LIQUID BIOPSIES MAY IDENTIFY MINIMAL RESIDUAL DISEASE AFTER RESECTION IN LUNG CANCER

Non-invasive liquid biopsies may transform the management of patients with cancer. Circulating tumour DNA (ctDNA) derived from cancer cells can be identified in most patients with advanced cancer, representing a potential non-invasive source of tumour DNA. The analysis of ctDNA may be useful to genotype the cancer, to select treatment options and to monitor response to treatment. ctDNA is often at a low level in plasma, requiring highly sensitive and accurate assays for ctDNA analysis. ctDNA was detected and profiled together with primary tumour DNA obtained from surgical specimens in 40 patients with lung cancer with localised disease who were diagnosed at stages I–III and operated on with curative intent. In a study carried out by investigators at the University of Stanford and recently published in Cancer Discovery, more than 90% of relapsing patients were found to have ctDNA 1 month after resection. This indicates a valuable detection of minimal residual disease. Moreover, ctDNA was able to show residual disease earlier than 5 months, compared with conventional follow-up imaging.

The most frequently detected mutations in surveillance samples included mutations in TP53, KRAS, EGFR and KEAP1. Patients with detectable ctDNA at any post-treatment time point had significantly lower freedom from progression and survival than those in whom ctDNA was not detectable after completion of therapy. These findings suggest that ctDNA analysis is a promising approach for minimal residual disease detection in patients with localised lung cancers and that it can identify recurrence significantly earlier than routine CT imaging. The sensitivity and specificity of this diagnostic approach for detecting ctDNA were very high. In this series, all patients with detectable ctDNA during post-treatment surveillance developed progressive disease, whereas all patients whose ctDNA remained undetectable remained disease free.

The earlier detection of ctDNA compared with imaging confirmation of progressive disease opens a window of opportunity in which to treat patients, while tumour burden and heterogeneity are at their lowest. Given the poor outcomes observed in patients with detectable post-treatment ctDNA, it is likely that this subgroup could benefit from adjuvant treatment. ctDNA is a promising biomarker for early detection of minimal residual disease in patients with localised lung cancer and can reliably identify patients at high risk for recurrence. Tracking multiple mutations improves the sensitivity of minimal residual disease detection, and both driver and passenger mutations are useful for tracking and monitoring disease. Validation of these findings and prospective clinical trials testing therapeutic strategies based on ctDNA assessment will be required to establish clinical utility.

In an accompanying editorial, Comino-Mendez et al underline some of the limitations and relevant findings of this article. The potential of ctDNA detection of residual disease is clear. We may be able to identify who is at risk of relapse with high accuracy, and this information could be used to precisely deliver adjuvant therapy to those patients who may need it. However, we are far from routine clinical application. There is no evidence yet that using ctDNA assays in this setting can improve outcome. However, this article reinforces the potential of non-invasive ctDNA assays to transform how we monitor patients with early-stage cancer and the potential to tailor adjuvant therapies.

ORGANOIDS FROM HUMAN LIVER PRIMARY CANCER MAY HELP IN IMPROVING PERSONALISED MEDICINE DEVELOPMENTS

The main goal of personalised medicine in cancer is to identify the most appropriate treatment modality for the genetic landscape of a individual’s tumour. Despite advances in cancer genomic analysis and discovery of druggable targets, a large number of patients do not respond to therapies as predicted, indicating the need for improved models to predict therapeutic outcome.

Organoids, which are cellular structures grown in in vitro 3D cell-culture systems that retain interactions both between cells and between cells and the extracellular matrix that surrounds them, could be one
of these valuable models. These cultures, derived from the patients’ tumour cells, offer better preservation of the biological characteristics of tissues than do the more commonly used monolayer cell cultures. Organoids provide a large-scale platform for drug-sensitivity screening that offers an acceptably fast turnaround time, which could enable clinical application on the basis of results obtained.

Primary liver cancer (PLC) is one of the human tumours in which such predictive models were lacking. In a recent publication in Nature Medicine, a group of investigators from the University of Cambridge reports on the use of patient-specific organoid strategies to model cancer therapeutic responses in patient-specific tissue. In this study, Broutier et al used patient tumour biopsy tissue to generate and characterise organoid models of three types of PLC: hepatocellular carcinoma (HCC), cholangiocarcinoma (CC) and combined HCC/CC cancer (CHC).

PLC-derived organoid cultures preserve the histological architecture, gene expression and genomic landscape of the original tumour, allowing for discrimination between different tumour tissues and subtypes, even after long-term expansion in culture in the same medium conditions. Xenograft studies demonstrate that the tumorigenic potential, histological features and metastatic properties of PLC-derived organoids are preserved in vivo. Moreover, PLC-derived organoids are amenable for biomarker identification and drug-screening testing and led to the identification of the extracellular signal-regulated kinase inhibitor SCH772984 as a potential therapeutic agent for PLC, demonstrating the wide-ranging biomedical utilities of PLC-derived organoid models in furthering the understanding of liver cancer biology and in developing personalised-medicine approaches for this disease. The authors demonstrate proof of concept that PLC tissue grown as organoid cultures faithfully models the genetic complexity of human PLC in vitro. This study opens a potential to improve drug-screening programmes in liver cancer.

MOLECULAR DETERMINANTS OF PROGRESSION FROM PREMALIGNANT LESIONS TO GASTRIC CANCERS ARE BETTER UNDERSTOOD

Intestinal metaplasia is well recognised as a premalignant condition of the gastric mucosa that is associated with an increased gastric cancer transformation. This metaplasia is defined as an intestinal replacement of gastric mucosa in some patchy areas, which may suffer evolution to neoplastic tissue. However, the molecular features determining this neoplastic transformation were not well understood. Current recommendations mandate that all patients with intestinal metaplasia should undergo screening for active Helicobacter pylori infection as H. pylori antibiotic eradication reverses early histological changes in patients with gastritis and may slow the progression of intestinal metaplasia to gastric cancer. A recent publication by the group of Patrick Tan at the Duke University in Singapore in Cancer Cell provides some important clues to better understand this relevant step towards malignant transformation.

These investigators performed genomic and epigenomic profiling of 138 cases of intestinal metaplasia from 148 cancer-free patients, recruited through a 10-year prospective study. Compared with gastric cancers, intestinal metaplasias showed low mutational burdens, recurrent mutations in certain tumour suppressors (FBXW7) but not others (TT53, ARID1A), chromosome 8q amplification and shortened telomeres. Moreover, sequencing identified more patients with intestinal metaplasia with active H. pylori infection compared with histopathology (11%–27%). Several intestinal metaplasias presented hypermethylation at DNA methylation valleys. However, intestinal metaplasias generally lack intragenic hypomethylation signatures of advanced malignancy. Patients with intestinal metaplasia with shortened telomeres and chromosomal alterations were associated with subsequent dysplasia or evolution to gastric cancer. On the other hand, patients exhibiting normal-like epigenomic patterns were associated with regression.

As a potential significance of these findings, the authors state that genomic data may prove useful in risk-stratifying patients with intestinal metaplasia, by identifying individuals at high gastric cancer risk who may benefit from targeted screening and also additional patients who could receive treatment for eradication of H. pylori. These results thus enable a molecular framework for the precision prevention of gastric cancer. Moreover, the observation of increased DNA methylation in a significant proportion of intestinal metaplasia raises the potential for low-dose epigenetic therapy as a potential chemopreventive strategy, using clinically approved demethylating agents such as 5-azacitidine and decitabine.

Contributors AC is the sole author.

Funding This work was supported by grant PI15/02180 from Fondo de Investiguaciones Sanitarias (Instituto de Salud Carlos III) from the Spanish Government and CIBERONC.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

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