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Ca colon-retto: i risultati clinici con l'applicazione della medicina di precisione

Andrea Sartore Bianchi

The concept that tumors are heterogeneous both within a single tumor lesion and between tumor lesions in the same patient (intratumor heterogeneity) has become well established (Burrell RA , Swanton C. Mol Oncol 2014). As tumors consist of diverse subclonal populations with differing genomes related through a common progenitor, the capacity to evolve and develop resistance in response to selective pressures such as prolonged exposure to targeted therapies presents a significant clinical challenge. We were among the first in reporting that, in metastatic colorectal cancer, *KRAS*-activating mutations are the primary abnormality found in patients progressing on EGFR blockade (Misale et al, Nature 2012), and that this can be monitored by liquid biopsy through analysis of circulating tumor DNA (ctDNA) (Siravegna et al, Nature Med 2015). The analysis of single tissue biopsies in patients with multiple sites of disease may not indeed fully reflect the complex subclonal genetic landscape and the diversity of potential resistance mechanisms that may ensue at the time of progression on therapy. Several effectors of resistance discovered studying primary or secondary resistance to EGFR-targeted drugs turned out to be also targets for therapeutic intervention, such as *Her2* amplification (Sartore-Bianchi et al, Lancet Oncol 2016 in press) and *BRAF* mutations. In this talk an updated overlook of clinical and research scenarios of the potential use of liquid biopsy together with a review of the most promising molecular therapeutic targets on the horizon for metastatic colorectal carcinomas will be provided.