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LETTER TO THE EDITOR

Circulating tumour DNA in gastrointestinal cancer in clinical practice: Just a dream or maybe not?

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Abstract

The evaluation of circulating tumor DNA (ctDNA) is increasingly integrated into the management of diagnosis and treatment of gastrointestinal cancer as it represents an innovative and minimally invasive biomarker that could allow us to reach clinical needs not met yet in randomized clinical trials. Recent research provided an interesting overview of the role of circulating tumor DNA in gastric, biliary, liver, pancreatic, and colorectal cancer. Data regarding upper gastrointestinal tumors are currently not practice changing. Tumor detection rates are low in the early stages, while in advanced stages ctDNA is useful for molecular tracking evaluation. Most of the evidence comes from colorectal cancer studies, where ctDNA was evaluated both in the early and advanced stages with the post-surgery minimal residual disease assessment and the response assessment, respectively. ctDNA qualifies as a promising tool in the era of precision medicine, with potential applications in the entire management of gastrointestinal cancer patients. Further evidence is needed to establish which setting may be influenced greatly by liquid biopsy in clinical practice.

Key Words: Circulating tumor DNA; Gastrointestinal cancer; Liquid biopsy; Esophageal cancer; Gastric cancer; Liver cancer; Bile duct cancer; Pancreatic cancer; Colorectal cancer

Core Tip: Circulating tumor DNA is a promising tool in the era of precision medicine, with several potential applications in the entire management of gastrointestinal malignancies. Further evidence is needed to assess in which setting liquid biopsy might have a greater impact in clinical practice.

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TO THE EDITOR

We read with great interest the minireview by Kirchweger *et al*[1], entitled "Circulating tumor DNA (ctDNA) for diagnosis, prognosis and treatment of gastrointestinal malignancies". This paper provides a comprehensive overview on available literature data regarding the potential role of ctDNA in the management of gastric, biliary tract, liver, pancreatic and colorectal cancer (CRC). The authors discuss the application of ctDNA detection from diagnosis to prognosis and treatment monitoring of each disease analysed, by critically presenting to the readers the advantages and limitations of this tool.

We strongly agree with authors that ctDNA represents an innovative, minimally invasive biomarker that might allow us to reach unmet clinical needs in clinical practice for gastrointestinal cancer patients if further validated in randomised clinical trials. Indeed, considering the dynamic nature of tumor biology and the genetic heterogeneity of diseases such as CRC, the serial assessments of biomarkers of interest through liquid biopsy might reflect the continuous changes of tumour itself and be useful to clinicians[2].

Notably, not a large amount of data is available about the application of ctDNA for diagnosis, as well as about its role in gastric and liver cancer. We greatly appreciate the authors' effort to analyse these particular aspects and cancer types which are not the main field of research for this topic.

Indeed, main evidences regard prognosis and treatment monitoring, both in early stages (detection of minimal residual disease) and in advanced stages. Moreover, the majority of evidences derive from CRC studies.

Recently, Bregni *et al*[3] showed that baseline ctDNA was an independent prognostic factor for disease free survival (HR 3.35, 95%CI: 1.15-9.77, P = 0.03) in stage III CRC patients treated with neoadjuvant conventional 5-fluorouracil, oxaliplatin and folinic acid (FOLFOX) followed by surgery +/- adjuvant FOLFOX in the PePiTA trial[4]. These findings derive from a small sample size (80 patients) but represent a starting point needing to be confirmed in larger trials focusing on early-stage CRC.

Surely, as highlighted by the authors, ctDNA has been extensively studied for tailoring treatment with anti-EGFR in further lines for RAS wild type metastatic CRC[5]. Our group recently explored the liquid biopsy-driven cetuximab rechallenge in a *RAS* and *BRAF* wild type selected population[6]. This strategy was confirmed to be effective and despite the small sample size, clinical outcome was consistent with the findings of phase II studies. Moreover, we observed that in addition to the molecular selection through ctDNA analysis for *RAS-BRAF*, long anti-*EGFR* free interval was a prospective selection criterion for this therapeutic option. Thus, the combination of ctDNA analysis plus clinical elements might be a winning strategy overcoming the limitations of a single tool.

As for pancreatic cancer, the identification of prognostic and predictive biomarkers is an urgent medical need. Unfortunately, despite extensive research no robust validated factors to guide treatment choice are available, except for *BRCA* status, and no effective agents have drastically improved the management of this disease, including immunotherapy[7-10]. For this reason, we strongly agree with the authors that ctDNA detection appears as an appealing instrument to guide therapeutic choices across different treatment lines, in order to improve clinical outcomes pancreatic cancer patients. Indeed, liquid biopsy has shown to be more sensitive than carbohydrate antigen199 levels in predicting prognosis and treatment response[11].

Moreover, ctDNA evaluation has been shown to be more sensitive than current gold standard radiological methods (computed tomography) in the evaluation of the tumor burden at staging (for any micro dissemination or lymph node involvement) and for relapses detection[12-13].

At the present time, data regard small groups of patients and require validation in larger trials.

In conclusion, ctDNA qualifies as a promising main actor in the precision medicine era, with potential applications in the whole management of gastrointestinal cancer patients. Further larger and prospective studies are needed to assess the real impact of liquid biopsy in clinical practice, but for now, potential benefits are likely to overcome its limitations.

FOOTNOTES

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