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Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Esther Una Cidon, MD, MSc, PhD, Doctor, Department of Medical Oncology, Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, Bournemouth BH7 7DW, United Kingdom. aunacid@hotmail.com

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Liquid biopsy: Precise diagnosis and therapy for cholangiocarcinoma

Si-Qin Wang, Chu-Xing Chai, Bi-Rong Wang, Feng Zhu, Dan Shang, Min Li

ORCID number: Si-Qin Wang 0000-0002-8034-7471; Chu-Xing Chai 0000-0002-7361-0200; Bi-Rong Wang 0000-0003-3195-0407; Feng Zhu 0000-0003-0647-9537; Dan Shang 0000-0003-4585-2744; Min Li 0000-0002-0047-2804.

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Si-Qin Wang, Feng Zhu, Dan Shang, Department of Vascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei Province, China

Chu-Xing Chai, Min Li, Department of Hepatobiliary Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei Province, China

Bi-Rong Wang, Department of Breast and Thyroid Surgery, Wuhan Fourth Hospital; Puai Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China

Corresponding author: Dan Shang, MD, PhD, Associate Professor, Department of Vascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1277 Jiefang Avenue, Wuhan 430022, Hubei Province, China.
danshang@hust.edu.cn

Abstract

The following letter to the editor highlights the review titled "Liquid biopsy in cholangiocarcinoma: Current status and future perspective" in *World J Gastrointest Oncol* 2021; 13: 332-350. It is necessary to realize individualized therapy to improve the clinical prognosis of patients with cholangiocarcinoma.

Key Words: Liquid biopsy; Cholangiocarcinoma; Diagnosis; Therapy; Precision medicine

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Core Tip: Cholangiocarcinoma (CCA) is an aggressive biliary malignancy, and existing clinical tools cannot improve survival rates. The major goal of this letter is to stress the fascinating promise and challenge of liquid biopsy in the diagnosis and therapy of patients with CCA.

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TO THE EDITOR

We read with great interest the review titled “Liquid biopsy in cholangiocarcinoma: Current status and future perspective” by Rompianesi *et al*[1], and we believe that liquid biopsy (LB) has opened new avenues for personalized medicine in patients with cholangiocarcinoma (CCA). This review summarizes the present challenges of diagnosing, managing and monitoring CCA and the unique advantage of LB for these challenges. The authors conclude that a growing body of research supports the idea that LB can overcome the difficulties of traditional tools and might be particularly helpful in detecting early cancer, identifying therapeutic targets, predicting treatment response, and monitoring the genetic profile of CCA.

CCA is an aggressive biliary malignancy originating from cholangiocytes along the biliary tree, excluding the gall bladder and the Vater ampulla[2]. CCA is usually asymptomatic in the early stages. Therefore, the majority of CCA patients are generally diagnosed at an advanced stage. Because there are limited therapeutic options, advanced CCA has a dismal prognosis[3,4]. Even for patients with localized early disease who can benefit from surgery, the high recurrence rate may cause an inferior clinical outcome[5]. Despite recent advances in systemic chemotherapy, targeted therapy, and immunotherapy, the prognosis of patients with advanced unresectable CCA remains disappointing because of tumour heterogeneity and the variability of treatment response[6]. As the recognition of the importance of precision medicine by clinicians is growing, there is an urgent need for new, accurate tools for early cancer detection, monitoring of the tumour molecular profile, real-time assessment of therapeutic efficacy, and identification of therapeutic targets and resistance mechanisms in CCA.

Tumours can release their contents along with genetic material into body fluids such as blood, urine, saliva, bile, and cerebrospinal fluid[7]. LB is a novel, minimally invasive, and safe method for detecting tumour components in body fluids, including circulating tumour cells, circulating tumour DNA (ctDNA), circulating cell-free RNA, extracellular vesicles, and tumour-educated platelets[8]. Advances in the detection and characterization of ctDNA have enabled LB to be rapidly translated into the management of patients with advanced solid tumours. With the development of next-generation sequencing and oncology genomics assessment, researchers can identify and analyse a wealth of cancer genetic markers that contribute to the occurrence, progression and heterogeneity of cancer[9]. Analysing genetic markers or the molecular profile of solid cancers traditionally relies on tissue biopsy. However, limited accessibility to tumour samples and tumour heterogeneity present challenges for acquiring representative tumour samples throughout the disease course[10]. As a less invasive approach, LB can be used to track spatial and temporal heterogeneity and monitor dynamic changes in tumour biology at the molecular and genetic levels[11].

LB samples (in most cases, blood) are easy to obtain, and LB can be repeated in patients, enabling real-time molecular monitoring of CCA. LB approaches can also be used to detect abnormalities before imaging examinations. As previously reported, the detection of ctDNA precedes the radiological detection of early tumour recurrence by 3–5 mo in several cancers[11,12]. Furthermore, LB can be used to guide clinical treatment and monitor the treatment response. Among patients with biliary tract cancers who received systemic treatment after ctDNA analysis and drug matching, the matched targeted regimens showed longer progression-free survival and a better disease control rate than unmatched methods[9]. Characterized, therapeutically relevant ctDNA alterations can also be found in CCA patients after gene-targeted therapy[13]. Furthermore, since ctDNA may include DNA shed into the bloodstream from both primary and metastatic tumours, the genomic alterations of ctDNA can reflect the cancer heterogeneity of the whole body better than those found in tissue biopsy[14,15]. Cancer heterogeneity may be part of the reason for the unfavourable outcomes of several gene-targeted trials in CCA[16].

There remain several challenges for the clinical application of LB. The low concentration of ctDNA and difficulty in identifying ctDNA in peripheral blood may limit the accuracy of detection. There are also high sensitivity and specificity requirements of detection methods. Since various ctDNA assays are available, more comprehensive cross-platform comparisons are needed to standardize the preanalytical and analytical

procedures. Detectable genomic mutations are not always relevant to cancer biology or therapy, so ctDNA analysis and sequencing data should be carefully interpreted. The use of machine learning tools and artificial intelligence technology may efficiently aid the analysis of increasingly complex cancer LB data[17].

In conclusion, it is necessary to realize individualized therapy to improve the clinical prognosis of patients with CCA[5]. As an easy method for assessing genetic material and molecular profiling, LB can play an important role in early cancer detection, tumour heterogeneity assessment, therapy selection, and prognostic stratification in CCA. Although challenges exist for the clinical application of LB, its potential represents a movement towards precision medicine and individualized therapy. The scarcity of clinical data suggests that larger and deeper studies to define and validate the diagnostic and therapeutic roles of LB in CCA are needed.

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