Author's response to reviews

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

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We are submitting a manuscript entitled “Few additional genetic mutations accumulate during metastatic progression in high-grade serous ovarian cancer” for publication in BMC Cancer.

Your kind consideration of this paper would be greatly appreciated.

Next-generation sequencing (NGS) technology has led to progress in the evaluation of intra-tumor heterogeneity of various cancers, and shown the insights on tumor development. Recently, intra-tumor heterogeneity of high-grade serous ovarian cancer (HGSC) also has been evaluated within primary tumors and associated metastatic sites. However, little is known about how metastatic tumors further evolve compared to primary sites. Considering high recurrence rate and poor long-term survival of women with advanced stage disease, there is a strong need to document the unique metastatic patterns of epithelial ovarian cancer using NGS.
We performed whole exome sequencing and copy number analysis on 11 spatially separated samples from primary and associated metastatic sites with normal samples during surgery prior to chemotherapy. Although our study is performed with only one patient, to our knowledge, it is a NGS-based metastatic ovarian cancer study with the largest number of spatially addressed samples. By exploring the evolutionary relationship among tumor samples, we found two non-spatial clusters of primary tumor and one cluster of metastatic tumor. Even though the high level of intra-tumor heterogeneity was evident, the vast majority of somatic variants and gene copy number changes found in the metastatic samples were present in the primary tumor samples; only few additional mutations were found in peritoneal seeding samples.

We think that this work makes a unique contribution regarding the clinical importance of transcoelomic metastasis in HGSC. As transcoelomic metastasis arises with little accumulation of genetic alterations compared with primary tumors, debulking surgery might be useful in HGSC to achieve optimal cytoreduction and adjuvant chemotherapy. It also suggests that clones in peritoneal implants may not be more resistant than primary tumors. A complete staging operation should be performed to identify occult metastasis even in apparent early-stage disease. In this respect, we believe that our reports will be a meaningful insight on transcoelomic metastasis of HGSC and its management.
This work was briefly represented as poster format in American Association of Cancer Research (AACR) Annual Meeting 2014, and not being considered for publication elsewhere. Also, this work has been read and approved by all contributing authors.

Thank you in advance for your kind concern. I am looking forward to hearing a positive reply from you.

Sincerely yours,

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