasms	88.31%	98.92%	98.55%	91.08%

DISCUSSION:

According to WHO, ovarian neoplasms are classified as surface epithelial neoplasms (65%), germ cell (15%), sex cord stromal (10%), metastasis (5%) and miscellaneous based on most probable tissue of origin. Surface epithelial tumors which form the bulk are categorized by cell type as serous, mucinous, endometrioid etc. which are further classified as benign, borderline and malignant neoplasms. Most malignant tumors (90%) are of surface epithelial type[9]. Annual incidence rates of ovarian cancer range from <5/1,00,000 women in The Gambia, Brazil, Thailand, Algeria and India to >13/1,00,000 in the United Kingdom, United states, Germany and Scandinavia[2].

Surgery (total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, retroperitoneal lymph node dissection and peritoneal biopsies) is the primary modality of treatment in ovarian carcinoma. However, in young women who wish to conceive, fertility sparing surgery is preferred. Hence accurate categorization is needed on frozen section to choose appropriate surgery. Borderline ovarian neoplasms may pose diagnostic difficulties when invasion is questionable on frozen sections due to limited sampling. Hence the term with atleast borderline features should be used. Similarly, mucinous ovarian neoplasms have to be categorized as primary or metastatic as treatment protocol for both differs. However, a definitive diagnosis may not always be possible. If the tumor is bilateral and there is a suspicion of metastasis on frozen section the surgeon has to be informed and the diagnosis deferred to paraffin section study.

In the present study 170 cases of ovarian masses sent for frozen at our institute between 2017 and 2018 were analyzed retrospectively. There were 74 cases of benign lesions /neoplasms, 27 borderline and 69 cases of malignant neoplasms on FS which included both primary and metastatic. The age range was 17 -75 years with a median age of 46 years.

Of the benign tumors on frozen, surface epithelial tumors of the serous type were the most common with 34 cases followed by eight cases of benign mucinous neoplasms. One case of benign mucinous neoplasm was associated with Brenner tumor. The non-epithelial benign neoplasms included eight cases of mature teratoma and six cases of sex cord stromal tumors, five of which were fibrothecoma and one sclerosing stromal tumor. The benign lesions included two cases of endometriosis, two granulomatous inflammation and 14 cases of ovarian cyst which showed only inflammation and hemorrhage.

On final histopathology, there were 36 benign serous neoplasms, 11 mucinous neoplasms, eight mature teratoma and six sex cord stromal tumors of predominantly fibrothecoma group, three endometriosis, two tuberculosis and seven showed features of torsion and inflammation. Thirty-three cases of benign serous neoplasm on frozen were concordant on final histopathology.

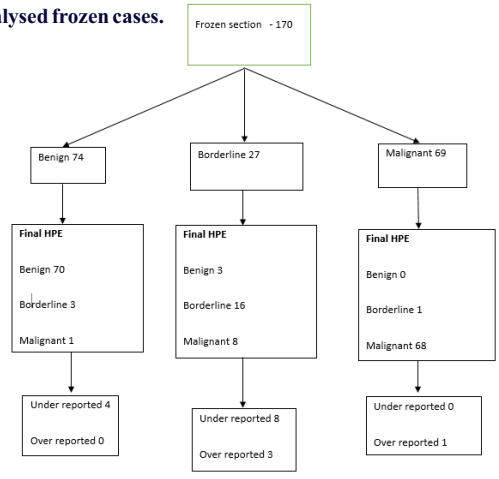
With adequate sampling three benign mucinous tumors on frozen turned out to be borderline on final HPE. One benign serous neoplasm showed a mural nodule with malignant features. Two cases of torsion on frozen showed features of serous neoplasm on final histopathology which were still considered concordant.

Sixteen of twenty-seven borderline neoplasms (59.25%) of serous and mucinous type (Table 2) were concordant on final histopathology which included nine and seven cases each of serous and mucinous neoplasms of borderline category. Of the 11 discordant cases reported on frozen section as borderline two cases turned out to be benign serous neoplasm, one benign mucinous neoplasm, two serous carcinoma, two mucinous carcinoma, three metastatic tumours and one clear cell adenocarcinoma on final histopathology. The highest discrepancy (underdiagnosis and overdiagnosis) in this category was due to inadequate sampling. Most studies and WHO 2014 advocate that >10% borderline histology within a cystadenoma or cystadenofibroma qualifies as borderline ovarian tumors (BOT). In contrast < 10% borderline histology are designated "cystadenoma/ fibroma with focal epithelial proliferation. [9-12]. Limited sampling on FS is the main reason for errors in reporting borderline tumors.

Sixty eight of sixty-nine (98.55%) malignant tumours diagnosed on FS were concordant on final histopathology. One malignant mucinous tumor on frozen showed borderline features on final HPE. Serous and other non-mucinous carcinoma accounted for 25 cases on FS. Final HPE revealed 30 cases of this subtype which included 8 cases upgraded from borderline tumors. 0f the 23 mucinous adenocarcinomas reported,19 were primary and 4 metastatic. In metastatic cases the primary sites included low grade appendiceal mucinous neoplasm (one case), stomach (two cases) and colon (one case).

The 7 poorly differentiated malignant neoplasms reported on FS turned out to be Mullerian carcinosarcoma (2) Granulosa cell tumor (2) high grade serous carcinoma (1), metastatic melanoma (1) and endometrioid variant of yolk sac tumor (1) on final HPE and IHC. All 9 cases of malignant germ cell neoplasms and 9 cases of Granulosa cell tumor reported on frozen was concordant on final HPE.

Analysed frozen cases.



Of the 16 cases of bilateral ovarian neoplasms, 11 were of serous type (7 serous carcinoma,1 benign serous and 2 borderline serous neoplasm) and the remaining 5 were metastatic (4 mucinous and 1 melanoma) described previously.

Being a tertiary cancer centre, malignant ovarian neoplasms formed the major bulk of frozen, with a sensitivity and specificity of 88.31% and 98.92% respectively.

The three pearls of intraoperative consultation are the patient's clinical history, macroscopic examination, and histomorphologic interpretation. The most important gross parameters of ovarian epithelial tumors are size, laterality (unilateral versus bilateral), the appearance of capsular status and cut surface (cystic versus solid). Malignant ovarian epithelial tumors usually are heterogeneous on cut surface with solid areas, at least partially, and often show a soft, fleshy areas with necrosis and hemorrhage[3].

Ovarian metastases with mucinous differentiation arise most frequently from appendiceal primary tumors, in particular low grade appendiceal mucinous neoplasms (LAMN). Consequently, most treatment guidelines recommend routine appendectomy in cases of MBT or mucinous carcinoma even if the vermiform appendix appears unremarkable intraoperatively. The second most common mimics of mucinous borderline tumors (MBT) are metastatic mucinous carcinomas of pancreaticobiliary origin[13].

In our study the sensitivity and specificity were 95.89%, 95.87% in benign tumors 80%, 92.66% in borderline and 88.3%, 98.92% in malignant tumors respectively. Similarly in a study by Atif Ali Hashmi the sensitivity and specificity was 100 % and 97% for benign, 83% and 99% for borderline and 96% and 100% for malignant tumors.[4-16] In a study by F. Mohammed et al the sensitivity for FS diagnosis was 100% for benign, 72.7% for borderline and 88.4% for malignant category, whereas the specificity was 97.3%, 97.9%, and 100.0%, respectively.[16] In our study the sensitivity in benign tumors was 95.89% which is in par with other studies of high sensitivity ranging from 92.8% - 100% (Ivanov et al 2005; Ilvan et al 2005; Suprasert et al 2008, Arshad et al 2018). In our study the sensitivity and specificity in borderline neoplasms was 80% and 92.66 % respectively. Similarly, a few other studies also reported low sensitivity values for borderline tumor (Ivanov et al 2005; Ilvan et al 2005; Suprasert et al 2008; Tempfer et al 2007) and Arshad et al 76.2% and 88.7%[17-21]. In our study malignant neoplasms showed a sensitivity and specificity of 88.3% and 98.92% respectively similar to a recent Cochrane Database publication that reviewed 38 retrospective studies reported that the average sensitivity in detecting malignant tumor by FS was 90.0% with most studies typically reporting a range of 71% to 100%, and average specificity ranging from 96% to 100% (Ratnavelu et al 2016)[14]. In a study by Tempfer et al, the sensitivity of detecting malignant ovarian tumor was 69.2% and the specificity was 100%, reflecting that FS examination was highly specific in diagnosing ovarian malignancy although the sensitivity was slightly lower as compared to other studies (Tempfer et al 2007; Oz et al., 2014)[20].

Frozen section reporting and studies revealed that the accuracy of frozen section reporting for ovarian tumors varied among different institutions and the sensitivity and specificity was lowest for borderline neoplasms.

CONCLUSION:

An accurate intraoperative frozen section evaluation of ovarian neoplasms is crucial in making surgical decisions, more so in young patients to preserve fertility. Evaluating borderline neoplasms still pose a diagnostic challenge to practicing pathologists. The clinician should be aware of limitations of borderline tumors in frozen section reporting. Relevant clinical details, representative tumor sampling is essential in making an accurate frozen section diagnosis of ovarian neoplasms.

Acknowledgment

All the authors are deeply thankful to the technical support from histopathology department of our institute.

Conflict of interest: None

Financial support: None

REFERENCES

1) Kurman, R.J., Ellenson, L. H., & Ronnett, B.M. (2019). *Blaustein's pathology of the female genital tract*. (seventh ed.) Newyork: Springer.
2) Sukumaran,R., Somanathan,T., Mathews, A., Kattor,J., Sambasivan,S.,& Nair ,R.P.,(2014). Role of frozen section in intraoperative assessment of ovarian masses: a tertiary oncology center experience. *Indian J Surg Oncol*, 5(2): 99-103.
3) Buza, N., (2019) Frozen Section Diagnosis of Ovarian Epithelial Tumors: Diagnostic Pearls and Pitfalls. *Arch Pathol Lab Med*, 143(1): 47-64.
4) Subbian, A., Devi, U.K., Bafna, U.D.,(2013). Accuracy rate of frozen section studies in ovarian cancers: a regional cancer institute experience. *Indian J Cancer*, 50(4): 302-5.
5) Geza, A. C. S., (2002). Intraoperative consultation in gynecologic pathology. *Semin Diagn Pathol,* 19(4): 237-54.
6) Houck, K., Nikrui, N., & Duska, L., et al. (2000). Borderline tumors of the ovary: correlation of frozen and permanent histopathologic diagnosis. *Obstet Gynecol*, 95(6 Pt 1): 839-43.
7) Ulbright,T.M., Roth,L.M., & Stehman FB.(1984). Secondary ovarian neoplasia. A clinicopathologic study of 35 cases. *Cancer*, 53(5): 1164-74.
8) De Waal, Y.R., Thomas, C.M., Oei, A.L., Sweep, F.C., & Massuger, L.F.,(2009). Secondary ovarian malignancies: frequency, origin, and characteristics. *Int J Gynecol Cancer,* 19(7): 1160-5.
9) Robert, J., Kurman, M.L., Carcangiu, C., Simon Herrington, & Robert H.Young.(2014). WHO Classification of tumors of Female Reproductive organsfourth ed. Lyon: *IARC*.
10) Tinelli, R., Tinelli, A., Tinelli, F.G., Cicinelli, E., & Malvasi, A., (2006).Conservative surgery for borderline ovarian tumors: a review. *Gynecol Oncol,* 100(1): 185-91.
11) Silverberg, S.G., Bell, D.A., & Kurman, R.J., et al. (2004). Borderline ovarian tumors: key points and workshop summary. *Hum Pathol*, 35(8): 910-7.
12) Bell, D.A., Longacre, T.A., & Prat, J., et al. (2004).Serous borderline (low malignant potential, atypical proliferative) ovarian tumors: workshop perspectives. *Hum Pathol*, 35(8): 934-48.
13) Seidman, J.D., Kurman, R.J., & Ronnett, B.M.,(2003). Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis. *Am J Surg Pathol*, 27(7): 985-93.
14) Ratnavelu, N.D., Brown, A.P., & Mallett, S., et al. (2016).Intraoperative frozen section analysis for the diagnosis of early stage ovarian cancer in suspicious pelvic masses. *Cochrane Database Syst Re,* 3: CD010360.
15) Hashmi, A.A., Naz, S., & Edhi, M.M., et al.(2016). Accuracy of intraoperative frozen section for the evaluation of ovarian neoplasms: an institutional experience. *World J Surg Oncol*, 14: 91.
16) Mohammed, A.B., Ahuja, V.K., & Farghaly, H., (2014). Role of frozen section in the intraoperative management of ovarian masses. *Middle East Fertil Soc J,* 20: 97-101.
17) Suprasert, P., Khunamornpong, S., Phusong, A., Settekorn, J., & Siriaungkul, S. (2008). Accuracy of intra-operative frozen sections in the diagnosis of ovarian masses. *Asian Pac J Cancer* Prev, 9:737–40.
18) Ivanov, S., Ivanov, S., & Khadzhiolov, N. (2005). Ovarian tumours –accuracy of frozen section diagnosis. *Akusherstvo i ginekologiia*, *44*(1), 11–13.
19) Ilvan, S., Ramazanoglu, R., & Ulker Akyildiz, E., et al. (2005). The accuracy of frozen section (intraoperative consultation) in the diagnosis of ovarian masses. *Gynecol Oncol*, 97:395–9.
20) Tempfer, C.B., Polterauer, S., Bentz, E.K., Reinthaller, A.,& Hefler, L.A. (2007). Accuracy of intraoperative frozen section analysis in borderline tumors of the ovary:A retrospective analysis of 96 cases and review of the literature. *Gynecol Oncol*, 107:248–52.
21) Md Arshad, N.Z., Beng Kwang, Ng., Md Paiman, N.A., Abdullah Mahdy, Z., & Mohd Noor, R.,(2018). Intra-Operative Frozen Sections for Ovarian Tumors – A Tertiary Center Experience. *Asian Pac J Cancer Prev*,19(1):213-218. doi: 10.22034/ APJCP. 2018.19. 1.213.