

Peer Review File

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Reviewer A

Comment 1: The offered article described the results of the diagnostic accuracy of intraoperative consultation (IOC) for the ovarian borderline tumors. The new finding was not found in the offered article. Usually, the analysis of IOC for ovarian borderline tumors shall be done on the various types (endometriosis, serous, mucinous and clear cell) respectively.

Reply 1: we regret the Reviewer A's opinion but disagree because there are few works investigating this specific issue and there are in different settings, than are difficult to compare with. Clear cell borderline tumor and endometrioid (don't endometriosis) borderline tumor are quite rare, together account for less than 1% of BOT. This explains what we do not have any case of them.

Changes in the text: none.

Reviewer B

The paper evaluates the performance of intraoperative consultation in a rather large number of ovarian borderline epithelial tumors. The study results are similar to those previously reported.

Recommendations:

1. The manuscript should be checked for typographical errors. English editing is also recommended.

Reply 1. We send the manuscript to a professional editing service. Then, we expect to achieve a good and readable manuscript.

2. In the methods section, it is helpful to the readers, who are not statistician experts, to understand the meaning of the accuracy terms (or how they are calculated) if the authors explain them in this section. It is quite confusing when "false negative" frozen section diagnosis would represent both over- and under-diagnosis compared to final diagnosis.

Reply 2. We agree and add a short section with a reference to the readers can understand these concepts. Also, we add a sentence about the importance of false negatives and positives in the introduction section.

Changes in the manuscript: page 6, lines 27 to 31. Page 7-8 lines 17-33.

3. In this study, there is no mention regarding the cases with deferred intraoperative diagnosis. The authors should describe how they considered or classified this type of results.

Reply 3. None case with IOC was deferred. We state this in the results section. Deferral rate between laboratories varies widely, from 0.05% in large centers (Arch Pathol Lab Med. 2008;132(1):29-36) to near 5% in small laboratories (Arch Pathol Lab Med. 1996;120(12):1087-1093). We work in a large third care national center, with well-trained gynecopathologist and onco-pathologists. Maybe this can explain the absence of deferral.

Changes in the manuscript: page 9 line 3.

4. Although the study was aimed only to evaluate the accuracy of intraoperative frozen section, it is useful to the reader if the authors could provide more information that can be applied to clinical practice, particularly the analysis of factors associated with diagnostic discordance and the causes of discordance (e.g. sampling, interpretation, etc).

Reply 4: this information is in the tables and we added a sentence about this at the end of the introduction section. Also, in the discussion section we analysis of factors associated with diagnostic discordance are already stated in the text (page 11-12, lines 17-30). We think that adding more information, the manuscript would be redundant.

Changes in the text: page 9-10, lines 23-30.

5. From data in Table 1, a comparison between frozen section diagnosis and final diagnosis should be made in another 3x3 table (benign / borderline / malignant x benign / borderline / malignant). This will help the reader to appreciate the accuracy value in Table 2 more easily.

Reply 5. We absolutely agree. We added a new table (Table 2) and rename the rest of tables in the text and tables section.

Changes in the manuscript: page 20 line 4.

6. In the result section, it is useful if the authors describe the consequence of over-/under-diagnosis here rather than mentioning it in the discussion, which is not very easy to follow.

Reply 6. We agree and add this information in the results section.

Changes in the text: page 9-10, lines 23-30.

7. It is useful if the authors provide the histologic type distribution of tumors/lesions in this series (e.g. serous: benign / borderline / low-grade CA, mucinous: benign / borderline / low-grade CA, etc). The histologic type distribution of tumors will allow the reader to appreciate the tumor type that has a high proportion for diagnostic discordance (e.g. mucinous type is most common for discordance due to the histotype factor, not due to the high frequency of mucinous tumor in this institution).

Reply 7. We agree, but we considered unnecessary to add so much data. Overall discrepancies are already described in table 6.

Changes in the text: none.

8. It is useful if the authors provide the reason for diagnostic discordance in Table 5. The reason for diagnostic discordance may be provided as an additional column in Table 5.

Reply 8. Reviewer had reason. We added the column in the table 6 (before table 5).

Changes in the text: page 21 and 22

9. In Table 5, the diagnosis “intraepithelial carcinoma” represents a variant of borderline tumor. It is not clear that this should be considered as a case of diagnostic discordance. In addition, the histologic type of intraepithelial carcinoma should be clearly stated (e.g. mucinous or endometrioid).

Reply 9. We agree, and as reviewer stated, this entity is controversial, then, in absence of clear evidence of behavior, we retain this diagnosis as discrepant one. We added the histologic subtype in the table 6 (before table 5).

Changes in the text: Page 23.

10. In Line 179, the authors mention the diagnostic discrepancy between serous borderline tumor/CA and endometrioid CA (high-grade). It is quite difficult to imagine how high-grade endometrioid carcinoma (with predomination of solid architecture and marked nuclear atypia) could be confused as serous BT/low-grade serous CA in frozen section. The authors may need to clarify this.

Reply 10. Page 11-12, lines 25-30. We are discussing the differential diagnosis between serous tumors and endometrioid carcinoma, not between serous BT and endometrioid carcinoma specifically, and even we describe here the reasons of such discrepancy and there is also a reference.

Changes in the text: none.

11. In this study, 27% of patients with borderline tumor in frozen section diagnosis turned out to have malignancy in the final diagnosis (Line 191). However, the patients were not undertreated because of the similar management between borderline tumor and CA. It sounds like that underdiagnosis does not have any impact in the authors’ setting. Could the authors explain the

lack of cases with fertility-sparing surgery whether this is because of patient age group in this study (lack of young women) or the tendency for extensive surgery in the institution.

Reply 11. We agree with the reviewer. The reasons of absence of fertility-sparing surgery are that our patients are not so young and the median age of the first pregnancy in our country is 21 years (<http://www.fao.org/3/a-as211e.pdf>). We added this information in the manuscript.

Changes in the manuscript: page 12, lines 45-49.

12. In conclusion section (“It is essential to account the characteristics of the disease and the experience of the personnel in charge of this type of analysis”), the authors did not evaluate the association between diagnostic discordance and level of pathologists’ experience. This conclusion is not based on the study result. It is also not very clear how the study results could help the clinician to select the cases that will get better accuracy of intraoperative diagnosis.

Reply 12. We agree with the reviewer. We re-write the conclusion.

Changes in the manuscript: page 14. Lines 3-6.

Reviewer C

Changes will be highlighted in lila in the manuscript.

Although the results do not add anything new to the literature, this is a well-executed study. Methodology should be reported as retrospective cohort study as this is not a cross sectional study.

Reply: We agree.

Changes in the text: page 3 line 5 and page 7 line 2.

Please use the term teaching hospital instead of school hospital.

Reply: we agree.

Changes in the text: page 11 line 6.

Please include these two studies either to introduction or discussion.

Reply: we agree. We read and added the references in the discussion section and re-organize the references according to the Journal style.

Changes in the text: page 11 line 9 and 21.

Basaran D, Salman MC, Calis P, Ozek A, Ozgul N, Usubutun A, Yuce K. Diagnostic accuracy of intraoperative consultation (frozen section) in borderline ovarian tumours and factors associated with misdiagnosis. J Obstet Gynaecol. 2014, 34(5):429-434.

Basaran D, Salman MC, Boyraz G, Selcuk I, Usubutun A, Ozgul N, Yuce K. Accuracy of intraoperative frozen section in the evaluation of patients with adnexal mass: retrospective analysis of 748 cases with multivariate regression analysis. *Pathol Oncol Res.* 2015;21(1):113-8.

Reviewer D

Changes will be highlighted in blue in the text.

The authors aimed to evaluate the diagnostic accuracy of intraoperative consultation (IOC) for the borderline ovarian tumors (BT) diagnosis. In this paper, the authors have analyzed the diagnostic accuracy of IOC for the BT diagnosis retrospectively. The methods of this study are appropriate and well described. The conclusions were drawn adequately supported by the data shown.

However, as the author stated in the paper, there are serious limitations of the study, including the similarity of the study design to the previous studies and the similarity of the results. One of their observations is that the most considerable discrepancies between IOC and the final report were in the mucinous tumors (benign, carcinomas, or metastatic), which is consistent with the literature and does not add to the existing knowledge about this subject.

As the author emphasized, the main strength of this paper is that it is also the only work (as far as they know) that reports this type of analysis in a specific population of Mexico and the large number of patients were analyzed in the study population. However, some points need to be added or revised before this paper can be considered for publication.

Here, I present recommendations of major revisions. I strongly recommend professional English proofreading before submission. Here's some sentences need to be corrected:

Reply general: we sent the manuscript to a professional English editing service.

1. Page 4 Line 50

Background. Borderline Ovarian tumors (BT) needs to be recognized in the surgery room by intraoperative consultation (IOC) to guide surgical treatment, but (however,) the diagnosis is often imprecise.

Reply: we make the suggested change.

Changes in the text: page 3, line 3.

2. Page 9 Line 135

(In spite) of observing that the same percentage of BT was diagnosed in the IOC and the final report, ~.

Reply: we make the suggested change.

Changes in the text: page 9, line 4.

3. Page 9 Line 150

This sentence is not clear to be understood. Please rewrite and clarify what you mean: “The diagnoses of false positives were broken down (?) during the transoperative period, where we evidenced that the mucinous metastatic disease, as well as the mucinous adenocarcinomas of the ovary, were the main discordances (Table 5).”

Reply: we make the suggested change.

Changes in the text: page 9, line 19-22.

4. Page 9 Line 165

On the contrary, its value is lower when it is sought to diagnose a BT by ruling out a carcinoma (LR + 5.05), (it is) because the morphological characteristics of the borderline tumor (BT) and the carcinoma are identical and ruling out invasion of the stroma depends on the experience and the sampling performed by the pathologist (1).

Reply: we make the suggested change.

Changes in the text: page 11, line 13-14.

5. Page 11 Line 185

Overtreatment or inadequate treatment was performed in 1.1% of the patients (, who were) those who had a BT report in the transoperative period and underwent staging surgery ~.

Reply: we make the suggested change.

Changes in the text: page 12, line 32.

6. Page 11 Line 188

This sentence is not clear to be understood. Please rewrite and clarify what you mean: “There was subtreatment or incomplete treatment in patients with false negatives (5.1%) that during the transoperative study was reported as a benign tumor (79.4%) or metastatic tumor (5%) and in the definitive one it was a BT.

Reply: we make the suggested change.

Changes in the text: page 12, lines 34-37.

7. Page 11 Line 200

Currently, the findings by ultrasound or tomography such as the presence of septa, vascularity, index values of resistance and pulsatility and velocimetry have been reported, but have not been useful (12).

Reply: we make the suggested change.

Changes in the text: page 13, lines 50-52