

RESEARCH HIGHLIGHT

Single whole-genome sequencing analysis of metastatic biopsy is sufficient for investigational treatment opportunities in cancer

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Cancer is the second leading cause of death worldwide, accounting for an estimated 9.96 million deaths in 2020 [1]. The global cancer burden is dominated by China, which has the largest population size worldwide [2, 3]. Cancer is a group of genetic diseases driven by a series of structural genomic changes [4]. Therefore, extensive analysis of somatic changes in cancer genomes can help us develop treatments that target changes in genomic drivers, thereby improving the life expectancy of cancer patients [5].

At present, a small number of cancer type-specific genomic targets are used as molecular biomarkers to guide the treatment of this particular cancer type in clinical practice [6, 7]. With the arrival of precision medicine era, a variety of biomarkers based on somatic genomic changes have been developed. Based on these new biomarkers, cancer patients are divided into more and more subgroups. In other words, these somatic genomic changes are present in increasingly smaller patient subgroups. Moreover, the list of indications for tumor agnostic treatment is expected to expand rapidly because some anti-cancer drugs have been found to be active in tumor-agnostic manner [8]. Therefore, treatment guidance strategies that group patients into specific tumor subtypes may limit their treatment opportunities, and it may be difficult for patients to benefit from new developments in precision medicine. Comprehensive genomic profiling techniques such as whole-genome sequencing, whole-exome sequencing and large

panel sequencing, could solve the issue mentioned above [9, 10] because they can help clinicians to identify a full set of actionable genomic changes for each metastatic cancer patient. Additionally, systematic collection of a full actionable genomic alteration data set from cancer patients can be used to better understand the genomic-related molecular mechanisms of drug resistance and monitor the treatment response. All of these have greatly promoted the development of precision medicine. However, if comprehensive genomic analysis is widely implemented in clinical practice, we could pay a high price for it as we still don't know how often this procedure should be repeated.

By analyzing the metastatic cancer genomes, some studies found that individual metastasis is dominated by a single clone with characteristic clone-driven mutations, therefore, the heterogeneity is much lower than that of the primary tumor [11]. This is consistent with the clinical observation that the driver gene heterogeneity between untreated metastases is very small [12], indicating that a single biopsy at diagnosis could be sufficient to guide first-line treatment option. Unfortunately, systemic therapy can stimulate tumor evolution by promoting genetic diversification [13, 14].

In a study recently published in *Nature Medicine*, titled "Limited evolution of the actionable metastatic cancer genome under therapeutic pressure", Prof. Joris van de Haar and colleagues analyzed the whole-genome

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sequencing data of metastatic cancer patients to explore how the actionable cancer genome evolves over the therapeutic course [15]. A total of 250 biopsy pairs longitudinally obtained from 231 patients with metastatic solid tumors over the treatment course were analyzed. Most of the enrolled patients received multiple lines of standard-of-care treatment. The authors reported that the biomarkers for clinical trial enrollment and standard-of-care treatment were identified in 72% and 23% of biopsies, respectively. Approximately 99% of patients had the same standard-of-care genomic biomarkers in the first and second biopsy. Moreover, 219 clinical trial enrollment biomarkers were identified in the first biopsies. Among them, 205 (94%) biomarkers were recovered in the follow-up biopsies. Second whole-genome sequencing did not identify additional clinical trial enrollment biomarkers in 91% of patients. When the authors considered specific genes targeted by hormonal therapies (22% of cases) or small-molecule inhibitors (21% of cases) over the therapeutic course, they observed more frequent genome evolution.

The data from this study indicated that the actionable metastatic cancer genome has not changed much during disease progression. This finding is consistent with a study that analyzed sequencing data from 76 untreated metastases from 20 cancer patients [12]. However, the paired biopsies analyzed in this study were all longitudinally sampled from patients receiving systemic anti-cancer therapy, which provides researchers with more important information. Furthermore, this study showed that whole-genome sequencing could be performed in the early stages of metastatic disease and only a single test was sufficient. If this strategy is finally validated for clinical application, it can overcome most of the difficulties caused by the continuous need to validate and implement new sequencing panels. This study also identified two situations in which a single genome analysis was not sufficient to achieve optimal patient care. The first one was when the patients received hormonal therapies or small molecule inhibitors. These patients usually have on-target genomic evolutions, so repeated genome analysis may be required. Second, single genome analysis was found limited in lung cancer patients who harbored standard-of-care genomic targets and were treated with small molecule inhibitors. It should be noted that these on-target genomic alterations only determine the response to the treatment that induced these alterations but do not alter the standard-of-care or investigational treatment indications for other anti-cancer drugs. However, for cases in which on-target evolution may affect clinical decision-making, repeating genomic analysis is necessary.

This study had several limitations. First, the median biopsy interval was short (6.4 months), so the findings of this study would not be applicable to cancer patients

with long-term survival. Second, this study only analyzed biopsy pairs collected from metastases. Therefore, whether the findings of this study are applicable to the biopsy of the primary tumor still needs further investigations. Third, due to the dataset heterogeneity and the small total numbers of gained/lost biomarkers in this study, the power of subgroup analysis was limited. Last but not least, due to the depth of whole-genome sequencing and the limited sampling range of core needle biopsy, this study had very limited detection capabilities for uncommon sub-clonal mutations. To more comprehensively study the evolution of sub-clonal mutations in the future, we can try to supplement whole-genome sequencing data with the deep sequencing of liquid biopsy.

Overall, this study analyzed a large representative group of metastatic cancer patients and demonstrated that the evolution of the actionable genome in treated metastases was limited. Additionally, the first whole-genome sequencing analysis of a metastatic biopsy is sufficient to identify the genomic biomarkers of standard-of-care and the opportunities for investigational treatment. These findings promote the optimization of cancer diagnostic strategies in the precision medicine era.

LIST OF ABBREVIATIONS

Not applicable.

DECLARATIONS

AUTHORS' CONTRIBUTIONS

All the authors made contributions to the conception and drafting. All authors read and approved the final manuscript

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COMPETING INTERESTS

The author declares no competing interests.

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Not applicable.

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