

Comparison and Analyses of Intraoperative Consultation and Paraffin Section Responses of Ovarian Lesions

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Cite this article as: Kimiloğlu E, Yanık İ, Gündoğar Ö, Bektaş S, Salman S, Comparison and Analyses of Intraoperative Consultation and Paraffin Section Responses of Ovarian Lesions. J Acad Res Med 2020;10(3):237-40

ABSTRACT

Objective: We aimed to analyze the sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) and the accuracy of frozen section (FS) method and compare the concordance of FS responses and paraffin section (PS) (final histopathological diagnoses) results of the ovarian mass operations in our hospital.

Methods: We retrospectively reviewed the cases of ovarian lesions operated between March 2008 and June 2018 in which FS was requested. In total 205 cases were found and the results were compared. The FS responses and PS results were classified as benign, borderline and malignant. Seventeen cases weren't responded in FS (and left to be diagnosed in PS) and they were left out of the study.

Results: According to the analyses; the sensitivity of benign, borderline and malignant tumors were 100%, 83%, 95%, and the specificity were 98%, 99%, 98%, respectively. The PPV of borderline and malignant tumors were 91%, 92% and the NPV were 98%, 99% respectively. Furthermore; both of their accuracy was 97%. The concordance between the methods was assessed with Kappa test and found as 94% ($p < 0.001$).

Conclusion: In our study we showed that even if all of the FS responses didn't match with its PS, FS has a very high rate of consistency. FS is a way to help the surgeon during the operation. However, it must not be forgotten that this method has its own pitfalls and limitations.

Keywords: Ovary, frozen section, paraffin section, diagnosis accuracy

INTRODUCTION

Intraoperative consultation, or more commonly referred as frozen section (FS), plays a crucial part in pathology. FS is especially important during ovarian mass surgeries since radiological imaging and biochemical markers are limited in determining these lesions' malignancy. Intraoperative consultations are performed to help operating surgeons decide the surgical approach.

This study intended to evaluate the concordance of FS responses and paraffin section (PS) (final histopathological diagnoses) results of ovarian neoplasm surgeries conducted in our hospital and to determine the sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV), and accuracy of FS in categorizing ovarian lesions as benign, borderline, and malignant.

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Received Date: 12.09.2020 **Accepted Date:** 14.10.2020

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METHODS

Subjects

The study retrospectively reviewed cases of ovarian neoplasms operated in our hospital between March 2008 and June 2018 in which intraoperative pathology consultation (FS) were done. A total of 205 cases were included. The reports of the pathologists, who were working in our department during this time, were reviewed, and the FS responses and final PS results were grouped accordingly. PS results were grouped as benign (both neoplastic and non-neoplastic lesions), borderline, and malignant (including metastasis cases), and FS responses were grouped as benign, borderline (including "at least borderline" responses), and malignant. Juvenile and adult granulosa cell tumors, which are considered "low potential of malignancy," were included in the borderline group (1).

Seventeen cases with no definitive FS responses were excluded from this study as they have no equivalent PS results.

The study was approved by the Taksim Training and Research Hospital, Clinic Research Ethics Committee (approval number: 89, date: 19.09.2018).

Statistical Analysis

Data were presented as frequency and percentage, and concordance between the methods was evaluated using the Kappa test. Sensitivity, specificity, PPV, NPV, accuracy, and 95% confidence interval were determined. The limit of significance was set at $p < 0.05$ and bidirectional. Analyses were conducted using the NCSS 10 program (Kaysville, UT, USA).

RESULTS

During FS, 127 cases were identified as benign, 22 borderline, and 39 malignant. Of the cases, 17 had a definitive response in FS for varying reasons, and they were left to be determined in PS and, therefore, excluded from this study.

PS results showed that there were 126 (67%) benign cases: 62 (33%) non-neoplastic and 64 (34%) neoplastic. Furthermore, 24 (13%) cases were reported as borderline. Finally, 38 cases were diagnosed as malignant, of which 33 (16%) were primary ovarian tumors and 7 (4%) metastases (Table 1).

Of the 17 cases that were left to be determined in PS, 12 were benign, 3 borderline, and 2 malignant.

The PS and FS responses were compared numerically (Table 2), and 1 of the 127 benign cases in FS was later reported as borderline, 2 of the 22 borderline cases were later reported as malignant, and 3 of the 39 malignant cases were later diagnosed as borderline.

In this study, the mean age of all 188 cases was 49.5 years. When all cases were reviewed, 182 of 188 cases, for which a FS response was given, were compatible with the final paraffin diagnoses, and the outcome showed a consistency of 96.8%.

According to statistical analyses (Table 3), the sensitivities of FS responses of benign, borderline, and malignant tumors were 100%, 83%, and 95%, and the specificity results were 98%, 99%, and 98%, respectively. The PPVs of borderline and malignant tumors were 91% and 92%, and NPVs were 98% and 99%, respectively. Also, both tumors have an accuracy of 97%. The concordance between the methods was evaluated using the Kappa test and was $94\% \pm 0.03\%$ ($p < 0.001$).

DISCUSSION

Intraoperative pathology consultation (or FS) is an essential method that must be done meticulously since it helps surgeons perform optimal operations for patients. The FS method preserves its significance because of non-specific biomarkers, which also frequently result in false positive or false negative results, and limited preoperative radiological imaging in ovarian neoplasm adequacy. Overdiagnosis during FS will extend the operation time, which may increase mortality and morbidity,

Table 1. Numerical distribution of cases

| | | | |
|------------|-----------------|------------|-----------|
| Benign | Non-neoplastic | 62 (33%) | 126 (67%) |
| | Neoplastic | 64 (34%) | |
| Borderline | - | - | 24 (13%) |
| Malignant | Primary ovarian | 32 (17%) | 38 (20%) |
| | Metastases | 6 (3%) | |
| Total | | 188 (100%) | |

Table 2. Numerical comparison between paraffin and intraoperative consultation result

| | | Paraffin results | | | Total |
|-------------------------------------|------------|------------------|------------|-----------|-------|
| | | Benign | Borderline | Malignant | |
| Intraoperative consultation results | Benign | 126 | 1 | 0 | 127 |
| | Borderline | 0 | 20 | 2 | 22 |
| | Malignant | 0 | 3 | 36 | 39 |
| Total | | 126 | 24 | 38 | 188 |

Table 3. Statistical analyses of cases classified as benign, borderline, and malignant

| | Benign | Borderline | Malignant |
|----------------------|---------------|------------------|------------------|
| Sensitivity (95% GA) | 1 (0.97-1) | 0.83 (0.63-0.95) | 0.95 (0.82-0.99) |
| Specificity (95% GA) | 0.98 (0.91-1) | 0.99 (0.96-1) | 0.98 (0.94-1) |
| PPV (95% GA) | 0.99 (0.95-1) | 0.91 (0.71-0.98) | 0.92 (0.80-0.97) |
| NPV (95% GA) | 1 (0.92-1) | 0.98 (0.94-0.99) | 0.99 (0.95-1) |
| Accuracy (95% GA) | 0.99 (0.97-1) | 0.97 (0.93-0.99) | 0.97 (0.94-0.99) |

PPV: positive predictive value, NPV: negative predictive value

whereas underdiagnosis may require reoperation or cause tumor to spread (2).

Cases that were inconsistent with PS were reviewed, and it was found that errors might have occurred in some steps. The intraoperative consultation process consists of some crucial parts, including proper macroscopic examination and appropriate sampling. Errors in these parts could be avoided by proper training and experience. Tissue freezing can also result in frozen/freezing artifacts, which might cause the cells to look different than in formalin-fixed tissue samples, thus completely altering the diagnoses. Another important step is the staining part, and errors here might cause the nuclei to appear more hyperchromatic than they are. After meticulously performing all these steps, the pathologists should provide a result in the shortest possible time.

In our study, the group classified as benign contained both non-neoplastic and neoplastic lesions. Endometriosis, follicle cysts, corpus luteum cysts, and abscesses were considered non-neoplastic, whereas cystadenomas, cystadenofibromas, mature cystic teratomas, fibromas, thecomas, and fibrothecomas were neoplastic. During FS, the pathologists did not provide a result (left it to be decided in PS) for some of these benign lesions, such as fibromas/thecomas/fibrothecomas.

Of the 127 cases, which were considered benign during intraoperative consultation, only one did not correlate with the final PS report. During consultation, the case appeared "benign" on FS slides and was thought to be a sex-cord stromal tumor. After 24 hours of formalin fixation, more samples were taken. All the PS slides were evaluated both morphologically and immunohistochemically. The final diagnosis was "adult granulosa cell tumor," which is considered "low malignant potential," and in our study, it is classified as borderline tumors.

The correlation in the benign group was 99.2%. Similar to our study, other studies also have high sensitivity to benign lesions: Sukumaran et al. (2) reported 99.2%, Bige et al. (3) 99.2%, and Arshad et al. (5) 95.6% (2-6).

Borderline tumors make up close to 15%-20% of all ovarian malignancies (7). Borderline epithelial tumors and some sex-cord-stromal tumors (which are considered low/unknown malignant potential tumors like adult/juvenile granulosa cell tumors) were included in the borderline group in our study. The borderline group had the lowest concordance and sensitivity rate at 90.9% and 83%, respectively. Similar sensitivity results were reported in

other studies: 88.46% (3), 77.8% (4) and 76.2% (5), thus supporting our findings.

During intraoperative consultations, 2 of 22 border lesions were later categorized as malignant in PS. These tumors were large, and only a limited amount of sampling was done from the areas most suspicious for invasion. No evidence of invasion was found in the frozen slides; however, suspicion of malignancy remained. Therefore, they were reported as "at least borderline" during intraoperative consultation. More samplings were performed from macroscopically detected suspicious thickening of the lesion wall and from the papillary appearing areas after the 24 hours formalin fixation. Routine staining limited the number of invasive areas identified, and therefore, these tumors were later reported as malignant during PS.

The remaining 20 cases were compatible. The two cases, which the pathologists classified FS as "at least borderline" may be statistically seen as an error. However, the surgeons knew the possibility of them being malignant during the operation, and they proceeded accordingly. Since sampling problems during FS for borderline tumors are widely known, the term "at least borderline" as a response is supported by other authors (8).

Tempfer et al. (9) collected data from four studies (including their own) and evaluated borderline tumors during FS. Results showed that consistency between FS and PS was observed in 62.8% of the cases. According to them, because of this high ratio of underdiagnosis/overdiagnosis (37.2%), when FS is classified as borderline, surgeons should not take any further action during the operation and wait for PS reports. It is also suggested that for larger lesions (>5 cm), after a thorough macroscopic evaluation, multiple samples might be used to answer FS or intraoperative consultation might not be done at all (9).

An additional observation showed that subspecialization of pathologists in gynecologic pathology yielded better results (9). For example, Bige et al. (3) presented two sets of data from gynecologic and non-gynecologic pathologists and found that percentages of sensitivity, specificity, PPV and NPV were higher in gynecologic pathologists, especially in the borderline group. According to Açikalin et al. (4), gross examination conducted by gynecologic pathologists during FS is an important factor to increase FS accuracy. This factor might be one of the limitations of our study because our department has no subspecialized pathologists.

Other reasons that borderline tumors are challenging to assess during FS include their heterogeneous component and size. Only a limited amount of sampling can be done in FS; however, after fixation, more lesions can be sampled, and this may very well change the diagnosis (2,6,10).

In the malignant group, there were two cases of primary ovarian tumors and metastases. In 36 of the 39 malignant cases, the FS responses and PS results were consistent. However, the remaining three cases were later reported as borderline lesions because the cells that were considered invasive were actually pseudoinvasions and the nuclei appeared more hyperchromatic because of staining and improper sectioning (such as section thickness).

The concordance rate and sensitivity of the malignant group were 92.3% and 95%, respectively. Açikalin et al. (4) and Bige et al. (3) had sensitivities of 95.6% and 95%, respectively, which are similar to our study. However, Sukumaran et al. (2) had a slightly lower sensitivity (82.95%), and Takemoto et al. (10) had slightly higher data (99.2%).

According to statistical findings, a high consistency was found between these methods (Kappa 0.94, $p < 0.001$). The benign lesion group had the highest sensitivity and accuracy rates (100% and 99%, respectively), whereas the borderline group had the highest specificity (99%).

CONCLUSION

Although the coherency between FS and PS is not 100%, it is still high, and that is why FS still plays a crucial part in pathology practice. Considering these findings, surgeons must not forget that FS might be limited and have pitfalls; therefore, they should plan their operations accordingly.

Ethics Committee Approval: The study was approved by the Taksim Training and Research Hospital, Clinic Research Ethics Committee (approval number: 89, date: 19.09.2018).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.K., Design - İ.Y., Supervision - E.K., S.S., Resources - E.K., S.B., S.S., Materials - S.S., Data Collection and/or Processing - İ.Y., Ö.G., Analysis and/or Interpretation - İ.Y., Ö.G., Literature Search - S.B., Writing Manuscript - İ.Y., Ö.G., Critical Review - E.K., S.B.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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