

Metastatic Colorectal Cancer to the Liver: Involve the Surgeon Early and Often

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Hepatic resection for limited metastatic colorectal cancer to the liver (CRLM) is a surgical success story. An associated long-term survival after resection of CRLM has been known for decades. Furthermore, it has now been demonstrated that complete resection of limited CRLM is associated with cure, meaning alive and free of disease 10 years after resection. In most modern series, 5-year survival rates after complete resection are more than 50 % with actual cure rates estimated to be as high as 20–25 %.^{1–4} For example, at Memorial Sloan Kettering Cancer Center patients with limited CRLM treated on trial with adjuvant hepatic artery infusional (HAI) floxuridine (5-FUdR) and systemic 5-fluorouracil (5-FU) had 5- and 10-year survival rates of 59 and 40 %, respectively.⁵ More recently, in our patients treated on trial with adjuvant HAI and modern systemic chemotherapy, the 5-year survival rate has increased to greater than 70 %.^{6–8} While selection bias has an impact on some of the overall survival statistics, the potential for cure truly drives the incentive to operate. An important point also is that hepatic resection is now a safe procedure. Many may recall the days of massive blood loss and high mortality rates, but currently hepatic resection for metastases is performed with low blood loss and mortality rates of approximately 1 %.^{1,9}

Chemotherapy for metastatic colorectal cancer has significantly improved during the past two decades. Response rates in excess of 50 % are commonly reported and 5-year survival rates approaching 10 % are seen in selected patients on trials.¹⁰ Unfortunately, systemic chemotherapy

alone does not cure patients with CRLM and mandates chronic therapy. Interestingly, this improvement in outcomes seen in patients with unresectable disease has not translated into an improved survival when systemic therapy is given as an adjuvant following hepatic resection. This has now been shown in four randomized trials.^{11–14} Therefore, hepatic resection for limited liver-only metastatic colorectal cancer is the only potentially curative treatment option.

In this nicely written manuscript by Krell et al., it is well demonstrated that medical oncologists (at least in Michigan) are not consistent in their referral practices for patients with CRLM. The majority of the surveyed oncologists work in a community setting that is likely representative of most of the country. Another interesting point is that approximately one-third of the oncologists stated that they did not have a liver surgeon whom to refer patients. As in most good studies, the authors demonstrate some simple but important points. The heterogeneity in referral practices is staggering. Referral rates to liver surgeons range from nearly never to nearly always. Single prognostic factors are commonly used by these oncologists to help decide whether to refer a patient. Many (approximately 40 % of respondents) consider metastasis size and presence of bilateral disease each to be contraindications to hepatic resection. This is troubling, because neither of these findings alone precludes cure or long-term survival. As an example, if a patient presents 2 years after resection of a node-negative primary colon cancer with two or three small hepatic metastases that happen to be on both sides of the liver (bilateral), many of the surveyed oncologists stated that they would not refer to a surgeon. This patient's disease is potentially curable and should be assessed by a hepatic surgeon. It is unclear why patients are not being referred; is it lack of a liver surgeon in the oncologist's practice area? Is it misinformation or misconceptions about

outcomes after hepatic resection? Is it unrealistic or misguided expectations regarding the efficacy of chemotherapy? Regardless of the actual causes of nonreferral, there is a large gap in education about and/or a lack of access to the appropriate treatment.

How do we predict who will benefit from hepatic resection? The problem is that we are not very good at prognostication. In contrast to the commonly held attitudes, now well demonstrated by Krell et al., single prognostic factors, such as tumor size, bilateral disease, and synchronous presentation have never been shown to preclude long-term survival or cure.^{2,15} Prognostication with clinical risk scoring systems that incorporate groups of prognostic factors is the best method we have, but even among patients with high-risk scores, cure remains a possibility.² The only factors that preclude the possibility of cure are the presence of either extrahepatic disease (even if resectable), or a positive hepatic margin (not always predictable preoperatively).^{2,16} Despite the fact that cure is exceedingly rare in patients with extrahepatic disease or a positive hepatic margin, long-term survival is a possibility.^{2,16} For example, it has been shown that low-volume resectable lung metastases do not preclude long-term survival after hepatic resection.^{16–18} As the number of liver tumors increases beyond four, the cure rate decreases but does not reach zero.² Even in these patients with the worst risk factors, it has been suggested that selective use of hepatic resection is associated with improved long-term outcomes.

Who are the gatekeepers of treatment and referrals for patients with CRLM? Undoubtedly, these patients end up in the hands of medical oncologists. Gastroenterologists and colorectal surgeons may see such patients but very likely still defer to medical oncologists in treatment decisions about metastatic disease. How should medical oncologists obtain information and guidelines about who should be referred for hepatic resection? Where should the guidelines come from? Postgraduate training programs alone are unlikely to be the best source of education, because it is likely that there are huge variations in referral patterns among training institutions. ASCO does not provide guidelines. The NCCN guidelines indicate that patients with limited and “resectable” CRLM should be referred for surgery.¹⁹ The problem stems from the fact that there is no common definition of resectable. Even clinical trials evaluating resection as an endpoint fail to provide a consistent definition of resectability. The recent CELIM trial showed dramatic differences among hepatic surgeons (forget the medical oncologist for a minute) and what they consider resectable.²⁰ Consensus statements supported by the AHPBA also do not provide details on extent of disease and resectability.²¹ Therefore, with such unclear guidelines and difficulty with prognostication, the current referral practices and the results from Krell et al. are not surprising.

We believe that this manuscript is relevant and should help to engender enthusiasm for development and dissemination of more thoughtful and comprehensive guidelines for the surgical treatment of CRLM. Meanwhile, the simple answer is that surgeons should become more involved in clinical decision-making. One cannot read a paper about cancer treatment without seeing reference to the importance of multidisciplinary management. Metastatic colorectal cancer to the liver truly requires a multidisciplinary approach, and it is our conviction that surgeons should be involved early and often in the treatment decisions for these patients. Whereas this study may be “preaching to the choir” in a surgical journal, it is a call for surgeons to be more involved in medical oncology societies, conferences, and literature to ensure that the outcomes of surgery for CRLM are known by the practitioners who currently exercise the most control over treatment decisions.

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