According to the American Cancer Society, in 2020 an estimated 42,810 Americans will be diagnosed with cancer of the liver. Liver cancer incidence rates have more than tripled since 1980, while the death rates have more than doubled during this time. Getting these patients on the right treatment faster can make all the difference.

The adoption of precision medicine can have a substantial effect on survival in patients with liver cancer. However, the ability of patients with liver cancer to undergo tumor molecular profiling or receive targeted therapies is a challenge in the U.S. healthcare system.

The advent of next-generation sequencing (NGS) has dramatically revolutionized the molecular knowledge of cancer by increasing the feasibility and possibility of DNA sequencing.

**CIRCULOGENE’S comprehensive liver panel is a non-invasive technique that can be combined with traditional tissue biopsy to track cell-free DNA and detect disease biomarkers in blood faster and more accurately.**

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**Clinical Cancer Research, September 2019 – “Comprehensive Liquid Profiling of Circulating Tumor DNA and Protein Biomarkers in Long-Term Follow-Up Patients with Hepatocellular Carcinoma”**

“Our strategy of comprehensive mutation profile integration could accurately and better evaluate patients’ prognostic risk…”

“Real-time monitoring of tumor burden for patients with HCC, which could greatly benefit prognostic evaluation and treatment selection, remains a critical challenge.”

“One major advantage of cfDNA is its unique ability for containing comprehensive somatic information with regard to primary HCC and/or metastatic lesions, thus allowing it to overcome the inference of tumor heterogeneity.”

**Oncogene 2020 – “Immune-based Therapies for Hepatocellular Carcinoma”**

“The systemic management of cancer has been recently revolutionized by the advent of immune checkpoint inhibitors (ICPI).”

“…PD1/PDL1 as forerunner molecular targets of cancer related immune exhaustion has rapidly extended to HCC based on promising results of ICPI therapy in multiple indications.”

**Nature Medicine, September 2019 - “Liquid versus tissue biopsy for detecting acquired resistance and tumor heterogeneity in gastrointestinal cancers”**

“In patients with multiple post-progression tumor biopsies…in all patients, individual resistance mechanisms emerging in distinct metastatic lesions were detectable in plasma cfDNA.”
80-Year-Old Patient

LARGE LIVER MASS WITH TISSUE BIOPSY ‘LOW-GRADE’ NEUROENDOCRINE TUMOR WITH LACK OF MITOTIC FIGURES

This case presents a divergence of the histologic tissue pathology and plasma ctDNA findings, forcing a treatment dilemma that is tough enough given her age. Typically, low-grade/grade 1 neuroendocrine tumors carry an indolent tumor biology and prolonged survival potentials even with radiographically bulky disease. That is what the tissue histology is indicating. However, the circulating tumor DNA is portending a far different tumor biology.

The findings of 9 ctDNA mutations reflect an aggressive tumor biology and shortened survival. In a study of over 400 patients with a variety of advanced cancers, the 20-30% who were non-shedders of any ctDNA had a markedly longer median overall survival, whereas those shedding more than 5 ctDNA mutations had a survival of just 5 months. A cancer shedding ctDNA has a far worse prognosis than those not shedding. The genomic make-up of grade 1 neuroendocrine tumors is different than grade 3 tumors. SMAD4 mutations are associated with poorer survival in a variety of GI cancers, including colorectal and pancreatic adenocarcinoma. Although a full elucidation of the genomics of neuroendocrine tumors is still a work in progress, rarely are SMAD4 and/or p53 mutations part of the low-grade tumor genomics; rather, they are associated with a larger tumor burden and the high-grade/grade 3 neuroendocrine tumor spectrum.

This is what we often have seen clinically…a tumor biology that ends up having a much more aggressive tumor biology than the histologic biopsy would suggest. Intratumoral heterogeneity is always limiting for tissue biopsies. Only one small area at one point in time is sampled. The metastatic clone is different than the stationary clone. Plasma ctDNA can identify the more aggressive clone that reflects the tumor biology and has the most important treatment need.

Very sadly, given the ctDNA findings, her prognosis is extremely poor with a much shorter survival outcome than the typical grade 1 neuroendocrine tumors, also limiting any benefit of the standard-of-care, low-grade neuroendocrine tumor treatment approaches. However, this can also spark a goals-of-care and end-of-life-with-quality discussion. Sometimes, even with our advances in cancer treatment, that is still the kindest personalized cancer care there is.

Case Study Prepared by Doctor Paul Walker
Chief Medical Officer, Former Director of Thoracic Oncology at East Carolina University

Sources:
- JCO Precis Oncol 4:192-201