French Editorial Commentary from the ACHBPT

Utility of circulating tumor DNA in patients undergoing hepatectomy for colorectal liver metastases

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Comment on: Newhook TE, Overman MJ, Chun YS, *et al.* Prospective Study of Perioperative Circulating Tumor DNA Dynamics in Patients Undergoing Hepatectomy for Colorectal Liver Metastases. Ann Surg 2022. [Epub ahead of print]. doi: 10.1097/SLA.0000000000005461.

Keywords: Circulating tumor DNA (ctDNA); colorectal liver metastases (CRLM); somatic mutations; hepatectomy; survival

Submitted Jun 28, 2023. Accepted for publication Jul 28, 2023. Published online Sep 18, 2023.
doi: 10.21037/hbsn-23-310
View this article at: https://dx.doi.org/10.21037/hbsn-23-310

In this study recently published in *Annals of Surgery*, Newhook *et al.* studied the influence of circulating tumor DNA (ctDNA) in the management of patients undergoing hepatic resection for colorectal liver metastases (CRLM) (1). The primary objective was to study the association between the dynamic of ctDNA and somatic mutations with survival after resection of CRLM. The secondary objectives were to evaluate the impact of surgery on perioperative ctDNA dynamics and the impact of its detection on survival.

This was a prospective, single-center study conducted from January 2013 to March 2017. A total of 56 patients were included, 52 of whom underwent surgery, while 4 were excluded due to quality issues in the analyses. Thus, a total of 48 patients were included in the study. The majority of patients (88%) received prehepatectomy chemotherapy, most commonly (54%) FOLFOX (bi-chemotherapy combining 5-fluoro-uracil and oxaliplatin) or XELOX (bi-chemotherapy combining oral capecitabin and oxaliplatin) regimens, with a median of 4 cycles.

The management approach for the primary tumor was not an exclusion or non-inclusion criterion, although a reversed strategy involving primary hepatic management of synchronous CRLM was preferred. Therefore, patients requiring one- or two-stage hepatectomy with or without portal embolization were included. Additionally, 52% of patients received postoperative adjuvant chemotherapy. Exclusion criteria were defined as R2 resection, non-resectability after the first hepatic stage, and extrahepatic extension of the carcinological disease beyond the presence of non-typical lung nodules.

Somatic mutations (*RAS*; *TP53*; *SMAD4*; *FBXW7*) were detected using next-generation sequencing (NGS) from formalin-fixed samples of the primary tumor and/or CRLM. CtDNA was analyzed preoperatively (median at preoperative day 4) and postoperatively (median at postoperative day 18). The analyses were conducted blindly. Three methods were used to define the positivity of ctDNA.

A total of 34 patients (70.8%) had detectable ctDNA preoperatively, and 18 patients (37.5%) had detectable ctDNA postoperatively. Among these 34 patients, several patient profiles were defined: patients with detectable ctDNA both pre- and postoperatively ("+/+" group) (15 patients, 44%), patients with detectable ctDNA preoperatively and undetectable postoperatively ("+/–" group) (19 patients, 56%).

Among the 14 patients with non-detectable ctDNA preoperatively, there were patients with undetectable ctDNA preoperatively and detectable postoperatively ("–/+" group) (3 patients, 6.3%), and patients without detectable ctDNA both pre- and postoperatively ("–/–" group) (11 patients, 21.2%).

The median follow-up for this cohort was

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56 months, with a median recurrence-free survival (RFS) of 10 months and a median overall survival (OS) of 58 months. Postoperative recurrence occurred in 34 patients (71%), with 26 patients (54%) experiencing recurrence within 12 months postoperatively. Preoperative detection of ctDNA was not associated with RFS or OS. However, the presence of postoperative ctDNA was significantly associated with RFS (7.5 *vs.* 33 months, P=0.005) and OS (42.0 *vs.* not reached, P=0.015). It should be noted that the median OS in patients without detectable ctDNA postoperatively was not reached due to a short follow-up period in the study. Consistent with these results, the perioperative dynamics of ctDNA were significantly associated with OS and RFS. Specifically, the "–/–" and "+/–" profiles (ctDNA clearance) were more strongly associated with survival outcomes than the "+/+" profile.

In univariate analysis, the presence of bilateral CRLM was significantly associated with the detection of postoperative ctDNA (P=0.009). Additionally, patients with positive postoperative ctDNA more often received adjuvant chemotherapy and had a higher median level of carcinoembryonic antigen postoperatively (3.2 *vs.* 1.9 ng/mL, P=0.04). It should be noted that the analyses were conducted in a univariate manner due to the small sample size of this cohort.

The parameters significantly associated with decreased RFS and OS in this study, in univariate analysis, were the presence of bilateral CRLM [hazard ratio (HR) =2.32] and the detection of postoperative ctDNA (HR =3.23).

Regarding somatic mutations, they were present in 81% of patients. The most frequently identified mutations were *APC* mutation (56%), *TP53* mutation (54%), and *RAS* mutation (48%), and they were identified in patients with both preoperative and postoperative detectable ctDNA. However, the presence of these mutations was not significantly associated with the detection of ctDNA.

The authors conclude on the importance of a "dynamic" measurement of ctDNA, both preoperatively and postoperatively, to better stratify the risk of recurrence and define the prognosis of patients with resectable CRLM. Indeed, standalone preoperative or postoperative measurements have limited utility. However, postoperative clearance of ctDNA is associated with a better prognosis. Measurement of ctDNA would provide more precise and reliable results than the detection of somatic tumor mutations, thus opening the door to personalized and non-invasive management.

Patients with CRLM have a high rate of postoperative recurrence (60% to 80% at 3 years) (2,3). Identifying the profiles of patients at the highest risk would enable a more tailored therapeutic approach in preventing recurrence.

CtDNA is distinguished from healthy circulating DNA by the presence of oncogenic mutations, similar to the mutations found in the tumor from which the ctDNA fragments originate. The detection of ctDNA is a technique that is currently being developed in many cancers, including lung, colorectal, breast, pancreatic, and others. CtDNA is gradually emerging as a highly sensitive marker in patient monitoring, significantly correlated with residual tumor mass and postoperative recurrence in both metastatic and non-metastatic patients (4). To date, studies on ctDNA have focused on small, heterogeneous cohorts, mostly examining pre- or postoperative detection without exploring the dynamics and changes in measurements (5).

While the prognostic value of postoperative detection of ctDNA is well-established in several studies, the negation of postoperative measurements is demonstrated for the first time as a favorable prognostic factor in this study (2,5). These results suggest a new objective in the surgical management of CRLM, namely achieving negative ctDNA postoperatively.

However, there is a lack of closer follow-up in ctDNA measurements, particularly at the time of diagnosis and in the postoperative period. The preoperative measurement could have been influenced by chemotherapy administration or surgical intervention for the primary tumor. Nevertheless, the value of preoperative measurements did not show significance in this study, contrasting with the existing literature. In fact, some authors even recommend surgery for patients with negative preoperative ctDNA after chemotherapy.

The findings reported in this study are consistent with current literature. Although still experimental, ctDNA appears to be a highly sensitive marker in evaluating recurrence, with a high positive predictive value (2-7).

Taking into account somatic tumor mutations was stated as one of the objectives of this study. Although the results were not significant regarding the detection of ctDNA, a conclusion from the authors on this matter would have been interesting.

The strengths of this study, as highlighted by the authors, were the extended follow-up and the consideration of somatic mutations. Additionally, the use of three methods for detecting ctDNA and their comparison likely allowed for better detection of ctDNA, thus yielding more reliable results. However, the authors did not specify whether

positivity of ctDNA needed to be obtained through all three measurements or just one. Lastly, a notable strength of this study was its prospective nature.

The limitations of the study, as mentioned by the authors, were the small sample size and the lack of longitudinal follow-up in DNA measurements, particularly during chemotherapy and/or recurrence. Indeed, the persistence of ctDNA after chemotherapy appears to be a marker of poor prognosis and residual disease. Furthermore, the "reappearance" of ctDNA at the time of recurrence would provide further support for its use in the oncological follow-up of patients. One weakness worth noting is the lack of precision regarding the management of the primary tumor and the necessity of two-stage hepatectomy with portal embolization. Due to the small sample size of this study, a multivariate analysis could not be conducted. Furthermore, if the sample size were larger, the authors could have created subgroups of patients (with or without the primary tumor in place and with or without two-stage hepatectomy) that could have provided more detailed results and avoided biases.

Finally, it is important to highlight the heterogeneity in the management of patients, as not all of them received neoadjuvant and/or adjuvant chemotherapy or followed the same protocols. Indeed, some studies report a clearance of ctDNA following chemotherapy. This heterogeneous population reduces the internal validity of the study.

This study paves the way for further research on larger cohorts regarding the use of ctDNA measurements in the management of CRLM. Its value is certain, but the specific measurement methods and timing remain poorly defined. The reproducibility of this work is hampered by the practices unique to each center and the available technical resources.

In conclusion, the measurement of ctDNA remains experimental to this day. Its high prognostic value and non-invasive nature make it a promising marker for follow-up in the management of patients with resectable CRLM. Further studies with larger sample sizes and a more homogeneous population will be necessary to confirm these results and potentially bring about changes in our follow-up practices and provide new therapeutic goals such as the clearance of macroscopic and biological disease through the clearance of ctDNA.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *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-23-310/coif). The 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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