



Patient with unresectable colorectal liver metastases and asymptomatic primary tumor: end of the debate!

Marc-Antoine Allard^{1,2}, René Adam^{1,2}

¹Centre Hépato-Biliaire, Hôpital Paul Brousse, APHP, Villejuif, France; ²Équipe Chronothérapie, Cancers et Transplantation, Université Paris, Saclay, France

Correspondence to: Marc-Antoine Allard. Centre Hépato-Biliaire, Hôpital Paul Brousse, APHP, Villejuif, France; Équipe Chronothérapie, Cancers et Transplantation, Université Paris, Saclay, Villejuif, France. Email: marcantoine.allard@aphp.fr.

Comment on: Kanemitsu Y, Shitara K, Mizusawa J, *et al.* Primary Tumor Resection Plus Chemotherapy Versus Chemotherapy Alone for Colorectal Cancer Patients With Asymptomatic, Synchronous Unresectable Metastases (JCOG1007; iPACS): A Randomized Clinical Trial. *J Clin Oncol* 2021;39:1098-107.

van der Kruijssen DEW, Elias SG, Vink GR, *et al.* Sixty-Day Mortality of Patients With Metastatic Colorectal Cancer Randomized to Systemic Treatment vs Primary Tumor Resection Followed by Systemic Treatment: The CAIRO4 Phase 3 Randomized Clinical Trial. *JAMA Surg* 2021;156:1093-101.

Submitted May 07, 2022. Accepted for publication May 17, 2022.

doi: 10.21037/hbsn-22-176

View this article at: <https://dx.doi.org/10.21037/hbsn-22-176>

In patients with definitively unresectable colorectal liver metastases, whether the primary tumor should be resected prior to chemotherapy is an old question.

Several retrospective studies (1-5) and a meta-analysis with individual data (6) had suggested that primary resection of the primary tumor followed by chemotherapy was associated with better survival than the chemotherapy-first strategy. The prevention of complications related to the primary tumor (occlusion, perforation, bleeding) as well as a better response to chemotherapy were usual justifications to explain the superiority of primary tumor resection-first.

However, the absence of any randomized study made it difficult to conclude on this question due to the numerous selection biases related to these retrospective analyses.

The year 2021 was marked by the publication of two randomized trials (a Japanese iPACS and a European trial: CAIRO4) (7,8) comparing upfront surgery for the primary tumor versus chemotherapy-first in patients with colorectal liver metastases and asymptomatic primary tumor.

In a Japanese multicenter randomized trial, Kanemitsu *et al.* (7) have included 165 patients with asymptomatic colorectal cancer (excluding cancers of the lower and middle rectum) and unresectable liver metastases, thus constituting two comparable groups, one treated by resection-first of the primary tumor followed by chemotherapy (experimental group) and the other by chemotherapy-first (control group).

The hypothesis tested by the authors was that surgery-first may be superior to chemotherapy-first for overall survival.

After a median follow-up of 22 months, the first interim analysis concluded that the probability of demonstrating the superiority of the primary resection-first was very low, which led to stopping the trial prematurely. The median overall survival was 25.9 months in the experimental arm and 26.7 months in the control group, with postoperative mortality of 4% after colorectal surgery. Resection of the primary tumor was finally required in only 13% of patients in the chemotherapy-first group because of the onset of primary tumor-related complications. The subgroup analysis failed to identify a particular group of patients who might benefit from surgery of the primary. Still, it showed that surgery in patients with a performance status of 1 (outpatient but decreased physical activity) was associated with an increased risk of postoperative mortality. Finally, 6% of patients in the chemotherapy-first group underwent a secondary R0 resection of the metastatic lesions, after an excellent response to chemotherapy, compared to only 2% of patients in the primary resection group.

With similar inclusion criteria and design, the CAIROS-3 trial (196 patients included) conducted by a Danish-Dutch group reported a 60-day mortality of 11% in the primary surgery group versus 3% in the chemotherapy-first group. Among the 5 early deaths after primary tumor

resection, one was attributed to surgical complications, and the other four were related to disease progression after colorectal surgery. So far, these results are those of preliminary analysis, and the data on overall survival are not yet available. However, there was a significantly increased risk of early mortality after surgery of the primary tumor compared to chemotherapy-first.

These two trials concluded that primary surgery in patients with unresectable liver metastases and an asymptomatic primary tumor could not be recommended. In addition, a subgroup that could potentially benefit from primary surgery could be identified.

While some methodological purists will argue that these results do not demonstrate the superiority of chemotherapy-first in terms of overall survival, our analysis of these results is different. Indeed, given the increased early mortality observed after surgery, the low risk of primary tumor-related complications while on chemotherapy, and the trend towards better control of the disease with a higher chance of secondary resection after chemotherapy, we believe that primary chemotherapy should be the standard treatment in these patients with unresectable liver metastases and asymptomatic primary tumor.

Two trials are currently underway (9,10) and will probably provide additional answers to this question if it has not already been definitively settled.

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-22-176/coif>). RA serves as an unpaid editorial board member of *Hepatobiliary Surgery and Nutrition*. The other author has 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.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

- Galizia G, Lieto E, Orditura M, et al. First-line chemotherapy vs bowel tumor resection plus chemotherapy for patients with unresectable synchronous colorectal hepatic metastases. *Arch Surg* 2008;143:352-8; discussion 358.
- Ferrand F, Malka D, Bourredjem A, et al. Impact of primary tumour resection on survival of patients with colorectal cancer and synchronous metastases treated by chemotherapy: results from the multicenter, randomised trial Fédération Francophone de Cancérologie Digestive 9601. *Eur J Cancer* 2013;49:90-7.
- Ahmed S, Leis A, Fields A, et al. Survival impact of surgical resection of primary tumor in patients with stage IV colorectal cancer: results from a large population-based cohort study. *Cancer* 2014;120:683-91.
- Gresham G, Renouf DJ, Chan M, et al. Association between palliative resection of the primary tumor and overall survival in a population-based cohort of metastatic colorectal cancer patients. *Ann Surg Oncol* 2014;21:3917-23.
- Ishihara S, Hayama T, Yamada H, et al. Prognostic impact of primary tumor resection and lymph node dissection in stage IV colorectal cancer with unresectable metastasis: a propensity score analysis in a multicenter retrospective study. *Ann Surg Oncol* 2014;21:2949-55.
- Faron M, Pignon JP, Malka D, et al. Is primary tumour resection associated with survival improvement in patients with colorectal cancer and unresectable synchronous metastases? A pooled analysis of individual data from four randomised trials. *Eur J Cancer* 2015;51:166-76.
- Kanemitsu Y, Shitara K, Mizusawa J, et al. Primary Tumor Resection Plus Chemotherapy Versus Chemotherapy Alone for Colorectal Cancer Patients With Asymptomatic,

- Synchronous Unresectable Metastases (JCOG1007; iPACS): A Randomized Clinical Trial. *J Clin Oncol* 2021;39:1098-107.
8. van der Kruijssen DEW, Elias SG, Vink GR, et al. Sixty-Day Mortality of Patients With Metastatic Colorectal Cancer Randomized to Systemic Treatment vs Primary Tumor Resection Followed by Systemic Treatment: The CAIRO4 Phase 3 Randomized Clinical Trial. *JAMA Surg* 2021;156:1093-101.
 9. Rahbari NN, Lordick F, Fink C, et al. Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS--a randomised controlled multicentre trial (ISRCTN30964555). *BMC Cancer* 2012;12:142.
 10. Karoui M. Colectomy in Patients With Asymptomatic and Unresectable Stage IV Colon Cancer (CLIMAT). Available online: <https://clinicaltrials.gov/ct2/show/NCT02363049>

Cite this article as: Allard MA, Adam R. Patient with unresectable colorectal liver metastases and asymptomatic primary tumor: end of the debate! *HepatoBiliary Surg Nutr* 2022;11(3):412-414. doi: 10.21037/hbsn-22-176