Reviewer’s report

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

Version: 3
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Reviewer:Hal Hirte

Reviewer’s report:

This is a well written manuscript addressing an important question regarding the biology of low grade serous ovarian cancer, which comprises approximately 10% of all serous ovarian cancers.

The methods used in the generation of the data are appropriate and well described. The major criticism of this manuscript is the small number of patients and tumour samples used to generate the data. Thus, the results and conclusions of this manuscript should be seen as hypothesis generating rather than giving us definitive answers regarding the underlying biology of this disease. As the authors indicate, to do this moving forward will require ongoing international collaboration, likely in the form of a worldwide registry, so that information on this uncommon tumour may be collected in the most efficient and comprehensive way. The results from the ctDNA in one patient are tantalizing, and suggest this may be a simple way to follow mutational changes in the tumour over the course of the illness in these patients.

Minor essential revisions

Methods 2nd paragraph - normal samples – should indicate what specifically these were – were they normal ovarian surface epithelium (which would be the most appropriate normal control), normal ovarian stroma, or other normal tissue?

Results – 1st paragraph – most patients (6 of 11) had no somatic mutations detected. Although the use of the hotspot targeted gene panel may have missed somatic mutations in other parts of the genome, whole genome sequencing of LGSC has indicated that these are much less common than in HGSC. The authors should comment in the discussion on what potential drivers of this disease are in the absence of such mutations. Are there epigenetic or other mechanisms in play? What role would these play in the transformation of SBT to LGSC, and in the transformation of LCSC to become more aggressive with subsequent recurrences, and what role do they play in mediating sensitivity to targeted therapy such as MEK inhibitors, even in the absence of upstream mutations, and the resistance to chemotherapy that we see in these cancers.

Results – last paragraph – since only one sample showed mutational variability over time, it is very difficult to draw any firm conclusions from this. The loss of mutations at the time of disease progression would seem counter-intuitive – the authors should further elaborate on this as noted above.
Discussion – 2nd paragraph – the presence of KRAS and/or BRAF mutations appear to predict a more favourable outcome. This also seems counter-intuitive. Could the authors comment on this?

Figure 2 - D. arimidex should be replaced by generic name anastozole, E. caelux is misspelled and should be replaced by generic name pegylated liposomal doxorubicin.

Level of interest: An article of importance in its field

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.