Ann Surg Oncol (2024) 31:19–20
https://doi.org/10.1245/s10434-023-14445-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – HEPATOBILIARY TUMORS

Adjuvant Hepatic Artery Infusion Chemotherapy: Still Swimming in Dark Water?

Alejandro Brañes, MD[1,2], and Paul Karanicolas, MD, PhD, FRCSC, FACS[1,3]

[1]Division of General Surgery, Department of Surgery, University of Toronto, Toronto, ON, Canada; [2]Department of HPB Surgery, Complejo Asistencial Dr. Sótero del Río, Santiago, Chile; [3]Division of Surgical Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Canada

Hepato-pancreato-biliary surgical oncology is a unique specialty in many ways. It encompasses a group of extremely aggressive cancers that require very complex and highly demanding medical and surgical treatment; however, probably one of its most distinctive features, very different from other specialties, is its role in the treatment of patients with metastatic disease, mainly from colorectal malignancies.

Colorectal cancer accounted for more than 900,000 deaths worldwide in 2020, being the second most common cause of cancer death.[1] Approximately 25–30% of these patients present with metastases at diagnosis and 30% of this group will have liver metastases as the only site.[2,3] To date, surgical resection is the only potentially curative strategy for patients with colorectal cancer liver metastases (CRLM), achieving a 5-year overall survival of approximately 50%;[4] however, 60–70% of patients will develop recurrence after surgery, mostly in the remnant liver.[5,6]

Monumental efforts have been made to improve outcomes in patients with resectable CRLM. Multiple clinical trials studying perioperative or adjuvant systemic chemotherapy have failed to show a benefit in survival in this patient population.[4,7] Until now, the only adjuvant treatment strategy showing a signal of better overall survival has been the use of hepatic artery infusion (HAI) chemotherapy with the use of concomitant systemic treatment.[8,9] The rationale for this technique is based on two specific concepts. First, liver metastases receive blood supply mainly from the hepatic artery, whereas the normal liver parenchyma is supplied primarily from the portal flow. Second, floxuridine (FUDR), the most common drug used for HAI chemotherapy, has the ideal characteristics of a short half-life and a near total hepatic extraction, which allows the use of extremely high doses in the liver with minimal systemic toxicity. A recent systematic review and meta-analysis studying the role of HAI chemotherapy for the treatment of CRLM in the adjuvant setting showed a survival benefit in the pooled analysis (including randomized controlled trials [RCTs] and retrospective studies), but failed to demonstrate a better overall survival analyzing only RCTs.[10] As oncologists in the current era of precision oncology, we seek to identify patients who are most likely to benefit from this therapy; primarily, patients at risk of liver-only recurrence.

In the accompanying article, Filipe and colleagues analyzed the ability of histopathological growth patterns (HGPs) to predict the effectiveness of adjuvant HAI chemotherapy concomitantly with perioperative systemic chemotherapy in patients with resected CRLM.[11] In recent years, HGPs have been shown to be a prognostic biomarker in patients undergoing surgery for CRLM. The desmoplastic HGP (dHGP) type has been associated with a superior overall and progression-free survival in retrospective studies compared with the non-dHGP type.[12,13] In addition, the dHGP type has shown a higher rate of liver-only recurrence, whereas the non-dHGP type has been associated with a higher rate of extrahepatic metastases. This specific characteristic motivated the authors to assess whether HGPs could be a helpful tool in deciding which patients will benefit from adjuvant HAI chemotherapy. In the analysis, HAI chemotherapy and dHGPs were independently associated with improved overall, progression-free and hepatic progression-free survival. However, there was no interaction between dHGPs and HAI chemotherapy, suggesting that a dHGP is a prognostic rather than predictive biomarker. In consequence,

First Received: 21 September 2023
Accepted: 2 October 2023
Published online: 13 October 2023

P. Karanicolas, MD, PhD, FRCSC, FACS
e-mail: paul.karanicolas@sunnybrook.ca

HGPs cannot be recommended as a tool to guide the use of adjuvant HAI chemotherapy in patients with CRLM.

Even though dHGPs do not seem to be a predictive biomarker in this setting, the apparent effectiveness of HAI chemotherapy is compelling. Once again, this therapy showed that, when used concomitantly with systemic chemotherapy, it has the capacity to improve survival. However, considering the costs and adverse effects inherent to it, a means of identifying which patients will benefit the most from this treatment is sorely needed.

There are several potential reasons why HGPs were not useful as a biomarker in this study. First, most patients in the analyzed cohort received neoadjuvant chemotherapy (79%), which increases the rate of dHGP in the resected specimen compared with chemotherapy-naïve patients.[12] Given that the development of a dHGP depends on a strong immune response,[14] it is unknown whether chemotherapy-induced dHGPs have the same biological behavior as chemotherapy-naïve dHGPs. Second, there may be differences in the tumoral microenvironments of dHGPs and non-dHGPs. As a dHGP is characterized by less contact between tumoral cells and blood vessels at the microvascular level,[14] this might actually confer some degree of chemotherapy resistance at the macrometastatic level and explain the lower rate of extrahepatic metastases. In prior work, Buisman and colleagues showed that in patients with non-dHGPs who did not receive neoadjuvant chemotherapy, receipt of adjuvant chemotherapy was associated with improved survival, but not in patients with dHGPs.[15] However, this might be different at the micrometastatic level, explaining why adjuvant HAI chemotherapy was associated with improved survival in both groups after removing all macrometastases.

Further research is urgently needed to increase our understanding of HAI and aid in patient selection. The PUMP trial is an ongoing, phase III, RCT analyzing whether adjuvant HAI chemotherapy has a benefit in survival compared with resection alone.[16] We are eagerly awaiting its results. HAI chemotherapy continues to show a role in improving survival after resection in patients with CRLM. Living in an era of precision oncology, our efforts must be placed on identifying which patients will benefit the most from this promising treatment, sparing unnecessary harm and cost.

DISCLOSURE Alejandro Brañes and Paul Karanicolas declare no conflicts of interest.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–49. https://doi.org/10.3322/caac.21660.
2. Engstrand J, Nilsson H, Strömberg C, Jonas E, Freedman J. Colorectal cancer liver metastases: a population-based study on incidence, management and survival. *BMC Cancer*. 2018;18(1):1–11. https://doi.org/10.1186/s12885-017-3925-x.
3. D'Angelica M, Kornprat P, Gonen M, et al. Effect on outcome of recurrence patterns after hepatectomy for colorectal metastases. *Ann Surg Oncol*. 2011;18(4):1096–103. https://doi.org/10.1245/s10434-010-1409-1.
4. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2013;14(12):1208–15. https://doi.org/10.1016/S1470-2045(13)70447-9.
5. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol*. 2007;25(29):4575–80. https://doi.org/10.1200/JCO.2007.11.0833.
6. Wensink GE, Bolhuis K, Elferink MAG, et al. Predicting early extrahepatic recurrence after local treatment of colorectal liver metastases. *Br J Surg*. 2023;110(3):362–71.
7. Kanemitsu Y, Shimizu Y, Mizusawa J, et al. Hepatectomy followed by mFOLFOX6 versus hepatectomy alone for liver-only metastatic colorectal cancer (JCOG0603): a phase II or III Randomized controlled trial. *J Clin Oncol*. 2021;39(34):3789–99. https://doi.org/10.1200/JCO.21.01032.
8. Kemeny N. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *Nejm*. 1999. https://doi.org/10.1056/NEJM199912303412702.
9. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med*. 2005;352(7):734–5. https://doi.org/10.1056/nejm200502173520723.
10. Buisman FE, Filipe WF, Galjart B, et al. Adjuvant intra-arterial chemotherapy for patients with resected colorectal liver metastases: a systematic review and meta-analysis. *HPB*. 2022;24(3):299–308. https://doi.org/10.1016/j.hpb.2021.10.014.
11. Filipe W, Meyer Y, Buisman F, et al. The effect of histopathological growth patterns of colorectal liver metastases on the survival benefit of adjuvant hepatic arterial infusion pump chemotherapy. *Ann Surg Oncol*. 2023. https://doi.org/10.1245/s10434-023-14342-1.
12. Galjart B, Nierop PMH, van der Stok EP, et al. Angiogenic desmoplastic histopathological growth pattern as a prognostic marker of good outcome in patients with colorectal liver metastases. *Angiogenesis*. 2019;22(2):355–68. https://doi.org/10.1007/s10456-019-09661-5.
13. Höppener DJ, Galjart B, Nierop PMH, et al. Histopathological growth patterns and survival after resection of colorectal liver metastasis: an external validation study. *JNCI Cancer Spectr*. 2021;5(3):1–9. https://doi.org/10.1093/jncics/pkab026.
14. Vermeulen PB, Colpaert C, Salgado R, et al. Liver metastases from colorectal adenocarcinomas grow in three patterns with different angiogenesis and desmoplasia. *J Pathol*. 2001;195(3):336–42. https://doi.org/10.1002/path.966.
15. Buisman FE, van der Stok EP, Galjart B, et al. Histopathological growth patterns as biomarker for adjuvant systemic chemotherapy in patients with resected colorectal liver metastases. *Clin Exp Metastasis*. 2020;37(5):593–605. https://doi.org/10.1007/s10585-020-10048-w.
16. Buisman FE, Homs MYV, Grünhagen DJ, et al. Adjuvant hepatic arterial infusion pump chemotherapy and resection versus resection alone in patients with low-risk resectable colorectal liver metastases: the multicenter randomized controlled PUMP trial. *BMC Cancer*. 2019;19(1):1–9. https://doi.org/10.1186/s12885-019-5515-6.