Reviewer's report

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

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Reviewer: Dr. Yikan Wang

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This manuscript describes a study on mutational profiles and copy number alterations of whole-exome sequenced samples, along with SNP6 array data analysis, from primary tumors and the associated metastatic lesions in a single patient. Together with the somatic mutations and somatic copy number alterations, the authors further explored the clonal evolution patterns of tumors between primary and metastatic sites by constructing phylogenetic trees.

The paper is relevant to understand the clonal evolutionary processes in disease progression and metastasis. The data collection and bioinformatics workflow is fairly well established. However, the a few major concerns I have with this manuscript are summarized below.

Major Compulsory Revisions

1. The number of study case in this manuscript is limited. High-grade serous ovarian cancers are heterogeneous diseases. Different patients may have different patterns in mutational profiles, genomic instability and clonal diversity. The study as described in this manuscript only focused on one high-grade serous stage IIIC ovarian patient, 71-year-old. The size of the cohort, i.e. one case, is not an adequate representative of HGS ovarian cancer patients. The authors claimed that “Our study has clinical implications” (Line 317), yet more than one high-grade serous ovarian cancer case should be studied in order to support the “clinical implications” and to verify the conclusions in Line 74-76.

2. Lack of novelty. Previous studies have revealed that HGSC are genomically diverse across spatially separated samples collecting from individuals. HGSC are frequently characterized by genomic instability in terms of variation across population in copy number profiles, rearrangement profiles and loss of heterzygosity events. The study concluded that “HGSC has diverse intratumour heterogeneity in terms of somatic mutation and copy number variation profiles” which is a fairly well established knowledge in the previous studies of HGS ovarian cancers. The authors pointed out that “… but transcoelomic metastasis arises with little accumulation of genetic alterations”, yet based on a single patient data, this is not an adequate summary of the HGS ovarian cancer.

3. The authors pointed out “This study has important implications for the future design of personalized therapeutic solutions and investigation of drug-resistance mechanisms in HGSC” (Line 325-326). However, the rest of the section (Line
does not clearly support this claim and no further discussion is related to the statement. The authors should discuss the biological implication and relevance of their results in more depth and cite relevant literatures to support their findings.

Minor Essential Revisions

1. In the description of patient information (Line 109 - 117), it is not clear whether the patient underwent BRCA1/2 germline mutation testing, although the authors mentioned in the results (Line 212) no pathologic BRCA1 and BRCA2 germline mutation was found in this patient. No information related to the patient’s CA125 level is provided. It is not clear whether the patient relapsed or not – the platinum response information of this patient is not provided. Does the patient have personal or family history suggestive of hereditary breast or ovarian cancer syndrome? More details are needed here.

2. Line 179 – Line 181 describe the segregation of samples into clusters P1, P2 and M according to somatic mutations. Does the statement “… at least three of four in ‘cluster P1’…” refer to “three out of four samples in cluster P1”? The same question applies to “… at least two of three in cluster P2…”. A concise description is needed here.

3. Line 190 – 191 “The segments were classified as cluster P1, cluster P2, and cluster M as well, but more stringent criteria were used”. This is confusing – does it refer to a classification of segments or a classification of samples based on altered segments? Moreover, Line 191-Line193 describe “the segment was altered…”, but it is not clear how “… more stringent criteria were used…” was applied, along with the classification, to generate the clusters. A more detailed concise description is needed.

4. Line 216 “… formed cluster M (Figure 1B)…”, Should “Figure 1B” be “Figure 1B”?

5. Line 311, “our results suggest that some clones in the primary tumor already have metastatic potential…”. The authors do not clarify that this statement is only supported by the data from an individual patient data. Also, it is not clear why “… transcoelomic metastasis is a simple process” and what results support this statement.

6. Line 333 – 337 “Third, genomic alterations other than …” it is not clear how this section follows the previous context. This section needs to be rephrased.

7. Figure legends and Figure numbers do not match. Figures are numbered as Figure 1, Figure 2 … Figure 6. However, only three figure legends are provided (Line 388 - 403). It seems to be a miss-labeling for Figure 1 (A) – Figure 1(D)

8. Supplementary Table S1 needs a descriptive legend, i.e. what does ‘o’ and ‘x’ stands for? The same question applies to the Supplementary Table S3 (columns F-H)

9. Supplementary Table S8 has the last three columns color filled with blue or red for Del and Amp, yet no corresponding text is found in the legend.
Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests