Reviewer's report

Title: Loss-of-heterozygosity on chromosome 19q in early-stage serous ovarian cancer is associated with recurrent disease

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Reviewer: Patricia Tonin

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This study describes genomic alterations associated with recurrent disease in ovarian serous carcinomas in early stage disease that are grouped according to tumor grade. Results are presented suggesting that loss of heterozygosity of a region on chromosome 19q in early stage disease might be associated with recurrent disease. Results are also presented suggesting that p53 aberrations may also be linked to this association. The begins with a cohort of 51 cases but due to quality of DNA the analyses was performed on a subset of 37 cases. Comparative analyses involve assessing loss of heterozygosity, copy number gain and copy number loss of genotyping results derived from parraffin embedded tissue samples.

Major Compulsory Revisions:

The results are interesting but the rationale for study design requires further explanation to fully appreciate the research findings:

1) There is a valid argument that comparative analyses should contain results from common histological types of epithelial ovarian carcinomas as described in the Introduction section unless the purpose of the study is to define differences in the various subtypes of ovarian cancer. However, it is questionable if the present study should have compared low/moderate-grade serous tumors with high-grade serous given recent molecular genetic findings that low-grade and high-grade carcinomas may represent distinct diseases. Progression free survival may also differ from patients with low grade versus high-grade disease. Therefore, the authors should rationalize the comparison of low-grade versus high-grade serous carcinomas.

2) It is also likely that medium grade (G2) serous tumor resemble grade 3 not grade 1 serous tumors at the molecular genetic level. If this is the case, then it would be important to rationalize why the low and medium grade cohorts were combined for data analysis rather than the medium- and high-grade groups (or treatment of each grade as a independent group though sample numbers would be limiting for such a comparative analysis).

3) Another issue involves the association of 19q anomaly with TP53 mutation status. It is well established that p53 immunostaining would more readily detect products derived from missense mutation than null mutations. It has also been demonstrated that about while TP53 mutations are nearly ubiquitous in
high-grade serous tumors, about 60% would stain positive in immunohistochemistry analyses as they contain missense mutation and the remainder would be null mutations. Low-grade serous tumors do not always harbor TP53 mutations but do harbor mutations in KRAS/BRAF, that latter of which rarely appear in high-grade serous carcinomas (thus supporting notion that low and high grade serous ovarian carcinomas develop through distinct but possibility unrelated pathways). Statements about correlations with TP53 mutation status should be clarified in this study, given that authors are including data from previous studies and it appears that TP53 status was assessed by immunohistochemistry alone.

4) Third paragraph in the Discussion section states that the ‘findings of recurrent gain and loss were in agreement with other studies on ovarian cancer in all stages” and the authors rationalize suggest that it ‘indicates that for this disease, the early stage pattern resembles that of disease in general, and that adjusting for the copy number analysis for aberrant average ploidy does not significantly alter the regions with observed recurrent gain and loss”. However, there was no discussion nor comparison of data with published groups. Also are the authors comparing genomic anomalies described for similar histotypes or tumor grade?

Minor Essential Revisions:

1) clarify in the abstracts that the genotyping results and analyses were derived from a cohort 37 cases not 51 cases.
2) Also clarify the study cohorts based on grade and stage of disease (Table 2) for recurrent and non-recurrent cases.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests