Hepatic metastases remain a lethal and recalcitrant problem in the management of malignant disease, and the review by Drs. Zani and Clary of the role of hepatic metastasectomy for patients with stage IV melanoma or breast cancer is timely and welcome. They focus on surgical resection, but questions about other ablation techniques follow similar patterns. Faced with a patient with liver metastases, the oncologic team needs to decide whether surgical resection of liver metastases will 1) alter the course of the patient’s disease, 2) be successful in resecting all tumor, and 3) accomplish these goals with acceptable morbidity and mortality. The latter two are technical issues and somewhat easier to resolve. The first is the crucial question, and it is relevant here that Zani and Clary refer several times to the possibility of cure, a term that should be used with caution for most stage IV solid tumors. As they articulate nicely, it is clear that there are some long-term survivors among carefully selected patients who undergo resection of hepatic metastases of breast cancer and melanoma. However, the word “cure” is laden with emotional significance, and it is rarely used in the literature on this issue. In our view, the word “cure” should be avoided in discussions with patients who are considering hepatic resection for metastatic lesions. That said, it remains true, as they point out, that the desire for prolonged survival drives patients and their physicians towards aggressive surgical management for patients with stage IV disease. This desire must be coolly balanced against the known evidence, which, as illustrated by this review of breast cancer and melanoma, is lacking in many respects.

The melanoma data reviewed point out that systemic therapy for melanoma has historically been ineffective and that the overall median survival for stage IV melanoma is dismal. The six published studies reviewed describe a much improved median survival among patients who undergo metastasectomy, with 5-year survival rates approaching 30%. The lack of effective systemic therapy for melanoma renders surgical resection both more attractive (nothing else to offer) and less attractive (high probability of hepatic and non-hepatic recurrence). The importance of biology appears again in the clear difference in outcomes of patients with ocular and non-ocular melanoma, but it is impossible to ferret out any impact of systemic or intra-arterial therapy. Good prognostic indicators include R0 resection and longer disease-free interval, as well as young age, a lower disease burden, and the absence of extra-hepatic disease.

Among patients with breast cancer, the survival of those with stage IV disease has increased to 25%, although the median survival for all patients with liver metastasis remains only 12 months.[1] It is important to remember that this estimate is unlikely to apply to the most favorable subset of patients who are considered for resection of liver lesions (resectable hepatic-only disease, with a long disease-free interval). Notably, there is little information available as to the prognosis of this subset of patients without resection. The degree of selection in reported series is reflected by the fact that among 19 studies included in a systematic review and spanning a range of 10 to 20 years each, a total of 553 patients with breast cancer underwent resection of hepatic metastases, with a median of 1.8 resections per year.[2] More recent studies discussed by Zani and Clary demonstrate a 5-year survival in the 30% to 40% range with low mortality. Multivariate analysis of these studies demonstrated that good prognostic indicators for patient selection included R0 resection, hormone receptor positivity, good response to chemotherapy, longer disease-free interval, and the ability to undergo repeat metastasectomy.

Given the uncertainties of limited data, it is helpful to turn to the larger literature on the results of hepatic metastasectomy for colorectal and neuroendocrine tumors, a treatment that was once viewed with skepticism but that is now accepted as standard of care in appropriate patients, without...
randomized trial evidence.[3] This experience demonstrates that resection of up to 80% of liver volume can be accomplished with mortality rates of less than 5%.[4] The now large numbers and long follow-up of patients treated surgically for liver-only metastases of colorectal cancer have led to a consensus that resection prolongs survival. In contrast, the literature on hepatic resection for both metastatic breast cancer and metastatic melanoma is based on small retrospective case series. Larger studies are difficult because of the small number of patients with isolated liver metastases suitable for resection who are seen in centers that are willing to offer resection. Here, researchers in the breast cancer and melanoma fields can follow the lead of colorectal cancer researchers, who have organized multi-institutional and international databases that allow the accumulation of larger numbers of patients and the analysis of meaningful subsets to guide patient selection for surgery.[5] Relevant subsets among breast cancer patients include biologic subtypes, which now govern the choice of systemic therapy and which are beginning to show relevance to local therapy decisions.[6] Similarly, the emergence of a biologic classification of melanoma will lead to related initiatives, and the existence of large repositories of clinical data will be immensely useful. Furthermore, the use of comparison groups of patients who are roughly similar and contemporaneous to those undergoing resection will enable initial analyses of the important issue of selection bias in surgical series.[7]

The recent course of the literature for colorectal cancer illustrates additional issues that need to be resolved in an organ-specific fashion when considering resection of metastatic lesions. Primary among these is the use of systemic therapy; recent studies of metastasectomy for colorectal cancer show improvements in long-term survival resulting from the incorporation of increasingly effective systemic agents in the treatment plan for patients with hepatic metastases, including the pre-operative use of systemic therapy as a means of selection for surgery,[7] again demonstrating that the use of local treatment modalities in the face of systemic disease is unlikely to be helpful unless the disease is responsive to systemic therapy. If surgical selection on the basis of systemic therapy response is valid for colorectal cancer, which has an anatomic predilection for isolated hepatic metastases, it can only be more relevant in breast cancer and melanoma patients, in whom the likelihood of occult nonhepatic disease is higher. New targeted therapy options are appearing for melanoma patients—and increasing for breast cancer patients. Any surgical strategy must therefore incorporate systemic therapy, given the high likelihood of intrahepatic and extrahepatic recurrence. In breast cancer, where durable responses to systemic therapy used to be infrequent, the example of trastuzumab (Herceptin) therapy for HER2-positive disease[8] illustrates the advances that can potentially be achieved by the development of additional targeted agents.

All in all, the growing literature on the potential benefits of surgical and nonsurgical ablation of hepatic metastases needs to be recognized and incorporated into our treatment plans for the appropriate (highly selected) patients. Equally importantly, we owe it to our patients to address gaps in knowledge by pooling our data, by setting up collaborative prospective registries that better define questions and that ultimately lead to robust conclusions, or by helping design efficient and focused randomized trials on the important questions surrounding hepatic metastasectomy.

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