Combined-modality therapy has rendered disease-free an increasing number of patients who were previously considered to be incurable. Still, despite myriad advances in imaging, and in surgical and therapeutic modalities, many patients who undergo resection of limited metastatic disease with curative intent ultimately relapse.

It is sometimes easy to forget what the field of cancer therapy used to look like. In an early report on the natural history of 125 patients with isolated metastases from colorectal cancer (CRC), no one received any effective therapy for liver metastases, and most received no therapy at all.[1] The median survival of the patients in this series was 12.5 months, and all patients were dead at 5-year follow-up, mostly of causes related to inexorable tumor burden in the liver. Fast forward a few decades—more recent series have reported 5-year survival rates following hepatic resection of CRC metastases as high as 58%.[2-4] Acknowledging the limitations of this comparison, it is testimony to the progress that has been made.

This is the perspective with which we have read and commented on the article by Bartlett and Chu, focusing on the therapeutic tools and decisions that make cure of metastatic CRC a possibility. Just as the article is a collaboration between a surgeon (Bartlett) and a medical oncologist (Chu), so is the multidisciplinary management that can render selected patients with metastatic CRC disease-free for extended periods.

Bartlett and Chu are comprehensive in their review of current standards for management of liver metastases with combinations of surgery and systemic chemotherapy, and there is little substantive to add, with one exception: they neglect to mention hepatic artery infusion (HAI) for locally directed chemotherapy administration as a therapeutic option. This method of delivering higher doses of chemotherapy to an anatomically directed region of the liver, while sparing normal liver tissue, has been studied in multiple trials evaluating its application in neoadjuvant therapy, conversion of hepatic metastases to resectability, and in the adjuvant setting following resection of either synchronous or metachronous liver metastases.[5] Two recent Cochrane reviews have demonstrated rates of response to HAI that are superior to fluoropyrimidine-based systemic chemotherapy; however, the few randomized trials that exist have not compared HAI against the combination systemic regimens that are currently the standard of care, and overall survival (OS) benefit has not been consistently demonstrated.[6,7]

The omission of HAI treatment from the review by Bartlett and Chu likely reflects the failure of this complex approach to gain traction beyond the Upper East Side of Manhattan and to become an accepted form of treatment for hepatic metastases from CRC. Indeed, the current generation of surgeons and medical oncologists may never see an HAI pump. While its use remains confined to a few institutions with expertise in the surgical and medical oncologic aspects of this procedure,[8] we consider the results reported by Kemeny and colleagues too good to dismiss, and we endorse the value of HAI in carefully selected cases, if performed at an institution with appropriate expertise. While the authors’ prevailing focus on liver metastases is fitting and understandable, this is not the only scenario in which cure is achieved for patients with metastatic CRC. Bartlett and Chu dedicate only one sentence to the curability of select patients with lung or ovarian metastases and then proceed to endorse curability of patients with peritoneal carcinomatosis. Differences in opinion are a part of the fabric that informs research and patient care, so here we will emphasize the curability of patients with limited lung and ovarian involvement.

Lung metastases will be seen in 10% to 20% of patients with CRC,[9] with studies reporting 5-year survival rates between 24% and 64% in patients who undergo resection.[10] A disease-free interval of less than 36 months and multiple vs single pulmonary metastases are factors that have been found to be associated with worse prognoses.[9,11] The role for neoadjuvant or adjuvant chemotherapy as an adjunct to surgery has not been studied systematically; however, the relapse rate following pulmonary metastectomy is approximately 70%.[10] and adjuvant therapy following
The paradox is that extrahepatic disease historically precluded the possibility of liver metastasectomy for cure, yet patients with limited oligometastases in one other anatomic location may in fact be curable as well. Independent successes in the resection of hepatic and pulmonary metastases have resulted in the expansion of indications for combined resections in patients with resectable liver disease and limited pulmonary metastases. Long-term survival is possible in a subset of patients who undergo resection for both liver and pulmonary metastases; thus, combined resections may be considered in highly selected cases. Five-year survival rates have been reported in the range of 30% to 50%.[12-14]

Ovarian metastases occur in about 3% of all CRC patients and make up between 5% and 10% of all CRC metastases.[15] While these are published numbers, they are undoubtedly an underestimate of the true incidence, since younger women whose lives are prolonged by effective systemic therapy will often demonstrate discordant disease behavior, with an ovarian component that is sequestered from exposure to systemic chemotherapy progressing while other sites of disease respond to therapy. Ovarian metastases are diagnostically treacherous, particularly in cases of an occult CRC primary, and are generally associated with a poor prognosis. However, in several retrospective case series of ovarian metastases from CRC, a complete R0 resection was associated with an improvement in OS for both synchronous and metachronous tumors.[16-19] In each of these series, a small number of patients was alive and disease-free after 5 years, suggesting that a complete metastactectomy may result in cure in those with disease confined to the pelvis who are able to undergo a complete surgical resection.

In 25% of CRC cases, the peritoneal cavity is the only site of metastatic disease.[20] While Bartlett and Chu use limited and select data to suggest that radical cytoreductive surgery together with hyperthermic intraperitoneal chemotherapy (HIPEC) is potentially curative and associated with a trend towards improved OS when compared with chemotherapy alone, in our view there is insufficient evidence to conclude that any survival advantage is due to the intervention itself. Rather, a perceived trend towards survival benefit may be due to the biologic features of the disease that allow small numbers of highly selected patients to undergo this procedure in the first place. Moreover, the authors fail to mention that treatment-related mortality for patients undergoing HIPEC is substantial, between 4.1% and 8%. [20-22] The recommendations of the NCCN state that this approach should not be considered standard at present and, if pursued, should be only be performed in the context of a clinical trial.[8] ACOSOG Z6091, a phase III trial for patients with limited peritoneal disease dissemination of CRC, was recently closed due to poor accrual. The failure of this trial, which randomized patients to receive either standard chemotherapy only or standard chemotherapy following cytoreductive surgery with intraperitoneal mitomycin, highlights the divide between two camps who either believe fervently in the modality’s value or are dubious of the entire approach. We acknowledge that HIPEC has a clear role in some patients, such as those with pseudomyxoma peritonei (false mucinous tumor of the peritoneum), but for most patients with peritoneal carcinomatosis from CRC we remain skeptical that any survival benefit can actually be ascribed to the treatment itself.

Combined-modality therapy has rendered disease-free an increasing number of patients who were previously considered to be incurable. Still, despite myriad advances in imaging, and in surgical and therapeutic modalities, many patients who undergo resection of limited metastatic disease with curative intent ultimately relapse. Curability is indeed a function of careful patient selection, and identification of these curable cases remains a colossal challenge. Along those lines, we caution that the distinction between neoadjuvant therapy and conversion therapy for hepatic metastases set forth by Bartlett and Chu is, in reality, vague and subject to surgeon discretion, due to the lack of widely accepted guidelines for determining which patients with hepatic metastases should undergo immediate surgery and when more complex care is indicated. In the absence of more definitive prediction tools, chemotherapy before surgery currently serves as the best bioassay for surgical suitability, as it commonly excludes patients with refractory disease. Looking to the future, advances in understanding gene signatures of individual tumors likely represent the next step in identification of the tumor biology with the best possibility for cure—and of those patients who should be treated with our most aggressive approach.

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