Reviewer's report

Title: Intratumoral heterogeneity in a minority of ovarian low-grade serous carcinomas

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Reviewer: Patricia Tonin

Reviewer's report:

This study describes mutational spectrum of specific genes known mutated in low-grade serous ovarian carcinomas (LGSC) in multiple samples derived at different time points in the disease. The study includes samples from 11 patients. A mutational screen was performed using a commercially available assay that detects specific mutations (mutational hotspots) in known cancer associated genes, which include KRAS and BRAF – genes mutated in a fraction of LGSC. Samples derived from primary and recurrent disease were investigated. Based on the presence of mutation and percentage of cells mutated the authors conclude that with the exception of one sample, mutations observed in primary tissues were also present in tissues derived from recurrent disease. The authors suggest that this information could inform treatment strategies where specific mutated genes are concerned.

The results are interesting and provide insight into maintenance of a mutational phenotype in LGSC during disease progression. This disease is very rare in comparison to other more common subtypes of ovarian cancer, such as high-grade serous ovarian carcinomas (HGSCs). Moreover, the mutational spectrum and disease course differ considerably from HGSCs. The results of the study are unique and would be of interest to both the basic and clinical ovarian cancer research community.

Major compulsory changes:

1) The number of cases studied (n=11) is very small. Although the authors acknowledge that this study is limited by sample size, largely due to the paucity of cases and rarity of disease, the data analysis should reflect this fact. At best, this is a case study of a very small number of cases as reflected in the presentation of results. Of the 11 cases examined, mutations were found among the 5 cases and so follow-up of additional samples could only be performed with these 5 cases. Moreover, there was only sufficient samples from 2 of the 5 cases to assess mutational stability over time and from 3 (other) of 5 cases to assess mutational stability over space and time. So it is somewhat misleading to interpret results and present as percentages (examples, Page 9, line 25; Page 13, line 2). This is particularly evident when relating results to independently published work as in the Discussion section (second paragraph) when the authors relate their findings to frequencies observed in other reports. Moreover, the authors should qualify their observation that a “trend for increased mean
overall survival in study patients with a MAPK pathway mutation compared to patients with wildtype status" given sample size (last sentence in second paragraph of Discussion section).

Minor Essential Changes

2) Methods Section: Clarify the number of genes/mutation-types screened in the analysis. Mention is made that targeted hot spot panel of 46 cancer-associated genes were screened in the Discussion section but the targets are not provided. The Ion Torrent AmpliSeq Cancer Hotspot Panel Version 1 was used but this study information is not readily assessable (I was only able to assess version 2).

3) Discussion section (Page 13): The first paragraph of the this section specific reference is made to number of mutations observed in HGSC and clear cell carcinoma in light of the few mutations observed in LGSC. But a targeted panel was used in LGSC in the present study. Was this also the case with HGSC and CC study? Is this a valid comparison or generalization?

Discretionary Changes:

4) It found it interesting that the one case (LGSC 10) which was “unstable in both space and time” differed from the other cases with respect to late stage at disease diagnosis, stage IV rather than stage III, and treatment where radiation was used unlike any of the other cases. The authors should comment on the implications (if any) of these facts with respect to mutational spectrum.

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

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests