Editorial Commentary

Perioperative safety in patients with resectable synchronous colorectal liver metastases

Lucas D. Lee, Y. Nancy You

Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Correspondence to: Y. Nancy You, MD, MHSc. Associate Professor, Department of Surgical Oncology; Associate Medical Director, Clinical Cancer Genetics Program, University of Texas MD Anderson Cancer Center, 1400 Pressler Street, Unit 1484, PO Box 301402, Houston, TX 77230, USA. Email: ynyou@mdanderson.org.

Comment on: Wu Y, Liu F, Song W, *et al*. Safety evaluation of simultaneous resection of colorectal primary tumor and liver metastasis after neoadjuvant therapy: A propensity score matching analysis. Am J Surg 2018. [Epub ahead of print].

Submitted Jul 15, 2019. Accepted for publication Jul 17, 2019.
doi: 10.21037/cco.2019.07.08
View this article at: http://dx.doi.org/10.21037/cco.2019.07.08

Worldwide, at least a quarter of the patients with colorectal cancer (CRC) are diagnosed with metastatic disease at presentation and many of them eventually succumb to their disease. A third of these patients may have their metastatic disease burden confined to the liver. It has been estimated that about 15–25% of CRC patients initially present with synchronous resectable liver metastases (SRLM) (1). These patients represent a group whose oncologic prognosis has significantly improved over the past decades (2).

The successful treatment of CRC patients with SRLM depends on judicious assessment of their disease biology and technical resectability. Multiple effective systemic chemotherapy regimens and targeted agents have become available in the past decade and have allowed excellent control of a tumor's metastatic activity and potential (2). Tumor response to systemic chemotherapy has enabled identification and selection of patients most suitable for surgical resection of curative-intent (3,4). Concurrently, advances in surgical technique for both the primary CRC as well as for liver disease have enabled more patients to be technically resectable (5). Finally, induction chemotherapy can successfully convert additional patients with unresectable to resectable disease. Taken together, management of these patients epitomizes personalized medicine. Multidisciplinary evaluation centered on the individual patient's disease anatomy, biology and personal condition is essential to achieving the greatest oncological benefit. Successful treatment with a combination of systemic therapy and surgical resection of all gross disease provides the only effective chance at cure. Depending on the extent of liver metastases, the 5-year overall survival (OS) ranges from 38% to 71% (6).

Indeed, the clinical manifestations of CRC with SRLM is highly heterogeneous, and no single treatment algorithm is suitable for all patients. Ongoing discussions and controversies exist around several key issues: (I) the use of neoadjuvant chemotherapy in patients with technically resectable disease; (II) the optimal sequence of surgical resection for the primary tumor and the liver metastases when synchronous pathology is present; and (III) the role of systemic chemotherapy after resection of all gross disease. While neoadjuvant chemotherapy is well accepted when used as conversion therapy for rendering initially unresectable patients technical resectable, its use in patients with immediately resectable SRLM is more controversial. As oncologic benefit of adding chemotherapy in this setting has not been fully established, there is the theoretical concern that pre-operative chemotherapy could increase the risks of operative complications. In this context, the study of Wu *et al*. contributes to these ongoing discussions by investigating whether simultaneous resection can be safety performed after neoadjuvant systemic chemotherapy (NC). Specifically, the authors aimed to compare the rate of postoperative mortality and morbidity rates in patients who undergo simultaneous resection of their primary CRC and SRLM with *vs*. without preoperative chemotherapy, using a propensity score matched analysis.

The oncologic benefit of preoperative chemotherapy in patients who present with primary CRC and SRLM has been controversial. The rationale for NC is based on

the presumption that microscopic metastatic disease is present at the time of diagnosis, and that early systemic treatment of micrometastases could potentially reduce the risk of macrometastatic disease relapse after completion of curative-intent therapy. Additionally, NC could also serve as "test-of-time" to provide an understanding of disease biology and overall prognosis. Patients who progress under active treatment are likely poor candidates for resection. Available literature, however, indicated that clinical response to NC did not consistently correlate with OS after hepatic resection of SCLMs (7). A pooled analysis of data from multiple institutions also failed to definitively demonstrate an OS benefit from NC (8). Level 1 evidence is available from the EPOC trial, which compared perioperative FOLFOX4 plus surgery versus surgery alone. The results showed improved progression-free survival (PFS), but not OS (9). While the EPOC trial enrolled largely patients with very low burden of liver metastatic disease, an ongoing randomized trial CHARISMA is investigating perioperative chemotherapy in patients with a higher disease burden. In conclusion, as summarized at the Expert Group on OncoSurgery management of Liver Metastases (EGOLISM) meeting, most surgeons agree on the beneficial use of preoperative chemotherapy for downsizing and converting initially unresectable synchronous metastases to resectable disease, but there is less consensus for their use in the case of resectable SCLMs (10).

The risks associated with preoperative chemotherapy may include both acute toxicities that manifest during chemotherapy and longer-term negative impacts on the course of disease. Different NC regimens carry diverse toxicities profiles. In this study, the NC given most often included CapeOX, mFOLFOX6, and FOLFIRI. Targeted agents (bevacizumab/cetuximab) were used in only in the minority (20 patients, or one sixths) of the patient population. Prior studies have reported characteristic patterns of hepatic injury associated with prolonged administration of systemic chemotherapy (11). Specifically, oxaliplatin-based regimens can be associated with sinusoidal obstructive syndrome, while irinotecan-based regimens can led to steatohepatitis (12,13). The total duration of preoperative therapy in this study was heterogenous, ranging from 3 to 10 cycles. Indeed, because the risk of perioperative morbidity significantly increases when greater than 6 cycles preoperative chemotherapy is administered (11), we would suggest that the duration of neoadjuvant chemotherapy be a matched factor in the comparative analysis.

It is well established that when operative complications deviate the patient from the intended oncologic therapies, the risk of disease relapse increases (14,15). Therefore, it is critical to minimize complications in order to maximize the ability of patients to successfully complete resection of all gross disease and receipt of all intended cycles of perioperative chemotherapy (16). Indeed, we regard "return to intended oncologic therapy" (RIOT) as a novel metric for evaluating the quality of onco-surgical therapy for colorectal liver metastases (14). Patients with a rectal cancer primary and SRLM constitute a subgroup of patients in whom treatment sequencing is particularly challenging (16). While simultaneous resection of liver disease and colon primary is well accepted, simultaneous resection of liver disease and a locally advanced low lying rectal cancer requires more considerations. First, the use of pelvic radiation aimed to optimize local control is controversial in this setting of metastatic rectal cancer. The traditional indications for pelvic radiation had included clinical T3/4, clinical nodal positive, and/or involvement of circumferential resection margin at diagnosis. However, there is increasing evidence supporting the oncologic safety of omitting radiation in some of these rectal cancers. For example, the OCUM trial compared neoadjuvant chemoradiation *vs.* upfront resection in clinical ≥ T3 rectal cancers without threatened circumferential resection margin, and showed no compromise in local recurrence with upfront surgery (17). Second, rectal surgery and particularly that performed after preoperative radiation are likely to carry higher risks for anastomotic and infectious complications when compared to colon surgery (18). Therefore, some surgeons are cautious to isolate rectal resection and its attendant postoperative morbidity rather than performing it as a combine resection (16,19). In this study, half of the patients (51%) had rectal cancers and 13 had long-course pelvic radiation. Thus, the subgroup of patients who received neoadjuvant radiation differs from the remaining patients in both the total amount of preoperative therapy received and in the interval between end of systemic chemotherapy and surgical resection. Whether these differences contribute to the overall complication rate is unknown and matching the comparative groups for the use of neoadjuvant radiation in addition to neoadjuvant chemotherapy may be prudent.

The safety of simultaneous liver and colorectal resection in well selected patients has long been demonstrated in numerous series (20). Patient selection is required because complications rates significantly increase with greater magnitude of liver and with higher complexity of primary resections (18). In this study, the overall 90-day

complication rate was laudably low at 15%. Importantly, the study raised the further question of whether the addition of preoperative chemotherapy impacts on the morbidity rate of such simultaneous resections, and showed that the 90-day morbidity rate did not statistically differ in a matched analysis. There was also no detectable difference in the rates of Grade III-IV complications (non-NC =7.3% *vs.* NC =5.2), or in the distribution of hepatic *vs.* colorectal-related complications. Ultimately, the patients did not differ in the interval to adjuvant therapy. This study thus had re-demonstrated the safety of simultaneous resection in select patients, but the lack of detectable statistically significant difference may reflect the favorably low complications rates overall and the relatively small cohort sizes.

In summary, the study by Wu *et al.* addresses an important gap in our knowledge, which is whether preoperative systemic chemotherapy negatively impacts on the safety of simultaneous resection for primary CRC and SRLM. Although the reported event rates are low and the cohort size is relatively small, the findings add to the body of literature supporting that increased risk of postoperative complications is unlikely a substantial reason to preclude the use of preoperative chemotherapy. On the other hand, the questions of the oncological benefit of upfront chemotherapy in the setting of disease amendable to simultaneous resection and the key decision making factors for treatment sequencing will likely depend on multidisciplinary and risk-stratified discussions focused on the individual patients.

Acknowledgments

None.

Footnote

Conflicts of Interest: 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. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg 2006;244:254-9.
2. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 2009;27:3677-83.
3. Chun YS, Vauthey JN, Boonsirikamchai P, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. JAMA 2009;302:2338-44.
4. Shindoh J, Loyer EM, Kopetz S, et al. Optimal morphologic response to preoperative chemotherapy: an alternate outcome end point before resection of hepatic colorectal metastases. J Clin Oncol 2012;30:4566-72.
5. Torzilli G, Nagino M, Tzeng CD, et al. SSAT state-of-the-art conference: new frontiers in liver surgery. J Gastrointest Surg 2017;21:175-85.
6. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235:759-66.
7. Gallagher DJ, Zheng J, Capanu M, et al. Response to neoadjuvant chemotherapy does not predict overall survival for patients with synchronous colorectal hepatic metastases. Ann Surg Oncol 2009;16:1844-51.
8. Bonney GK, Coldham C, Adam R, et al. Role of neoadjuvant chemotherapy in resectable synchronous colorectal liver metastasis; An international multi-center data analysis using LiverMetSurvey. J Surg Oncol 2015;111:716-24.
9. 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;14:1208-15.
10. Adam R, de Gramont A, Figueras J, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. Cancer Treat Rev 2015;41:729-41.
11. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006;24:2065-72.
12. Robinson SM, Wilson CH, Burt AD, et al. Chemotherapy-associated liver injury in patients with colorectal liver metastases: a systematic review and meta-analysis. Ann Surg Oncol 2012;19:4287-99.
13. Zhao J, van Mierlo KMC, Gómez-Ramírez J, et al. Systematic review of the influence of chemotherapy-

associated liver injury on outcome after partial hepatectomy for colorectal liver metastases. Br J Surg 2017;104:990-1002.
14. Lillemoe HA, Marcus RK, Kim BJ, et al. Detours on the road to recovery: what factors delay readiness to return to intended oncologic therapy (RIOT) after liver resection for malignancy? J Gastrointest Surg 2019. [Epub ahead of print].
15. Tzeng CW, Vauthey JN. Postoperative complications and oncologic outcomes after resection of colorectal liver metastases: the importance of staying on track. Ann Surg Oncol 2013;20:2457-9.
16. Conrad C, Vauthey JN, Masayuki O, et al. Individualized treatment sequencing selection contributes to optimized survival in patients with rectal cancer and synchronous liver metastases. Ann Surg Oncol 2017;24:3857-64.
17. Ruppert R, Junginger T, Ptok H, et al. Oncological outcome after MRI-based selection for neoadjuvant chemoradiotherapy in the OCUM rectal cancer trial. Br J Surg 2018;105:1519-29.
18. Shubert CR, Habermann EB, Bergquist JR, et al. A NSQIP review of major morbidity and mortality of synchronous liver resection for colorectal metastasis stratified by extent of liver resection and type of colorectal resection. J Gastrointest Surg 2015;19:1982-94.
19. Tzeng CW, Aloia TA, Vauthey JN, et al. Morbidity of staged proctectomy after hepatectomy for colorectal cancer: a matched case-control analysis. Ann Surg Oncol 2013;20:482-90.
20. Silberhumer GR, Paty PB, Denton B, et al. Long-term oncologic outcomes for simultaneous resection of synchronous metastatic liver and primary colorectal cancer. Surgery 2016;160:67-73.

Cite this article as: Lee LD, You YN. Perioperative safety in patients with resectable synchronous colorectal liver metastases. Chin Clin Oncol 2019;8(Suppl 1):S23. doi:10.21037/cco.2019.07.08

