The liver is a frequent site of metastatic colorectal disease. Over the past 20 years, improvements in systemic chemotherapy and surgical techniques have improved the survival of patients with hepatic metastases. For 4 decades, fluorouracil and leucovorin were the only drugs available to treat metastatic colorectal cancer, but several new drugs and a variety of novel regimens are now available. Further improvements in results have been seen with the delivery of chemotherapy via the hepatic artery. Surgical resection of liver metastases has been encouraged when possible, and recent advances in surgery such as portal vein embolization, have made liver resection a possibility for more patients. This review considers the timing and sequence of chemotherapy and surgery in this setting, as well as the roles of cryoablation, radiofrequency ablation, and radiation therapy.

It has long been apparent that the liver is a preferred site of metastases in patients with colorectal cancer. The reasons for this behavior are not known: Is it purely due to anatomic considerations—portal venous blood flow draining from the large bowel into the liver—or due to some unique characteristics of colon cancer cells predisposing them to grow in the liver? What is known, however, is that liver involvement with colorectal cancer may reflect a relatively favorable prognosis in certain circumstances compared to other sites of metastatic involvement. This appears counterintuitive, given the vital role of the liver and the fact that hepatic failure will claim many such patients, but is borne out by the evolving literature.

This comprehensive Kemeny review covers a lot of territory but emphasizes one take-home message that should resonate with the practicing oncologist: Selected patients with colorectal liver metastases will be cured, and cure should be the goal in many patients. The proper approach to achieving that goal is not as simply stated.

Changing Landscape

It could be said that if there are a dozen or so different strategies applicable to patients with colorectal liver metastases, none of them is particularly effective. Kemeny traces the historical approaches to colorectal liver metastases, including many different modalities. This encompasses the changing landscape, from fluorouracil (5-FU) and other fluoropyrimidines as the only therapeutic option for such patients to today's panoply of active chemotherapeutics and biologics. It also stretches from an era when there was no such thing as "simple" liver surgery through the evolution of disparate ablative techniques. Because of the stuttering progress and overlapping studies, we are left with a hodgepodge of data for a disease entity that is quite complex.

In discussing the myriad approaches, this review starts with chemotherapy. The focus is on fluoropyrimidines, and the author devotes a moderate amount of space (some might argue too much) to hepatic arterial infusion (HAI) therapy with floxuridine, a 5-FU family member. Because it was the only active agent for many years, and because of pharmacologic properties favoring its selective delivery into the liver,[1] infusional administration of a fluoropyrimidine was the focus of numerous studies in the 1980s and 1990s. Indeed, Dr. Kemeny has led the effort demonstrating the efficacy and impact of HAI in patients with incurable metastatic liver involvement[2,3] or following curative metastasectomy.[4] Unfortunately, the role of HAI—which has no impact on nonhepatic metastases—in the current era is uncertain and needs to be critically evaluated.

Clearly, new systemic chemotherapies have had an impact on patients with colorectal metastases,[5] but as with HAI, the optimal time and place to employ these agents remains uncertain. There has been considerable discussion of downstaging liver metastases and of preoperative strategies even in patients with resectable metastases, and evolving data support the safety, prognostic value,[6] and efficacy[7] of such an approach. However, randomized data—neoadjuvant systemic chemotherapy vs adjuvant systemic chemotherapy—do not exist. As Kemeny reminds us, rushing to embrace this expanded role for chemotherapy may be a mistake,
given the evidence of hepatic toxicities associated with these agents. In the same vein, bevacizumab (Avastin) and cetuximab (Erbitux) need to be studied in this context as well.

Role of Surgery

After years of nihilism, the surgical community now embraces its role in the management of patients with colorectal hepatic metastases. But with what could be called overexuberance, the proliferation of techniques and surgical interventions for these patients has proceeded unencumbered by good quality data. As the Kemeny review shows us, there are many safe approaches to the destruction of hepatic metastases, although, if feasible, surgical resection remains the gold standard. Certainly, a subset of patients who stand to clearly benefit can be identified by clinical parameters,[8] and this concept has been spelled out in an interesting multidisciplinary decision tool called OncoSurge.[9] As with the other therapies already discussed, however, the right time and place for surgery cannot be generalized.

Optimizing Treatment

For all of the dramatic progress experienced by and then summarized by Kemeny, the review does not (and cannot) provide a roadmap for how best to reach the optimal result in an individual patient. Indeed, there are so many variables to include in decision-making that there can be no one-size-fits-all declaration. However, the various therapeutic options are clearly summarized and can be used as a broad menu from which to select a treatment strategy. At this point, such a review cannot discuss molecular or other prognostic markers that might allow us to enrich the population of patients who stand to benefit from liver-focused approaches or, in contrast, patients who need systemic therapy alone. Although some of the studies discussed above have analyzed tumor tissue for features that might predict outcomes (eg, thymidylate synthase or p53),[3] the data are sparse and inconclusive.

Conclusions

As Kemeny concludes, the treatment of liver metastases has become more challenging and rewarding. We have hurtled into an era where perhaps too many therapeutic options are possible. Studies exploring both interventions and tissue analysis are imperative. Our task moving forward is to simplify the decision-making and to select the patients who stand to accrue the greatest benefit from the least intrusive treatment.

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References:


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