Editorial

Does laparoscopic resection for colorectal cancer liver metastasis have a long-term oncologic advantage?

Yasushi Hasegawa, Minoru Kitago, Yuta Abe, Yuko Kitagawa

Department of Surgery, Keio University School of Medicine, Tokyo, Japan

Correspondence to: Yasushi Hasegawa, MD, PhD. Department of Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. Email: hasegawayas@keio.jp.

Comment on: Syn NL, Kabir T, Koh YX, *et al.* Survival Advantage of Laparoscopic Versus Open Resection For Colorectal Liver Metastases: A Meta-analysis of Individual Patient Data From Randomized Trials and Propensity-score Matched Studies. Ann Surg 2020;272:253-65.

Submitted Nov 24, 2020. Accepted for publication Dec 09, 2020.

doi: 10.21037/hbsn-20-807

View this article at: http://dx.doi.org/10.21037/hbsn-20-807

The long-term advantages of laparoscopic liver resection (LLR) over open liver resection (OLR) for colorectal cancer liver metastasis (CLM) have not been examined. Syn *et al.* (1) recently published an interesting article in the *Annals of Surgery*, titled "*Survival Advantage of Laparoscopic Versus Open Resection for Colorectal Liver Metastases: A Meta-analysis of Individual Patient Data from Randomized Trials and Propensity-score Matched Studies.*" The authors performed a meta-analysis of individual participant data from two randomized trials and thirteen propensity score-matched studies that compared long-term outcomes between patients undergoing LLR and OLR for CLM. A total of 1,275 patients who underwent LLR and 1,873 patients who underwent OLR were included. They found that LLR was associated with a lower risk of death and concluded that LLR had a long-term survival benefit compared to OLR.

The use of LLR for CLM has a relatively short history and its use is still limited. Discussion of the learning curve and operative devisal have shifted from favoring minor hepatectomy to favoring major hepatectomy or technically difficult resection within the last decade (2-4). The short-term advantages of LLR are well known, including fewer complications, transfusions, and analgesic requirements; less blood loss and pain; and shorter hospital stays (5,6). However, its superiority in terms of long-term outcomes compared to OLR for CLM had not been reported until this article was published. Therefore, we found this article remarkably interesting.

With the development of computer technology, statistical methods have improved. In response to limitations imposed by the traditional meta-analysis, an increasingly popular approach for data synthesis is performing individual participant data meta-analysis, in which the raw individual-level data for each study are obtained and used for synthesis (7). Further, the statistical methods developed in this study were used to download, pre-process, and digitize vector and raster images of Kaplan-Meier curves from the included studies to obtain the step function values and timings of the steps. Survival information of individual patients was then recovered based on the numerical solutions to the inverted Kaplan-Meier product-limit equations (1). When the number of enrolled patients in each study is not large enough, the statistical power is limited. This relatively new method is useful in overcoming this problem, which often occurs in clinical trials for surgical procedures, especially when examining long-term outcomes. Finally, their integrated data showed a significant advantage of laparoscopic procedures for oncologic outcomes.

However, Pan *et al.* (8) point out that the conclusion of this study should be interpreted with caution. First, synchronous resections should be excluded because two different surgical procedures lead to two kinds of prognostic patterns. Second, there was partial population overlap. Finally, some covariates, such as the location of the primary tumor, TNM stage of the primary tumor, tumor histological grade, R0 resection rate of the primary colorectal cancer and CLM, and adjuvant chemotherapy, were not selected as matching factors in each cohort study.

Additionally, we have a grave concern. In their Kaplan-Meier curve, the survival patterns of LLR and OLR were very similar until 60 months, and marked differences were noted after 60 months. There were also large differences in the number at risk between the two groups. The percentages of numbers at risk compared to the included patients were 77.5% at 24 months, 40.7% at 60 months, and 11.7% at 96 months in the OLR group. In contrast, the rates were 75.3% at 24 months, 30.7% at 60 months, and 1.1% at 96 months in the LLR group. Although the rate of death was lower in the LLR group, the number of patients with long-term follow-up was small. This would indicate that the number of censorings was significantly larger in the LLR group and that the follow-up periods differed between the two groups. We are afraid that these gaps in the numbers at risk could affect their conclusions.

The overall survival of patients with CLM has been improving annually (9,10). LLR has a short history compared to OLR; therefore, in general, patients who underwent LLR did so more recently than those who underwent OLR. Hence, there could be a time lag of hepatectomy in propensity score-matched studies, which would affect the overall survival periods between the LLR and OLR groups. Randomized controlled trials do not have this problem, but propensity score-matched studies with matched time periods might be required for proper analyses of long-term outcomes between LLR and OLR.

Nevertheless, it is true that LLR has several benefits compared to OLR. The authors discussed that these benefits, for example, earlier induction of adjuvant chemotherapy, lower the rate of postoperative morbidity, lower the burden of dense adhesions, create easier access for repeat hepatectomy, result in fewer pro-inflammatory molecules, and lower levels of surgical stress, which might lead to survival advantages (1). We also hope that the minimally invasive nature of LLR leads to not only improved short-term outcomes but also lower risks of cancer recurrence and longer survival times. Further studies with high levels of evidence are needed.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.
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-20-807/coif). Dr. YK reports grants from Ono Pharmaceutical Co., Ltd., grants from Bristol-Myers Squibb, during the conduct of the study; grants and personal fees from ASAHI KASEI PHARMA CORPORATION, grants and personal fees from TAIHO PHARMACEUTICAL Co., Ltd., grants and personal fees from CHUGAI PHARMACEUTICAL Co., Ltd., grants from DAIICHI SANKYO COMPANY, LIMITED, grants from Merck Serono Co., Ltd., grants and personal fees from EA Pharma Co., Ltd., grants and personal fees from Yakult Honsha Co., Ltd., grants and personal fees from Otsuka Pharmaceutical Co., Ltd., grants from Takeda Pharmaceutical Co., Ltd., grants and personal fees from Otsuka Pharmaceutical Factory Inc., grants and personal fees from SHIONOGI & Co., Ltd., grants from KAKEN PHARMACEUTICAL Co., Ltd., grants from Kowa Pharmaceutical Co., Ltd., grants and personal fees from Astellas Pharma Inc., grants from MEDICON Co., Ltd., grants and personal fees from DAINIPPON SUMITOMO PHARMA Co., Ltd., grants and personal fees from Taisho Toyama Pharmaceutical Co., Ltd., grants from Kyouwa Hakkou Kirin Co., Ltd., grants from Pfizer Japan Inc., grants and personal fees from ONO PHARMACEUTICAL Co., Ltd., grants and personal fees from NIHON PHARMACEUTICAL Co., Ltd., grants from Japan Blood Products Organization, grants from Medtronic Japan Co., Ltd., grants and personal fees from Sanofi K.K., grants from Eisai Co., Ltd., grants from TSUMURA & Co., Ltd., grants from KCI Licensing, Inc., grants from ABBOTT JAPAN Co., Ltd., grants from FUJIFILM Toyama Chemical Co., Ltd., grants from Nippon Covidien Inc., outside the submitted work. 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: Hasegawa Y, Kitago M, Abe Y, Kitagawa Y. Does laparoscopic resection for colorectal cancer liver metastasis have a long-term oncologic advantage? HepatoBiliary Surg Nutr 2021;10(2):246-248. doi: 10.21037/hbsn-20-807