Editorial

Extracellular vesicles small RNA clusters: hit the nail on the head of liver cancer detection

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Comment on: von Felden J, Garcia-Lezana T, Dogra N, *et al.* Unannotated small RNA clusters associated with circulating extracellular vesicles detect early stage liver cancer. Gut 2021. [Epub ahead of print]. doi: 10.1136/gutjnl-2021-325036.

Submitted Oct 11, 2021. Accepted for publication Oct 25, 2021.
doi: 10.21037/hbsn-21-421
View this article at: https://dx.doi.org/10.21037/hbsn-21-421

There is a very urgent need and clinical demand of robust biomarkers in cancer screening, especially in early hepatocellular carcinoma (HCC) surveillance as outlined by various professional international associations as the European Association for the study of the Liver (EASL), or the Asian Pacific Association for the Study of the Liver (APASL) and national professional organisations as the American Association for the Study of Liver Diseases (AASLD), besides others. Newest data on primarily HCC is still depicting this cancer entity as the sixth most frequently diagnosed cancer, with over 900,000 new cases and over 830,000 deaths worldwide (1). This type of cancer, therefore, remains at the forefront of malignant diseases. Thus, every element of patient management, including early diagnosis and prognosis of treatment response and survival, is a challenge.

Now, hepatic cancer screening, allowing a tight HCC surveillance in patients at risk, could increase HCC early detection rates manifold. Hepatic cancer-detecting, especially early HCC diagnosis, could be part of a comprehensive, personalized medicine approach combined with a convenient and patient-friendly liquid biopsy approach such as published by us and others (2-5). The term 'liquid biopsy' actually means the possibility of assessing various types of cancer biomarkers in readily available biological material, mainly peripheral blood, using a variety of laboratory methods. This technique is devoid of most of the side effects of standard tumour biopsy, is less invasive to the patient, and can be performed multiple times. Nevertheless, the lack of standardization of laboratory methods or the liquid version's high procedural and apparatus costs prohibit it from replacing the standard biopsy. The use of liquid biopsy and its undoubted advantages, e.g., drawing just a few millilitres of blood, would allow physicians and oncologists around the globe to render an earlier picture of the underlying hepatic malignancy, achieving a better individual outcome with a more prominent likelihood of reaching a fair 5-year survivable probability. Currently, the reported overall survival (OS) rates are for primary liver cancer overall low as 21.3% during 2000–2011 (5-year) and 58.1% during 2000–2015 (1-year) in the United States (US), both have been improved over the past decades (6).

Previously, many experimental and clinical studies on liquid biopsies in liver cancer were done, however, only few of those will result or initiated a phase 2 biomarker case-control study by FDA standards. July this year, the *GUT* published the original research results of von Felden *et al.* (7), in which the authors elegantly demonstrated that the use of small RNA clusters associated with blood extracellular vesicles (EVs) is an excellent

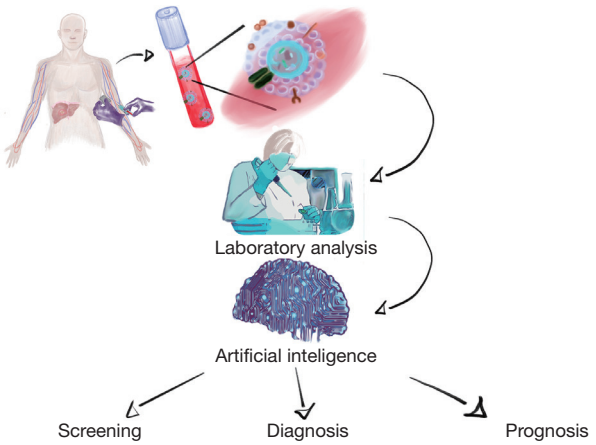

Figure 1 A simplified concept of the use of liquid biopsy in clinical oncology proposed by von Felden *et al.* (7). Thanks to innovative laboratory methods and IT technologies, it is possible to accurately and sensitively screen and diagnose liver cancers and assess their progression. Evaluation of EVs in readily available samples of biological material and analysis of results with AI can become part of personalized medicine, and replace the standard solid biopsy. EVs, extracellular vesicles; AI, artificial intelligence.

type of liquid biopsy, allowing HCC detection with very high sensitivity and specificity. So, what are EVs? EVs are membranous structures released from cells due to various biological processes, e.g., activation, inflammation and apoptosis. These structures are currently believed to include exosomes, ectosomes as microparticles (MPs), microvesicles (MVs) and apoptotic bodies. EVs display a variety of biologically active molecules on their surface, making them universal transmitters of information from cell to cell (8). Naturally, the manuscript of von Felden *et al.* (7) is not the only one showing the utility of EVs for diagnosing HCC. Previously, the main scientific focus was devoted to various forms of RNA associated with exosomes. However, this work by von Felden is unique, as it covers several experiments and has been validated in a phase 2 biomarker case-control study.

Importantly, von Felden *et al.* (7) demonstrated beautifully how current machine learning (ML), kind of artificial intelligence (AI), when ML driven modelling is pitching in *Figure 1*, ultimately allows us to exploit extensive data and analyse and identify complex patterns/profiles of various until now uncharacterized unannotated small RNAs, typical of a consensus sequence of 20 nt. Data management and data mining are crucial in AI-based future comprehensive cancer screening.

In our opinion, the work done by von Felden *et al.* (7) does fulfil the criteria to make a difference in the near future, a significant contribution in the desperate search for robust liquid biopsy biomarkers in HCC and might set a new medical standard in clinical oncology. The so far reported sensitivity and specificity of 86% and 91%, respectively, for the detection of early HCC from controls at risk to develop HCC as hepatic cirrhosis, is promising and much better then widely used alpha-fetoprotein (AFP), or carcinoembryonic antigen (CEA). Nevertheless, the final and complete report analysis of phase 2 biomarker case-control study by FDA standards will set the pace. Their key finding as that a certain so called 3-smRC signature allowed such separation of hepatic malignancy from non-malignant cirrhosis that is in fact a related pathological process in HCC development is remarkable and has similar value as the publication by Melo *et al.* (9) reporting that GPC1+ small EVs are highly beneficial in pancreatic cancer screening and kicking off many further exploitations. However, being enthusiastic about von Felden's publication, at the same time we have to be as much critical as enthusiastic and address some critical but necessary and fair questions such as: does their 3-smRC signature allow a separation between other cancer entities? Especially, does their 3-smRC signature allow a clear separation between HCC and intrahepatic CCA? Others tried this, even utilising circulating EVs as a novel biomarker (4,5,10). However, those questions remained unanswered yet. Probably, addressed in a future publication by von Felden and colleagues or others. Moreover, a relatively small number of patients and controls make us treat these results as preliminary. For the moment, this work as published in *Gut* is very promising and deserves visibility and further discussion.

Acknowledgments

Funding: This publication was funded by the Deutsche Forschungsgemeinschaft (DFG; German Research Foundation), grant number 410853455 to MTK and grant number 411345524 to VLK. We are remarkably grateful to Wioleta Chomko for assistance with the figure.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office of *Hepatobiliary Surgery and Nutrition*.

The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-421/coif). VLK and MTK report grant from DFG, German Research Foundation. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Słomka A, Wang B, Mocan T, González-Carmona M, Strassburg CP, Lukacs-Kornek V, Kornek MT. Extracellular vesicles small RNA clusters: hit the nail on the head of liver cancer detection. HepatoBiliary Surg Nutr 2022;11(1):100-102. doi: 10.21037/hbsn-21-421

