Chemotherapy Before Liver Resection of Colorectal Metastases: Friend or Foe?

To the Editor:

We read this systematic review with great interest and congratulate the authors on a comprehensive overview of the topic.[1] There is a paucity of comparative studies of neoadjuvant chemotherapy for resectable colorectal liver metastases (CRLM), making interpretation of available case series data difficult. We disagree with their conclusion that neoadjuvant therapy for resectable disease is not recommended.

Since 1996, we pursued a policy of neoadjuvant treatment followed by liver resection for synchronous and early (<2 years) metachronous CRLM, and for late metachronous CRLM with threatened resection margins. Our published 5-year survival rate for 283 patients with completed resection up to 2006 was 46.1%.[2] Over the 10 years, different chemotherapy regimens were used, reflecting the evolution of the standard of care. We believe the good results support the assertion that neoadjuvant therapy leads to control of concurrent micrometastatic disease. This is reflected in a significant partial or complete tumor response rate, an increased rate of clear resection margins and low repeat resection rate.[3] We agree that neoadjuvant treatment allows concentration of liver resection in patients with better prognoses, as progression of disease while on chemotherapy is an indicator of poor outcome. Although mortality is low, liver surgery is still associated with significant morbidity and time lost to recovery from surgery. Reserving surgical resection for patients with favorable tumor biology is sensible.

The authors quote a higher rate of postchemotherapy-related complications. However, this has not been our experience as we limit neoadjuvant therapy to between 4 and 6 cycles, unless there are exceptional circumstances.

We also question the authors' assertion that complete tumor response leading to disappearing liver metastases (DLM) is unwanted and potentially detrimental. Complete pathological response signifies a chemosensitive tumor and is associated with a high rate of long-term survival.[4] Although DLM may present particular challenges intraoperatively and during posttreatment surveillance, outcomes are still excellent with and without a liver resection. Van Vledder et al[5] found an overall 5-year survival of 46.2% in patients with resected DLM and 63.5% in patients with DLM left in situ. Auer et al[6] report an actuarial 5-year survival of 65% in patients with DLM.

With increasingly efficacious biological and cytotoxic chemotherapeutic compounds coming to market every year, the paradigm of neoadjuvant therapy-resection-adjuvant therapy is being applied successfully to gastrointestinal tract cancers, including esophagogastric cancer and rectal cancer. High rates of long-term survival and "cure" can be achieved only with multimodal therapy in patients with favorable tumor biology. In the continuing absence of proven predictive disease-specific and pharmacogenetic biomarkers, widespread utilization of upfront chemotherapy for CRLM can be associated with high rates of long-term survival, with appropriate individualization of both surgical and chemotherapeutic oncological treatments.

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Disclosure: No funding was received in support of this work. The authors declare there are no conflicts of interest.

ISSN: 0003-4932/14/26102-e0036
DOI: 10.1097/SLA.0000000000000807

Reply:

We appreciate the comments by Belgaumkar, Worthington, and Karanjia related to our article.[1] In contrast to our recommendation, this group advocates the use of neoadjuvant chemotherapy for resectable colorectal liver metastases (CRLM) according to their experience with 283 patients treated between 1996 and 2006. Although we would like to acknowledge the experience of this group, we must emphasize that no comparative study is currently available to demonstrate improved survival rates for this population of patients using a neoadjuvant chemotherapy approach. Their main argument for neoadjuvant chemotherapy is the preoperative control of putative micrometastases. We believe that the same argument can be applied to the adjuvant approach with possibly additional advantages. For example, intraoperative tumor manipulation may lead to tumor cell dissemination and therefore postoperative chemotherapy may offer a better control.[2,3] Some data are available supporting this concept, including the observation that a regimen with 5-FU only disclosed a benefit for CRLM in the adjuvant setting.[4] Similarly, a recent series in patients after cytoreductive surgery for peritoneal carcinomatosis demonstrated a benefit of adjuvant chemotherapy.[5]

Another argument to justify the use of neoadjuvant chemotherapy is a better selection of patients, who might benefit from surgery. We believe that this strategy is worthwhile for borderline resectable lesions,[6] but not for the clearly resectable cases. Indeed, patients with a large load of tumors or tumors located in difficult areas in the liver may benefit from chemotherapy before surgery and the progressive case would likewise not benefit from surgery.

Finally, Belgaumkar and colleagues claim that the use of chemotherapy up to complete disappearance of the lesion might be beneficial and quote a paper by Adam et al[6] to support this. We would like to challenge such an approach. Only a subset of disappearing liver metastases on radiology examinations are true pathologic responses.[6,7] Evidence of residual cancer cells has been documented in up to 80% of disappeared liver metastases.[8] Therefore, without radical resection, these apparently cured lesions are associated with a high rate of recurrence leading to unresectable situations, when patients do not remain under careful postoperative treatment.[7] It must be noted that favorable outcomes in patients with missing metastases were only observed, when hepatic intra-arterial chemotherapy was

Disclosure: No funding was received in support of this work. The authors declare there are no conflicts of interest.
DOI: 10.1097/SLA.0000000000000808

applied, or systemic chemotherapy was continued. Such strategy can be justified for advanced disease, but not in situations with resectable liver metastases.

As stated in our analysis, current evidence favors avoiding routine neoadjuvant chemotherapy for patients with resectable CRLM, which is in contrast to scenarios with borderline metastatic load to the liver or other hepatopancreaticobiliary tumors possibly such as resectable pancreas tumors.[9] Such recommendations might change in the future with the availability of new agents and convincing studies.

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