Clonal tracking and monitoring of minimal residual disease using longitudinal whole-genome sequencing of solid tumors and liquid biopsies in rectal cancer

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Background & objectives

Locally advanced rectal cancer (LARC) is treated with neoadjuvant chemotherapy, chemoradiation and surgical resection. Accurate diagnosis of complete clinical response (cCR) after neoadjuvant therapy (NAT) is critical to avoid unneeded surgery for patients with no residual disease and undertreatment of patients with occult residual disease. Even when the tumor is surgically removed, a third of all LARC patients will ultimately die from metastases that develop from clinically undetectable cancer cells that may have previously spread and evolve to achieve systemic tumor dissemination. Understanding the clonal origin of these metastases will improve patient selection for non-operative management and organ preservation.

Methods

We performed longitudinal whole-genome sequencing (WGS) of solid tumors and matched circulating tumor DNA (ctDNA) from 31 LARC patients. Patients with a cCR were enrolled in watch-and-wait, while the rest underwent surgical resection. Complete response (CR) after NAT was defined as pathological complete response or cCR sustained for ≥2 years. Solid tumors were sequenced before NAT, at surgical resection and at local and distant recurrences. Matched blood was used to filter germline variants. Plasma samples were sequenced before, during and after NAT, and also at follow-up visits. Ultrasensitive detection and quantification of ctDNA in blood was performed using the C2inform platform.

Results

Tumor detection in plasma during NAT correlated with lower CR (25% vs. 76.5%, p=0.010), and detection at follow-up correlated with increased recurrence (0% vs. 42%, p=0.037) . Unlike non-responders, patients with a CR showed clearance of ctDNA throughout NAT. We identified colibactin associated mutational signatures (SBS88) in several patients and

treatment-related signatures (SBS17b) in plasma samples sequenced after NAT. Clonal tracking in a patient with tissue analyzed at pre-treatment, surgical resection, local recurrence and distant recurrence identified a new clone with a distinct treatment-associated mutational signature in the surgical resection and the local recurrence. This clone was not detected in the distant recurrence, suggesting that this may have originated from hidden micrometastases prior to NAT.

Conclusion

Longitudinal analysis of matched tissue and plasma samples enables ultrasensitive detection of residual disease, while also providing translationally relevant insights into cancer etiology and clonal evolution throughout treatment.