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Original Article

Correlation of Biomarkers and Frozen Section Diagnosis with Paraffin Histopathological Diagnosis in Suspected Ovarian Cancer

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ABSTRACT

Introduction: Ovarian cancers pose diagnostic dilemma and is problematic for decision making for the gynecological oncologist as well as the pathologist. The use of intra-operative frozen section can aid significantly in decision making and assist in choosing the correct operative path once a mass lesion of ovaries is discovered.

Materials and Methods: Over a two-year period, 50 cases of Suspected Ovarian cancers were examined by intra-operative frozen section as well as followed up with histopathology in paraffin sections. Results were categorized in two strata—benign and malignant.

Results: A comparison between frozen-section diagnosis and findings on paraffin section showed that the sensitivity of frozen section in diagnosis of malignant lesions is 97.14%, with specificity 93.33%, positive predictive value 97.14% and negative predictive value 93.33%. Among 50 cases, one case was reported as false positive and one was reported as false negative.

Conclusion: Intra-operative frozen section is a highly sensitive and specific modality for the diagnosis of malignant lesions of the ovary.

Keywords: Biomarkers, ovarian cancer, frozen diagnosis

INTRODUCTION

Ovarian cancers pose diagnostic dilemma and is problematic for decision-making for the gynecological oncologist, as many times histology is not possible prior to surgery. Patients may be asymptomatic (incidental finding on clinical or radiological examination), or present with nonspecific symptoms, such as abdominal distension, pain, or bowel dysfunction. In many centers, the use of serum CA 125, in combination with the age/menopausal status and ultrasound features of complex adnexal masses, is used to calculate the Risk of Malignancy Index (RMI). Values of greater than 200 are used as an indicator of referral to a gynecological oncology center where optimal surgical staging can be performed if required.[1]

Although disseminated malignancy will be obvious at surgery, early-stage disease [International Federation of Gynecology and Obstetrics (FIGO) stage 1 or 2] may not. A diagnosis can be made on cytology, but tissue biopsy is generally required for a definitive diagnosis. When faced intra-operatively with an apparent early-stage ovarian cancer, the surgeon will have two management

options: to manage each case as a potential cancer and therefore perform an optimal staging procedure or to manage the case as benign without staging.[2] The former option will result in unnecessary surgery in about 30% of cases, with its potential significant morbidity, and the latter will result in suboptimal staging in cancer cases requiring either a second surgical staging procedure or empirical chemotherapy. This two-stage approach results in increased morbidity and risks for the patient, as well as added pressure on theater time and hospital resources.[3]

The use of intra-operative rapid/frozen section (FS) reporting of tissue taken at surgery is attractive, in that a diagnosis may be achieved intra-operatively. Such a diagnosis can inform the surgeon not only of the malignant nature of the ovarian lesion, but also of the possibility that it may represent a metastasis.[4]

METHODS

Two-year period was used to analyze the frozen diagnosis of the Suspected Ovarian cancers. The specimen, once removed, is transported by a hospital porter direct to the histology laboratory and handed over to the laboratory staff. The pathologist on duty inspects the specimen and, after describing it, routinely takes up to two pieces of tissue for FS analysis. These are then processed and, after hand staining, are given to the duty pathologist for reporting. The result is then telephoned to the surgeon involved in the operating theater. The data collected include the absolute numbers reported and the analysis of sensitivity and specificity. Likelihood ratios and post-test probability are also calculated. The FS service is audited every 6 months.

RESULTS

During the period between June 2017 and the end of May 2019, 50 ovarian lesions were sent for routine intra-operative FS reporting in line with the agreed protocol. Of these, five were histologically benign on final paraffin section [Figures 1 and 2], and the rest were malignant [Figures 3 and 4].

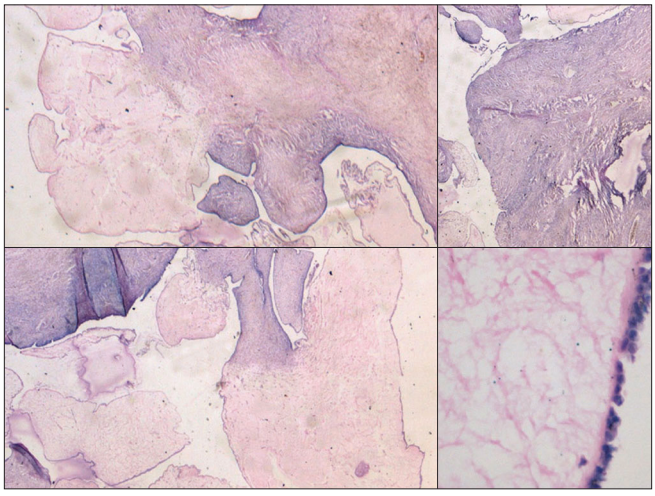

Figure 1: Showing photomicrograph of serous cystadenofibroma.

The overall sensitivity for the 2-year period in detecting malignancy was 97.14% with a specificity of 93.33%. The pre-test probability of an ovarian tumor being borderline[5] or malignant was 46%, as per prevalence of ovarian tumors sent for histopathology in this hospital in the previous year. When an FS was reported as positive (Tables 1–3), the post-test probability of an ovarian tumor being borderline or malignant was 97.14%. Conversely, when an FS was reported as negative, the post-test probability of malignancy was only 2.5%.

DISCUSSION

The clinical diagnosis of ovarian malignancy is problematic, given the nonspecific nature of presentation and the difficulty in obtaining a histological diagnosis prior to definitive treatment. The correct management approach depends on accurate diagnosis and staging. In stage 1 disease, this is even more essential, as accurate staging is required to ensure that stage 1 disease is not occult higher stage disease, with 18% being uplifted from FIGO stage 1 to stage 2 (or higher) with accurate surgical and pathological staging.[6]

A second surgical procedure for staging usually arises as a result of inadequate preoperative assessment of complex adnexal masses followed by inadequate surgery. The introduction of

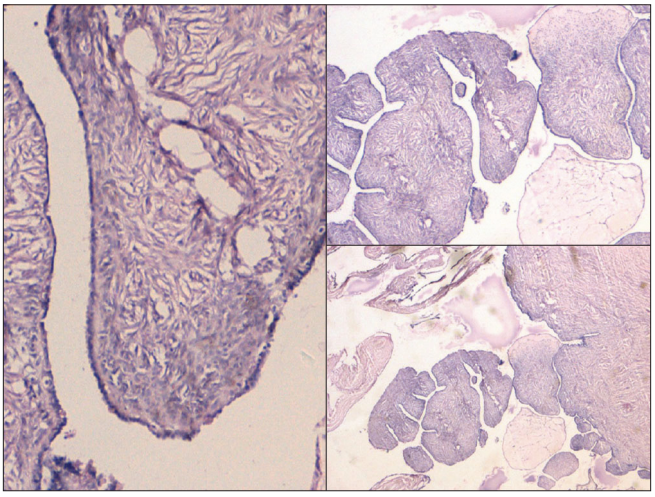

Figure 2: Showing photomicrograph of serous cystadenofibroma.

Table 1: Serous lesions (n = 35)

	PS benign	PS malignant	Total
FS benign	9	1	10
FS malignant	1	24	25
Total	10	25	35

FS, frozen section report; PS, final paraffin section report

Table 2: Overall frozen section reporting profile (n = 50)

	PS benign	PS malignant	Total
FS benign	14	1	15
FS malignant	1	34	35
Total	15	35	50
Sensitivity in detecting malignancy	34/35	0.9714	
Specificity	14/15	0.9333	
Positive predictive value	34/35	0.9714	
Negative predictive value	14/15	0.9333	
Likelihood ratio positive	14.57143	95% CI 14.57137–14.57148	
Post test probability (positive)	0.9254		
Likelihood ratio negative	0.03061		
Post-test probability (negative)	0.02540		

FS, frozen section report; PS, final paraffin section report

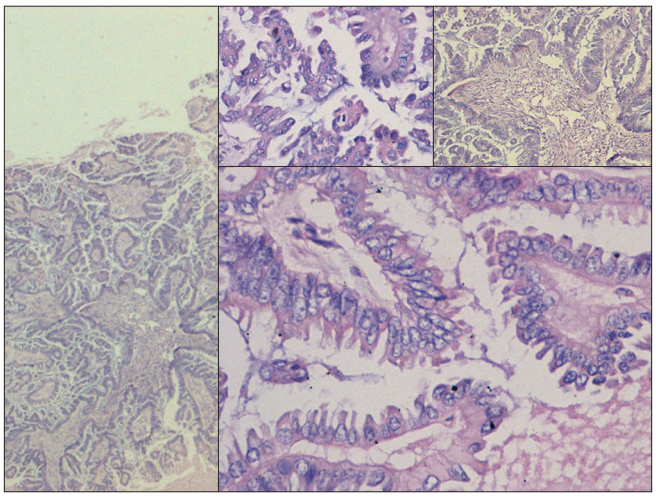

Figure 3: Showing photomicrograph of serous cystadenocarcinoma.

the RMI score in our network has resulted in 90% of ovarian cancers being referred to NGOC prior to treatment, making the need for a second surgical procedure uncommon.[7]

The use of an FS service for immediate intra-operative reporting is highly attractive for the gynecological oncology surgeon. It allows for a single optimal operative staging procedure where indicated and, likewise, for a non-staging procedure if not required. In the United Kingdom, the use of routine FS reporting is comparatively uncommon for ovarian lesions and is usually restricted to certain other organs (e.g. parathyroid gland identification, margins of skin malignancy excision, lymph node status in oncology surgery).[7] *Ad hoc*

Table 3: Mucinous lesions (n = 15)

	PS benign	PS malignant	Total
FS benign	5	0	5
FS malignant	0	10	10

FS, frozen section report; PS, final paraffin section report

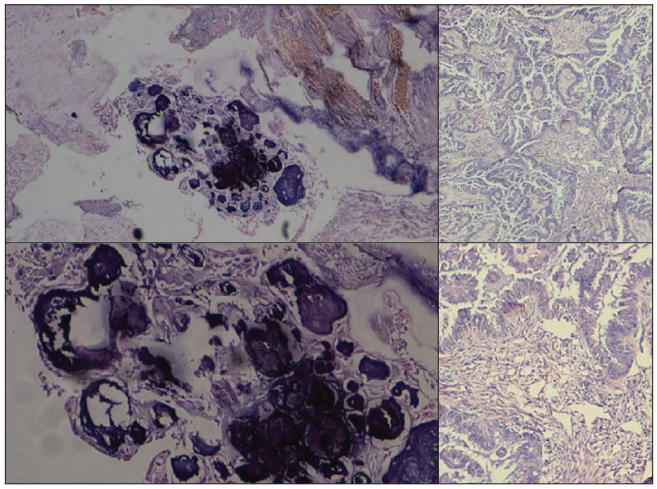

Figure 4: Showing photomicrograph of psammoma bodies serous cystadenocarcinoma.

FSs are also sometimes performed when a surgeon identifies an unexpected operative finding. The common theme is that an FS is only of value if it will actually alter the procedure that the surgeon performs at the time of the surgery. In the setting of possible ovarian cancer surgery, this is certainly the case. The taking of fresh tissue also allows for the development of a tissue bank, which we are also undertaking.

The setting up and running of an FS service can be an extra strain on an already busy cellular pathology laboratory. It requires staff (technical and medical) to be available and also a fully functional cryostat, and the unpredictability of the work can also disrupt the usual running of the laboratory. Our department runs a duty pathologist system and, as such, the duty pathologist reports any urgent work (especially biopsies and cytology), and so is available for any FSs that arrive. Our laboratory is also directly adjacent to the consultant offices, so no time is lost in finding the duty pathologist. We accept that not all departments may be as fortunate and may require some additional resources to operate such a service.

The literature, predominantly from the USA, is clear about the usefulness of FS reporting in gynecological surgery. A 2005 literature review identified 582 potentially relevant articles, but 557 had to be excluded because of a lack of relevance, or a lack of data. Ultimately, only 14 articles were found that allowed data analysis, covering 3659 women.[8] The breakdown of cases by category was as follows: benign, 71.6%; borderline, 5.5%; malignant, 22.9%. Our study has an

overall breakdown of 54.2%, 9.9% and 35.9%, respectively (based on the final histological diagnosis). This difference most probably reflects the referral pattern, in that the FS service for NGOC is for a cancer referral centre, and does not reflect a general hospital setting, where a lower percentage of malignant cases would be expected.

All histology reporting has an error rate, and FS reporting is no exception. Paraffin section histology reports are often taken as the "gold standard." The Royal College of Pathologists does not set an "acceptable error rate," but the literature suggests a diagnostic error rate of between 5% and 6%,[9] but this depends very much on the body system concerned and the definition of "error." The FS service described in this article has an error rate (if error is defined pathologically as benign to malignant, and vice versa, as diagnostic category changes) of 5% overall, which seems to be acceptable for what is an "interim" report.

In this study, this most often occurred in serous and mucinous tumors, but these two groups comprised 52.3% of the lesions subjected to FS overall. For reasons of timeliness, we routinely use two tissue blocks—any more would slow down the turnaround time to the surgeon, although arguably it would increase the accuracy of the FS report. Our data on the two most common primary ovarian epithelial tumors (serous and mucinous)[10] indicate that the false negative rate for serous tumors overall is 4% and that nil for mucinous tumors.

Ultimately, any FS service must be of clinical use. The surgeon must have confidence in the intra-operative report and must believe it to be sufficiently accurate to allow him or her to base appropriate surgical action upon it. The surgeon must also accept that there is an inherent error rate, and that this may vary by the type and size of the tumor. Regular dialog between the surgical and pathology teams is vital. Women presenting with a pelvic mass, and hence possible ovarian cancer, and an RMI greater than 200 have a 75% risk of being diagnosed with ovarian cancer.[11] The majority of these women will undergo laparotomy, with a probability of ovarian cancer being 75% purely based on their RMI. Obvious benign lesions (e.g. endometriosis or a simple cyst) or obvious ovarian malignancy observed intra-operatively do not require FS analysis. Excluding these cases, intra-operative FS analysis for an ovarian mass is only requested in suspected apparent early-stage ovarian cancers, and in those cases in which doubt exists as to whether the mass is malignant, or where spread from an extra-ovarian primary is suspected. For this reason, the RMI predicted probability of ovarian cancer cannot be applied directly as a pre-test probability of an FS. The recalculated pre-test probability of an ovarian tumor being malignant in this group prior to FS analysis is 46% (with disease among all cases). However, when an FS is reported as borderline or malignant, the post-test probability of an ovarian tumor being borderline or malignant increases from 46% to 97.4%. Conversely, if the FS is reported as benign, the post-test probability of an ovarian tumor being borderline or malignant falls from 46% to 2.5%. This high accuracy of FS allows gynecological oncologists to make appropriate intra-operative decisions in 95% of cases, and therefore prevent unnecessary morbidity of surgical staging in the vast majority of benign cases.

CONCLUSIONS

The use of an FS reporting is especially important for surface epithelial tumors where the radiology is not so corroborative and intra-operative ovarian tumor diagnosis can be highly effective and of great benefit to patient and surgeon alike. In our opinion, the data presented make a strong case for this type of service to be better adopted and used more widely in the diagnosis of ovarian tumors in gynecological oncology surgery.

Conflicts of interest

None of the authors have any interests to disclose.

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