



Controversies in the optimal surgical approach to colon cancer with isolated liver metastases

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Colorectal cancer (CRC) is the second leading cause of cancer-related death in North America (1). Synchronous hepatic metastases are diagnosed in 15% to 20% of patients with CRC. For these patients, it has become the standard that a multidisciplinary team tailor treatment approaches to the individual patient (2,3). For patients with resectable disease, aggressive surgical resection may be warranted. Currently, three surgical approaches are performed for resectable metastatic CRC: the conventional colorectal-first approach (CFA), simultaneous resection approach (SRA), and the liver-first approach (LFA). CFA, SRA, LFA are three surgical approaches with distinct advantages and limitations. Nonetheless, they have the same final objective: R0 resection of the liver metastases and the primary tumor.

The conventional CFA describes primary resection followed by liver resection. CFA has classically been advised for symptomatic patients in order to prevent further complications related to the progression of the primary tumor such as obstruction, perforation, or hemorrhage (4,5). However, CFA can delay the management of the liver metastases, especially in case of postoperative complications of colorectal surgery, and carries the risk of hepatic metastatic progression. Indeed, one study showed that less than 30% of patients undergoing conventional management complete the two operations, whereas up to 80% of patients undergoing the LFA do (6).

The SRA, born from a combination of advancements in surgical technique and evidence of chemotherapy

hepatotoxicity, has the advantage of avoiding multiple surgeries. It has been shown to be safe and effective except for patients requiring two major surgeries (7). However, a recent study showed that although the three approaches had similar outcomes, SRA had significantly more severe complications despite less aggressive liver disease and more limited liver resections (8).

LFA is usually reserved for patients with significant metastatic liver disease and an asymptomatic primary tumor. Indeed, in the case of numerous liver metastases, the prognosis of the disease is based on the liver. Also, for low rectal cancers, the primary tumor resection can lead to life discomfort, which is a risk that should not be taken if the liver metastases cannot be controlled (8).

Although multidisciplinary international consensus (5) has detailed recommendations for optimal surgical procedures, the optimal approach remains controversial because of the lack of strong evidence or a randomized clinical trial (9). Current recommendations state that chemotherapy and then SRA should be reserved for selected patients with both resectable lesions and not requiring two major surgical procedures (5). The consensus for asymptomatic CRC patients with large synchronous liver metastases tumor burden and impossibility of combined resection is to receive chemotherapy and then the LFA option if tumor shrinkage is achieved (5). On the other hand, the recommendation for symptomatic CRC patients is to receive the conventional CFA. Nonetheless,

there is a current gap in knowledge since these empirical recommendations are not supported by randomized trials. Additionally, current data from meta-analyses over the years have found no significant differences in survival outcome between the three approaches (4,10,11).

The study by Kurbatov *et al.* provides evidence for potentially favoring an LFA versus the CFA and SRA (12). They included in their analysis 21,788 patients with colon adenocarcinoma and isolated liver metastases that underwent surgical intervention from the National Cancer Database between 2010–2015, but only 2% of the patients received LFA treatment. The Kaplan-Meier analysis demonstrated an increased survival for the LFA cohort in the overall comparison and the comparison restricted to patients that completed their treatment operation. The resulting multivariable Cox proportional hazards analysis adjusted for patient and tumor characteristics confirmed this significant difference. However, the authors added the presence and timing of chemotherapy in a second multivariable Cox proportional hazards analysis and the LFA lost its significant difference, and only demonstrated a trend towards survival benefit.

The authors conclude that LFA for colon adenocarcinoma is significantly associated with a greater likelihood of receiving chemotherapy prior to surgery and an increased survival in selected patients. They do also caution that their results have to be interpreted in the context that due to selection bias, the patients who received an LFA were younger, less comorbid (by Charlson comorbidity score), received more commonly chemotherapy prior to surgery and may have had more favorable disease prior to the operation. Indeed, the loss of significance from including the chemotherapy timing variable and other limitations suggests that more research is necessary before a strong recommendation can be made. Kurbatov *et al.* propose the loss of significance to be due to upfront chemotherapy allowing time to select patients with more favorable biology for surgery. This phenomenon has been shown in the CFA as well (13), and enhances the selection bias the authors mention. In addition, LFA surgeries were much more likely to be performed at an academic center, and of those hospitals that performed an LFA resection, a majority only had a single operation in the 5-year span. These variables were not included in the multivariable proportional hazards analysis and may have influenced the survival as well. Furthermore, limitations of the dataset prevented the analysis of key variables such as size and number of liver metastases, number of resected segments, R0 rate, and

postoperative outcomes. Lastly, LFA could not be compared individually to CFA and SRA as the non-LFA cohort consisted of both simultaneous and conventional approaches. Overall, there is some promising evidence to show that LFA has potential in improving clinical outcomes for certain patients with metastatic colon adenocarcinoma. Future work utilizing propensity score matching analysis may provide more retrospective evidence in a more controlled setting. Clarifying the distinction between the effects of upfront chemotherapy and LFA will be key. Ultimately, a randomized clinical trial will need to be done to provide a definitive comparison, though that has its own limitations.

Two other aspects of the study design limit the generalizability to current practice. First, practices have evolved since 2015, and nowadays, treatment of metastatic colon cancers can be more aggressive, due to advances in technical surgical procedures that allow a better control of liver metastatic sites. For instance, portal embolization (possibly associated with hepatic vein embolization) allows an increase in the size of the future liver remnant and gives the option for more aggressive liver surgery techniques for patients previously considered as unresectable. Second, development of new imaging guided liver ablation techniques, also called thermal ablations, represent an important step in liver metastases management (14-16). Indeed, thermal ablation has proved to be non-inferior to surgery in treating lesions less than 3 cm, with a significant decrease in post-procedural morbidity and mortality, length of hospital stay and incremental costs, without compromising oncological outcome for patients with colorectal liver metastases (CRLM) (17,18). The common use of these techniques nowadays, alone or in combination with liver resection, will probably influence future therapeutic strategies, and require large randomized trials in order to establish the best possible strategies for these patients. Finally, recent breakthroughs in the field of artificial intelligence (i.e., radiomics, machine-learning, deep-learning) are increasingly studied in CRC patients with liver metastatic disease to decipher tumor imaging phenotype and use this information as clinical decision tools to forecast outcome and predict tumor sensitivity to systemic therapies (19-23). Ultimately, these technologies could be integrated to personalize treatment strategies and further modify the therapeutic landscape.

Still, there are important takeaways from this study. This is the first study regarding a surgical approach comparison in a population restricted to colon adenocarcinoma patients and excluding patients with rectal carcinoma. Indeed, management of patients with rectal carcinoma

with liver metastases commonly will involve radiotherapy for the primary tumor and simultaneous resection is not recommended. Just as the authors mentioned, the biology of colon cancer and rectal cancer has been shown to have clear differences in molecular carcinogenesis and pathology, which has even prompted the question of abandoning the term, CRC (24). This restriction can potentially reduce confounders and may be a design future studies can utilize.

The excellent work of Kurbatov and colleagues highlights the potential of an LFA for management of metastatic colon adenocarcinoma patients, but due to limitations in study design and data collection, cannot definitively guide management at this point in time. Further work is necessary to determine the true benefit of the liver-first technique.

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