A difficult balance of priorities when choosing management of colon cancer with synchronous isolated liver metastases

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We appreciate the thoughtful commentary by Sun *et al.* regarding our study on clinical outcomes with a liver-first approach (LFA) to liver metastases from colon cancer (1,2). We applaud their emphasis on a multidisciplinary, evidence-based approach. Our study adds to early accumulating evidence of the benefits of the LFA in select patients. We observed that younger, less comorbid patients managed largely at academic institutions and preferentially treated with upfront chemotherapy, saw a survival benefit when treated with a LFA. Furthermore, patients treated with the LFA were more likely to have complete resection of primary and metastatic disease, which Sun *et al.* note concurs with previously reported Swiss data (3).

There is no clinical trial to guide optimal surgical oncology treatment strategy for patients presenting with synchronous resectable liver metastatic colon cancer. The RVERS trial, aimed to discern the optimal surgical approach in a randomized fashion, did not yield results applicable to clinical practice (4). In this void of trial data, the National Cancer Database (NCDB) is a rich resource, as it captures data on approximately 70% of cancer care in the United States and reflects national practice patterns and associated outcomes (5). Using this database, we show that most patients undergo either synchronous or staged resections, with the primary colon tumor resected first. Approximately 2% of patients in the United States are selected for the LFA. While the retrospective nature of NCDB based studies does not allow one to draw causal relationships, our survey of this database reveals the profile of patients selected for the LFA and demonstrates that this strategy provides survival benefit in select patients.

Colon cancer with synchronous, isolated liver metastasis is usually treated with systemic chemotherapy to eradicate micrometastatic disease and surgical resection to address gross disease. Though the overall survival benefit of adjuvant systemic therapy was called into question by the EORTC Intergroup trial 40983, most medical centers continue to employ a multimodality approach (6). In this context, Sun *et al.* correctly point out that in our study population the LFA was associated with a high rate of subsequent completion resection and chemotherapy utilization. Aggressive chemotherapy appears to be integral to the successful implementation of the LFA. The benefits of neoadjuvant chemotherapy for metastatic colorectal cancer are poorly understood, yet may have the added advantage of converting select patients with unresectable disease into candidates for metastasectomy, and thus completion resection.

The role of thermal ablation in the LFA has not been reported (7). Particularly in the context of increasing sophistication in interventional oncology radiology, there is much active interdisciplinary collaboration in the management of metastatic disease. Studies examining efficacy and timing of modalities such as microwave ablation will be beneficial. The results from the COLLISION RCT comparing surgery *vs.* thermal ablation for colorectal metastases are anticipated in 2023 and will enhance management strategies (8).

Given the pace of innovation in the machine learning and frequent examples of clinical applicability, Sun *et al.* correctly invite computer scientists to the interdisciplinary team. Indeed, novel predictive algorithms have potential to help guide treatment algorithms by forecasting tumor biology. However, such models are early in development and will require robust validation before wide incorporation into clinical practice.

Footnote

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