Reviewer’s report

Title: Few additional genetic mutations accumulate during metastatic progression in high-grade serous ovarian cancer

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Reviewer: Dariush Etemadmoghadam

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Lee et al., performed exome sequencing and copy number analysis on eleven primary and metastatic deposits collected at primary surgery from one ovarian cancer patient. Phylogenetic trees were generated using somatic and copy number data, and somatic mutations were validated by deep sequencing. The authors identified two primary site clusters (P1 and P2) and a metastatic cluster (M), although these did not directly match spatial position of collected samples. A high level of intratumoral heterogeneity was observed, however few additional somatic or copy number changes were identified in metastatic compared to primary samples. The authors suggest this indicates that clones from primary sites have metastatic potential, however this can not be concluded from genomic analysis alone. The translational significance of the findings are unclear.

Major Compulsory Revisions

No major revisions

Minor Essential Revisions

1) The samples should be more clearly defined beyond what is shown in Figure 1. For example, were samples taken from the ovary multiple discrete deposits or part of a single tumor mass?

2) For clarity, Figure 1 and 2 ‘normal’ could also be labeled as ‘left fimbriae’ (or blood?). There is inconsistency between arrayed samples shown in Figure 3 and Supplementary Table 1 (i.e. bladder peritoneum indicated as arrayed but not in the figure).

3) Cut-offs (copy number/log2 ratio) used to define amplified and deleted segments should be defined.

4) Deep sequencing of 122 amplicons was performed, this number should be corrected in the results section (line 209).

5) Figure labels are inconsistent with the text and should be corrected.

6) Please clarify criteria for cluster-specific and sample-specific mutations. There appears to be ‘cluster-specific’ mutations present across individual samples in multiple clusters? How many samples within a cluster must be mutated for genes to be indicated as present in a cluster (Figure 4/Figure 1D)?
7) The final figure (Figure 6) could more clearly summarize the main findings. Perhaps sample names should be listed on the far right side and coded with cluster labels? The term ‘non-ovarian metastasis’ is not clear. Cluster P2 should be labeled as common/ancestral clones as is done with cluster P1 and M.

Discretionary Revisions

1) Did the authors look at druggable somatically mutated genes in addition to those within regions of copy number change?

2) The significance of pathway analysis is unclear and not referred to in the discussion section. Perhaps this section should be developed further or excluded?

Level of interest: An article of limited interest

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