Author's response to reviews

**Title:** Immunohistochemical profiling of benign, low malignant potential and low grade serous epithelial ovarian tumors

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**Author's response to reviews:** see over
Please find included the modifications we have brought to the manuscript in order to address the reviewer comments. Only one of the three referees asked for revisions

1. The terminology of “low-grade” and “G1 tumor” should be further defined. In the title, “low-grade” is used but in the text, “G1” is widely used. If they are the same, please just use “low-grade” through out this manuscript to avoid the confusion.

We modified the text so that all reference to G1 are replaced by ‘low grade’

2. In the Abstract, under Background, the statement “The molecular relationship between tumors of …remains unclear” should be modified. In fact, the relationship among borderline tumors, low-grade and high-grade serous tumors has been well characterized by several research groups including clinicopathological characterization, molecular genetic studies, gene expression arrays, SNP arrays, array CGH, SAGE… etc. It may be appropriate to modify the sentence as “Although the relationship…. has been well delineated, the expression of specific markers on those tumors has yet to be demonstrated”. The same is true for the first paragraph in the Discussion section.

We modified the manuscript as followed.
Abstract : Although the molecular characteristics of serous BOV, LMP and low grade TOV tumors has been initiated, definitive markers to distinguish between these tumor types have not been defined.
Conclusion : Only a few studies focus have focused on the molecular characterizing serous BOV, LMP and low grade TOV tumors, but the biological markers distinguishing between these three classes of tumors remains to be defined.

3. In the Abstract, under Conclusion, “comprehensive” should be better deleted as this study in not totally comprehensive.

The modification was made

4. In the Background, first paragraph, tubal origin of pelvic serous carcinoma should be discussed in addition of OSE and inclusion cysts as there is ample evidence to support that. Dr. Crum’s papers should be cited.

We modified the manuscript as followed
The majority of these tumors are derived from ovarian surface epithelial cells, from epithelial inclusion cysts confined in the stroma or from the epithelium of the fallopian
tube.
We have also cited the appropriate manuscript.

5. In the Background, Does “invasive (TOV)” indicate low-grade or high-grade tumor? The statement “LMP tumors account for 20% of malignant tumors…” should be modified as the data to support the argument are not updated. Also in the Background, the classification of TOV into well-, moderately- and poorly-differentiated tumors should be modified. There are several publications to support the two-tiered classification (LG vs. HG). Drs. Malpica’s and Shih’s papers can be considered to be included.

The sentence ‘LMP tumors account for 20% of malignant tumors and show a pluristratified proliferation of the epithelium’ was modified into ‘LMP tumors show a pluristratified proliferation of the epithelium’ in order to address the referee comment.

We modified the background section as followed and we added the references from Shih and Malpica.

According to the FIGO criteria, EOCs are graded according to degree of tumor differentiation: LMPs (referred to as grade 0, G0) while TOVs are separated in well (grade 1, G1, low grade), moderately (grade 2, G2), and poorly differentiated tumors (grade 3, G3). However, several papers now support a two-tiered classification that separate invasive tumors into low (G1) and high (G2 and G3) grades.

6. The potential use of Trail immunoreactivity in distinguishing non-invasive vs. invasive implants should be discussed as this is the difficult area in diagnostic pathology.

Our results do not support a role for Trail in distinguishing non-invasive vs invasive implants, and thus we have not modified the manuscript. We do comment however on p21, where statistical analysis does support further investigations.

7. The potential edge artifact of immunohistochemistry in cyst epithelium should be discussed. This artifact is common in cyst epithelium in TMA.

We modified the Method section by adding the following sentence to address the referee comment: Peripheral regions of the cores were not scored to eliminate edge effects.

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