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**Liquid biopsy: Precise diagnosis and therapy for cholangiocarcinoma**

Wang SQ *et al*. Liquid biopsy for cholangiocarcinoma

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**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.

**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.

**REFERENCES**

1 **Rompianesi G**, Di Martino M, Gordon-Weeks A, Montalti R, Troisi R. Liquid biopsy in cholangiocarcinoma: Current status and future perspectives. *World J Gastrointest Oncol* 2021; **13**: 332-350 [PMID: 34040697 DOI: 10.4251/wjgo.v13.i5.332]

2 **Banales JM**, Cardinale V, Carpino G, Marzioni M, Andersen JB, Invernizzi P, Lind GE, Folseraas T, Forbes SJ, Fouassier L, Geier A, Calvisi DF, Mertens JC, Trauner M, Benedetti A, Maroni L, Vaquero J, Macias RI, Raggi C, Perugorria MJ, Gaudio E, Boberg KM, Marin JJ, Alvaro D. Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). *Nat Rev Gastroenterol Hepatol* 2016; **13**: 261-280 [PMID: 27095655 DOI: 10.1038/nrgastro.2016.51]

3 **Cillo U,** Fondevila C, Donadon M, Gringeri E, Mocchegiani F, Schlitt H, Ijzermans J, Vivarelli M, Zieniewicz K, Olde Damink S, Groot Koerkamp B. Surgery for cholangiocarcinoma. *Liver Int* 2019; **39:** 143-155 [PMID: 30843343 DOI: 10.1111/liv.14089]

4 **Banales JM**, Marin JJG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, Cardinale V, Carpino G, Andersen JB, Braconi C, Calvisi DF, Perugorria MJ, Fabris L, Boulter L, Macias RIR, Gaudio E, Alvaro D, Gradilone SA, Strazzabosco M, Marzioni M, Coulouarn C, Fouassier L, Raggi C, Invernizzi P, Mertens JC, Moncsek A, Rizvi S, Heimbach J, Koerkamp BG, Bruix J, Forner A, Bridgewater J, Valle JW, Gores GJ. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 557-588 [PMID: 32606456 DOI: 10.1038/s41575-020-0310-z]

5 **Marin JJG**, Prete MG, Lamarca A, Tavolari S, Landa-Magdalena A, Brandi G, Segatto O, Vogel A, Macias RIR, Rodrigues PM, Casta A, Mertens J, Rodrigues CMP, Fernandez-Barrena MG, Da Silva Ruivo A, Marzioni M, Mentrasti G, Acedo P, Munoz-Garrido P, Cardinale V, Banales JM, Valle JW, Bridgewater J, Braconi C; working group 6 of the COST-action 18122 (Euro-Cholangio-NET) as part of the European Network for the study of Cholangiocarcinoma (ENSCCA). Current and novel therapeutic opportunities for systemic therapy in biliary cancer. *Br J Cancer* 2020; **123**: 1047-1059 [PMID: 32694694 DOI: 10.1038/s41416-020-0987-3]

6 **Roy D,** Lucci A, Ignatiadis M, Jeffrey S. Cell-free circulating tumor DNA profiling in cancer management. *Trends Mol Med* 2021; **27:** 1014-1015 [PMID: 34312074 DOI: 10.1016/j.molmed.2021.07.001]

7 **Bradley SH**, Barclay ME. "Liquid biopsy" for cancer screening. *BMJ* 2021; **372**: m4933 [PMID: 33397684 DOI: 10.1136/bmj.m4933]

8 **Alix-Panabières C**, Pantel K. Liquid Biopsy: From Discovery to Clinical Application. *Cancer Discov* 2021; **11**: 858-873 [PMID: 33811121 DOI: 10.1158/2159-8290.CD-20-1311]

9 **Okamura R**, Kurzrock R, Mallory RJ, Fanta PT, Burgoyne AM, Clary BM, Kato S, Sicklick JK. Comprehensive genomic landscape and precision therapeutic approach in biliary tract cancers. *Int J Cancer* 2021; **148**: 702-712 [PMID: 32700810 DOI: 10.1002/ijc.33230]

10 **Kilgour E**, Rothwell DG, Brady G, Dive C. Liquid Biopsy-Based Biomarkers of Treatment Response and Resistance. *Cancer Cell* 2020; **37**: 485-495 [PMID: 32289272 DOI: 10.1016/j.ccell.2020.03.012]

11 **Biswas D**, Ganeshalingam J, Wan JCM. The future of liquid biopsy. *Lancet Oncol* 2020; **21**: e550 [PMID: 33271107 DOI: 10.1016/S1470-2045(20)30687-2]

12 **Wang Y**, Li L, Cohen JD, Kinde I, Ptak J, Popoli M, Schaefer J, Silliman N, Dobbyn L, Tie J, Gibbs P, Tomasetti C, Kinzler KW, Papadopoulos N, Vogelstein B, Olsson L. Prognostic Potential of Circulating Tumor DNA Measurement in Postoperative Surveillance of Nonmetastatic Colorectal Cancer. *JAMA Oncol* 2019; **5**: 1118-1123 [PMID: 31070668 DOI: 10.1001/jamaoncol.2019.0512]

13 **Mody K,** Kasi PM, Yang JD, Surapaneni PK, Bekaii-Saab T, Ahn DH, Mahipal A, Sonbol MB, Starr JS, Roberts A, Nagy R, Lanman R, Borad MJ. Circulating Tumor DNA Profiling of Advanced Biliary Tract Cancers. *Jco Precision Oncology* 2019; 3 [DOI: 10.1200/po.18.00324]

14 **Balasaheb Mali S**, Dahivelkar S. Liquid biopsy = Individualized cancer management: Diagnosis, monitoring treatment and checking recurrence and metastasis. *Oral Oncol* 2021; **123**: 105588 [PMID: 34744021 DOI: 10.1016/j.oraloncology.2021.105588]

15 **Pectasides E**, Stachler MD, Derks S, Liu Y, Maron S, Islam M, Alpert L, Kwak H, Kindler H, Polite B, Sharma MR, Allen K, O'Day E, Lomnicki S, Maranto M, Kanteti R, Fitzpatrick C, Weber C, Setia N, Xiao SY, Hart J, Nagy RJ, Kim KM, Choi MG, Min BH, Nason KS, O'Keefe L, Watanabe M, Baba H, Lanman R, Agoston AT, Oh DJ, Dunford A, Thorner AR, Ducar MD, Wollison BM, Coleman HA, Ji Y, Posner MC, Roggin K, Turaga K, Chang P, Hogarth K, Siddiqui U, Gelrud A, Ha G, Freeman SS, Rhoades J, Reed S, Gydush G, Rotem D, Davison J, Imamura Y, Adalsteinsson V, Lee J, Bass AJ, Catenacci DV. Genomic Heterogeneity as a Barrier to Precision Medicine in Gastroesophageal Adenocarcinoma. *Cancer Discov* 2018; **8**: 37-48 [PMID: 28978556 DOI: 10.1158/2159-8290.CD-17-0395]

16 **Hezel AF**, Deshpande V, Zhu AX. Genetics of biliary tract cancers and emerging targeted therapies. *J Clin Oncol* 2010; **28**: 3531-3540 [PMID: 20547994 DOI: 10.1200/JCO.2009.27.4787]

17 **Im YR**, Tsui DWY, Diaz LA Jr, Wan JCM. Next-Generation Liquid Biopsies: Embracing Data Science in Oncology. *Trends Cancer* 2021; **7**: 283-292 [PMID: 33317961 DOI: 10.1016/j.trecan.2020.11.001]

**Footnotes**

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