Resectability of colorectal liver metastases: an evolving definition

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Approximately 15% of patients with colorectal cancer are found to have stage IV disease at diagnosis and up to 50% will develop metastatic disease in the liver at some point during the course of disease. Furthermore, only 10–20% of all patients with stage IV disease are eligible for potentially curative resection. Median survival in patients with untreated colorectal liver metastases (CLM) is 8 months. Previously, the only active chemotherapeutic agent for metastatic colorectal cancer was 5-fluorouracil (5-FU), which produced response rates of 10–20% and extended median survival to 1 year. The addition of novel cytotoxic drugs, such as oxaliplatin, irinotecan and capecitabine, and targeted therapies, such as bevacizumab, cetuximab and panitumumab, to standard regimens has dramatically extended overall survival to >20 months.

Despite this progress, 5-year survivors treated with chemotherapy alone are few. However, in parallel with the pace of drug development, increases in the utilization and safety of hepatic resection, as well as improvements in preoperative imaging and selection during this period, have doubled 5-year survival rates from 30% to 60%. Studies have confirmed that the use of combined-modality therapy has resulted in measurable 10-year survivors. However, several issues remain to be resolved, including that of how to properly identify candidates for curative resection. The liver surgeon is frequently presented with four categories of CLM patient: those who are easily resectable; those who are borderline resectable; those who are unresectable but may be converted to resectable, and patients who are unlikely ever to be resectable. Proceeding straight to surgery has been the paradigm for the first group and chemotherapy or other non-resection liver-directed therapies have been reserved for the fourth group. The second and third groups have more recently been managed with a trial of neoadjuvant chemotherapy intended to downstage the tumour, allow for parenchymal-sparing hepatectomy and increase the probability of a margin-negative resection. Evidence from the European Organization for Research and Treatment of Cancer (EORTC) Intergroup 40983 trial demonstrated that in patients who underwent resection of up to four metastatic liver lesions, perioperative chemotherapy with FOLFOX [folinic acid (leucovorin), 5-FU, oxaliplatin] increased 3-year progression-free survival by 9.2% compared with surgery alone. Recent refinements in surgical technique incorporating ablative techniques, portal vein embolization, staged resections and hepatic arterial pump therapy have allowed the definition of resectable CLM to evolve beyond the parameters of size, location and number of tumours. Presently, in order for CLM to be considered resectable, it must be removable with a negative margin and allow for the preservation of at least two contiguous, functional liver segments with intact portal and arterial inflow, venous outflow and biliary drainage. Additionally, as the future liver remnant (FLR) depends critically on functional liver parenchyma, it can be as small as 20% of total liver volume (TLV) in a patient with a normal liver, but an FLR injured by chemotherapy may need to represent 30% of TLV and one with fibrosis from cirrhosis may be required to represent as much as 40% of TLV. Lastly, the biologic behaviour of the tumour must be taken into account such that only those patients whose tumours contain limited, controllable extrahepatic disease should be considered for resection from an oncologic standpoint.

The current study by Mohammed et al. addresses contemporary hepatic surgeon perceptions of resectability of CLM. The authors presented 10 scenarios ranging from a solitary, peripheral lesion to extensive bilobar involvement to a cohort of hepatobiliary and transplant surgeons in Canadian academic centres. The surgeons were asked to evaluate cross-sectional computed tomography images and to determine whether they would be amenable to surgical removal in each case with or without adjunctive therapies such as radiofrequency ablation, portal vein embolization and staged resection. To control for medical and oncologic factors, the surgeons were told that patients had already received six courses of neoadjuvant chemotherapy (with no progression of disease) and were fit for an operation. Although there was absolute agreement in the two scenarios of clearly resectable and unresectable disease, there was a marked divergence in opinion on the remainder of...
the cases and only one additional case achieved a consensus. The observation of differing opinion in over half of the scenarios and little agreement on the type and number of non-resectional adjuncts to surgery\textsuperscript{11} highlights the need for a standardized approach to these patients based on the highest levels of evidence-based practice. Given the lack of randomized trials, varying definitions of resectability in different studies and rapid introduction of novel technologies, we must rely on established guidelines to direct therapeutic decisions. In fact, in the study by Mohammed et al.\textsuperscript{11} when the surgeons were asked to give reasons for their decisions, the majority referenced the 2006 American Hepato-Pancreato-Biliary Association (AHPBA)/Society of Surgical Oncology (SSO)/Society for Surgery of the Alimentary Tract (SSAT) Consensus Conference on the Multidisciplinary Treatment of Colorectal Liver Metastasis. Updated recommendations were presented last month in San Francisco at the 2012 American Society of Clinical Oncology Gastrointestinal Cancers Symposium, sponsored by the same societies, and a new consensus statement should be published within the year.

It is therefore not surprising that there exists significant heterogeneity in approaches to the patient with CLM in the hepatopancreatobiliary academic community and the present study\textsuperscript{11} only affirms that we still have much to learn. For example, other issues, such as the proper timing of chemotherapy, treatment of synchronous disease and management of disappearing lesions, still need further investigation. Meanwhile, as Mohammed et al.\textsuperscript{11} point out, it is imperative that CLM patients be evaluated in a multidisciplinary tumour board setting by all surgical and oncologic specialists who treat this disease in order to identify those who may potentially benefit from hepatic resection. The definition of this population is clearly still evolving.

Conflicts of interest
None declared.

References