French Editorial Commentary from the ACHBPT

CAIRO5 study from a surgical perspective

Andrius Meskauskas[1], **Maximiliano Gelli**[1,2]

[1]Gustave Roussy, Département de Anesthésie, Chirurgie et Interventionnel, Villejuif, France; [2]Université Paris-Saclay, Gustave Roussy, INSERM, Dynamique des Cellules Tumorales (U-1279), Villejuif, France

Correspondence to: Maximiliano Gelli, MD. Gustave Roussy, Département de Anesthésie, Chirurgie et Interventionnel, 114 Rue Edouard Vaillant, F-94805 Villejuif, France; Université Paris-Saclay, Gustave Roussy, INSERM, Dynamique des Cellules Tumorales (U-1279), F-94805 Villejuif, France. Email: maximiliano.gelli@gustaveroussy.fr.

Comment on: Bond MJG, Bolhuis K, Loosveld OJL, *et al.* First-line systemic treatment strategies in patients with initially unresectable colorectal cancer liver metastases (CAIRO5): an open-label, multicentre, randomised, controlled, phase 3 study from the Dutch Colorectal Cancer Group. Lancet Oncol 2023;24:757-71.

Keywords: Metastatic colorectal cancer (metastatic CRC); liver metastasis; immunotherapy

Submitted Nov 06, 2023. Accepted for publication Dec 20, 2023. Published online Jan 10, 2024.
doi: 10.21037/hbsn-23-582
View this article at: https://dx.doi.org/10.21037/hbsn-23-582

The assessment of resectability, as well as the optimal induction treatment to achieve secondary resectability in patients with colorectal cancer liver metastases (CRLM) remain debated. Bond *et al.* (1) recently presented the results of CAIRO5 trial in *Lancet Oncology*, comparing different chemotherapy regimens for initially unresectable CRLM.

CAIRO5 is a randomised phase 3 trial conducted by the Dutch Colorectal Cancer Group across 47 tertiary centres in the Netherlands and Belgium. The primary tumour sidedness and mutational profile were taken into account. Eligible patients had CRLM deemed initially unresectable by a panel of experts, without extra-hepatic disease, who had never received local hepatic treatment nor adjuvant chemotherapy for the primary tumour within 6 months before inclusion. The authors compared treatment with doublet chemotherapy (FOLFOX or FOLFIRI) plus bevacizumab (arm A) *vs.* triplet chemotherapy (FOLFOXIRI) plus bevacizumab (arm B) for the right-sided or RAS or BRAFV600E mutated tumours and treatment with doublet chemotherapy (FOLFOX or FOLFIRI) in combination with bevacizumab (arm C) or panitumumab (arm D) for non-mutated (RAS or BRAFV600E) left-side colic tumours. The choice between FOLFOX and FOLFIRI was at the investigator's discretion. The primary endpoint was progression-free survival (PFS), and the secondary endpoints were R0/R1 resection rate, PFS after treatment interruption of more than 3 months, overall survival, treatment-associated toxicity, radiological response, histological response, and postoperative morbidity. Technical resectability was evaluated at baseline (inclusion) and every 2 months by a panel of experts (15 liver surgeons and three radiologists). The correlation between the panel's assessment and the resulting outcomes was also examined.

A total of 521 patients with initially unresectable CRLM were studied in the final analysis. At diagnosis, 85% of patients were considered as potentially resectable by the expert panel. After a median follow-up of 51.1 months, triplet chemotherapy plus bevacizumab (arm B) resulted in a significant increase in median PFS [hazard ratio (HR) =0.76; 95% confidence interval (CI): 0.60–0.98; P=0.032] compared to doublet chemotherapy plus bevacizumab (arm A) in patients with right-sided or RAS or BRAFV600E mutated tumours. No difference in terms of PFS was observed in patients with left-sided tumours without RAS or BRAFV600E mutations between arms C and D (10.8 and 10.4, respectively; HR =1.11; P=0.46).

In terms of efficacy, significantly higher tumour response rates were observed in patients with right-sided or RAS or BRAFV600E mutated primary tumours treated with triplet chemotherapy plus bevacizumab (54% *vs.* 33%, P=0.0004) and in patients with left-sided tumours without RAS or BRAFV600E mutations treated with doublet chemotherapy plus panitumumab (80% *vs.* 53%, P<0.0001). Patients

in these treatment groups presented with higher severe toxicity rates.

The rate of conversion to secondary resection according to the expert panel was 57% in arm A, 64% in arm B, 73% in arm C, and 75% in arm D. The R0/R1 complete resection rates in patients with right-sided or RAS or BRAFV600E mutated colic tumours significantly increased in case of administration of triplet chemotherapy plus bevacizumab, passing from 37% (arm A) to 51% (arm B) (P=0.013). No difference was observed in terms of complete R0/R1 resection rates between arms C and D. The overall complete resection rate was 9% in the subgroup of patients initially considered as definitively unresectable.

In addition, the overall survival benefit of secondary resectability was confirmed in the different treatment arms with a significant increase in median PFS, with a similar magnitude (HR =0.5) across different arms. R0 or R1 resection and mutational status (RAS and BRAF) had no impact on PFS.

The significance of the CAIRO5 trial lies in the challenging nature of the management of patients with initially unresectable CRLM given the context of paucity of new drugs for metastatic colorectal cancer (CRC). Additionally, the advantages of immunotherapy are limited to a small subset of patients harbouring microsatellite instability (<5%). Nowadays, the progress in the efficacy of first-line chemotherapy relies on new drug combinations based on molecular biology and primary tumour sidedness.

In addition to the higher efficacy of the FOLFOXIRI-bevacizumab regimen in terms of objective response and PFS for BRAF/RAS-mutated or right-sided primary tumours, this study also carries some insights in the surgical field. Firstly, this study confirms the benefit in terms of PFS of complete local treatment in the different arms. Moreover, emphasizing the importance of routine resectability evaluation by multidisciplinary team is essential, as 9% of patients initially classified as definitely unresectable became eligible for surgery over the course of follow-up.

Comparing these findings to the existing literature, encouraging results in favour of the FOLFOX-panitumumab regimen in this subgroup of patients were recently reported by Watanabe *et al.* (2). In this phase 3 study involving 802 patients with unresectable metastatic CRC, the administration of FOLFOX in combination with panitumumab as first-line treatment was associated with an overall survival benefit without increased toxicity compared to the FOLFOX-bevacizumab regimen. Several other trials previously reported encouraging secondary resectability rates. However, as highlighted by Bond *et al.* (1), the heterogeneity in terms of resectability criteria and the chemotherapy regimens make the comparison between studies complex.

In 2015, in the phase II OLIVIA trial, Gruenberger *et al.* (3) reported similar resection rates: 49% and 61% after doublet and triplet chemotherapy combined with bevacizumab, respectively, in a population of 80 patients with initially unresectable CRLM. In the same study, the tumour response rate was 81% in patients receiving triplet chemotherapy-bevacizumab, significantly higher than the 61% in the doublet chemotherapy arm. The French phase II PRODIGE 14 (4) study compared doublet and triplet chemotherapy combined with targeted therapy (anti-EGFR or anti-VEGF depending on RAS status) in a population of 256 patients with exclusive CRLM, concluding that there was no benefit in terms of secondary resection. However, secondary resection rates remained comparable to those found in CAIRO5 and OLIVIA (3) (56.9% with triplet chemotherapy and 48.4% with doublet chemotherapy). Despite the absence of difference in terms of secondary resection rates in left-sided tumours without RAS or BRAF mutations in CAIRO5, we noted that the addition of panitumumab to triplet chemotherapy significantly increased the secondary resection rates (33.3% *vs.* 12.1%, P=0.02) in patients with unresectable metastatic CRC without RAS mutation in the VOLFI phase II trial (5). Future studies will help to better define the clinical benefit and toxicity in this patient population.

In methodological terms, Bond *et al.* (1) in the CAIRO5 study have remarkably addressed the primary sources of biases in the management of CRLM. The definition of the resectability of CRLM is marked by a wide heterogeneity in current practice, even amongst expert centres. The therapeutic options have recently been enriched with more complex procedures including parenchymal sparing techniques (6), two-stage techniques (7), and treatments using local destruction (8), making the assessment of initial resectability even more challenging. The establishment of a board of experts including hepato-pancreato-biliary (HPB) radiologists with predefined rules no longer seems to be a limiting factor in academic research, at least in The Netherlands. Thus, this type of approach should become the benchmark for future trials in this field. Bond *et al.* (9) have already presented preliminary results in the past highlighting a limited rate of agreement by the panel of experts (about a third of cases) and it has been confirmed in this latest update of the CAIRO5 study, with an overall

agreement at diagnosis not exceeding 66%. This relatively low rate, comparable to other studies (10), reflects the difficulty of assessing resectability and argues in favour of regular multidisciplinary and multicentric resectability boards among high-volume centres.

The prospective use of mutational status and the sidedness of the primary tumour as a decision-making factor in the choice of chemotherapy protocol is another strength of this study.

Unfortunately, the definition of resectability at diagnosis is relatively restrictive in this trial, as it is based on the impossibility to achieve a complete R0/R1 resection in a single stage, without considering radiological ablation techniques, portal embolization and two-staged hepatectomy. These techniques become available at re-evaluation, thus modifying the definition of resectability during the study. Also, the low rate of postoperative chemotherapy (36–48% in the different arms) in the CAIRO5 study needs to be mentioned. It is partially explained by the authors based on the current Dutch guidelines which do not recommend adjuvant chemotherapy, without assessing the general fitness of the patients to receive such treatment.

In summary, the CAIRO5 study shows that, subject to overall survival results still awaited, the FOLFOXIRI plus bevacizumab regimen should be considered as the optimal induction regimen for patients with right-sided or RAS or BRAFV600E mutated tumours with initially unresectable CRLM without extrahepatic disease. For patients with a left-sided primary tumour and without RAS nor BRAFV600E mutation, the addition of panitumumab showed no benefit in terms of secondary resectability or PFS and was responsible for a higher rate of severe toxicity compared to bevacizumab in combination with FOLFOX or FOLFIRI.

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: Both authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-582/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.

References

1. Bond MJG, Bolhuis K, Loosveld OJL, et al. First-line systemic treatment strategies in patients with initially unresectable colorectal cancer liver metastases (CAIRO5): an open-label, multicentre, randomised, controlled, phase 3 study from the Dutch Colorectal Cancer Group. Lancet Oncol 2023;24:757-71.
2. Watanabe J, Muro K, Shitara K, et al. Panitumumab vs Bevacizumab Added to Standard First-line Chemotherapy and Overall Survival Among Patients With RAS Wild-type, Left-Sided Metastatic Colorectal Cancer: A Randomized Clinical Trial. JAMA 2023;329:1271-82.
3. Gruenberger T, Bridgewater J, Chau I, et al. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. Ann Oncol 2015;26:702-8.
4. Ychou M, Rivoire M, Thezenas S, et al. Chemotherapy (doublet or triplet) plus targeted therapy by RAS status as conversion therapy in colorectal cancer patients with initially unresectable liver-only metastases. The UNICANCER PRODIGE-14 randomised clinical trial. Br J Cancer 2022;126:1264-70.
5. Modest DP, Martens UM, Riera-Knorrenschild J, et al. FOLFOXIRI Plus Panitumumab As First-Line Treatment of RAS Wild-Type Metastatic Colorectal Cancer: The Randomized, Open-Label, Phase II VOLFI Study (AIO KRK0109). J Clin Oncol 2019;37:3401-11.
6. Moris D, Ronnekleiv-Kelly S, Rahnemai-Azar AA, et al. Parenchymal-Sparing Versus Anatomic Liver Resection

for Colorectal Liver Metastases: a Systematic Review. J Gastrointest Surg 2017;21:1076-85.
7. Wicherts DA, Miller R, de Haas RJ, et al. Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. Ann Surg 2008;248:994-1005.
8. Oshowo A, Gillams A, Harrison E, et al. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. Br J Surg 2003;90:1240-3.
9. Bond MJG, Kuiper BI, Bolhuis K, et al. Intersurgeon Variability in Local Treatment Planning for Patients with Initially Unresectable Colorectal Cancer Liver Metastases: Analysis of the Liver Expert Panel of the Dutch Colorectal Cancer Group. Ann Surg Oncol 2023;30:5376-85.
10. Huiskens J, Bolhuis K, Engelbrecht MR, et al. Outcomes of Resectability Assessment of the Dutch Colorectal Cancer Group Liver Metastases Expert Panel. J Am Coll Surg 2019;229:523-532.e2.

Cite this article as: Meskauskas A, Gelli M. CAIRO5 study from a surgical perspective. HepatoBiliary Surg Nutr 2024;13(1):105-108. doi: 10.21037/hbsn-23-582