Management of hepatic metastasis from colorectal cancers: an update

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Abstract
Approximately 50%–60% of patients with colorectal cancers will develop liver lesions in their life span. Despite the potential of surgical resection to provide long-term survival in this subset of patients, only 15%–20% are found to be resectable. The introduction of new neoadjuvant chemotherapeutic agents and the expanding criteria of resection have enhanced the overall 5-year survival from 30% to 60% in the past decade. The use of technical innovations such as staged resection; portal vein embolization, and repeat resection have allowed higher resection rates in patients with bilobar disease. Extrahepatic primary and liver-exclusive recurrent disease no longer represent an absolute contraindication to resection. The role of regional therapy using hepatic arterial infusion is being redefined for liver-exclusive unresectable disease. Adjuvant chemotherapy in combination with regional therapies is being looked at from fresh perspectives. Ablative approaches have gained a firm role both as an adjunct to surgical resection and in the management of patients who are not surgical candidates. Overall, the management of hepatic metastasis from colorectal cancers requires a multimodal approach.

Key words Hepatic · Metastasis · Colorectal · Cancer

Introduction
Colorectal cancer (CRC) is the fourth most common cancer in the Western world and is the second most common cause of cancer-related mortality after lung cancer. Each year approximately 140,000 new cases are detected and roughly 50%–60% of them will go on to develop liver metastasis in their life span.1,2 Of those developing liver metastasis, approximately 20%–30% will have synchronous presentation and the rest will develop metachronous lesions over the course of their disease. Interestingly, 30% of all CRC patients with hepatic metastasis have liver-exclusive metastasis, resulting in a total of 15,000 patients seeking liver-directed therapies every year.3,4 Surgery remains the only option that has the potential of cure.5 This article provides a systematic analysis of the various issues which are relevant in the effective management of colorectal liver metastasis.

Natural history
Hepatic metastasis from CRC if left untreated carries a median survival of 3–20 months; the use of chemotherapy alone rarely achieves cure or 5-year survival. Factors associated with a significant survival disadvantage in the unresected group include extent of the liver disease, presence of extrahepatic disease, carcinoembryonic antigen (CEA) level, and the age of the patient. Surgical resection if done with a curative intent has the potential to achieve a 5-year overall survival of 35%–55%, a disease-free 5-year survival of 25%, and a median survival of 20–60 months.6 These figures are likely to increase further as more effective chemotherapeutic drugs are introduced.5,7–9 Historically, only 5%-10% of patients with colorectal liver metastasis (CRLM) were found to be resectable; at present, with the precipitous shift in the approach, the resectability rates have increased to 20%–25%.10 Even when liver resection is performed with curative intent, 60%–70% of the patients will develop local, regional, or distant recurrence.11 Eighty percent of all recurrences occur within 2 years; the median time to recurrence is 10 months. Recurrence occurs equally at intrahepatic and extrahepatic sites, one-half of all recurrences involve the liver and in one-third the liver involvement is exclusive.12,13
sible in 10%–15% of CRLM recurrent disease and can achieve a 5-year overall survival of 15%–40% in well-selected patients. Cure has recently been equated with the achievement of 10-year disease-free survival, as the presence of recurrent disease even beyond 5 years has been reported at 34%. None of the reported negative prognostic markers, except for the presence of positive margins, has negated the achievement of cure, which is reported to be 17%–25%.

Changing criteria of resection

The 5-year survival rates for CRLM patients have almost doubled, from 30% to 60%, in the past two decades. The introduction of new chemotherapeutic drugs and a paradigm shift in the criteria of surgical resection were major factors in this progress. The emphasis has shifted from what can be removed to what should be left. Clinicopathological adverse criteria such as the size, location, and number of intrahepatic metastases, and the presence of bilobar and extrahepatic disease, which have precluded an R0 resection in the past, no longer hold true. The current definition of resectability includes R0 resection (intra- and extrahepatic) with the sparing of two or more adjacent liver segments having an independent inflow, outflow, and biliary drainage. The amount of the future liver remnant should not be less than 20% and 30% of the total liver volume in normal and cirrhotic patients and can be predicted accurately by computed tomography (CT) or magnetic resonance imaging (MRI) in a preoperative setting.

Preoperative evaluation

An elaborate diagnostic workup for determining the extent of the disease and suitability for surgery should be done in all resectable patients. The past two decades have seen a consistent fall in operative mortality from 20% to near zero. The factors responsible for these results include careful patient selection and better perioperative care. A higher ASA (American Society of Anesthesia) or APACHE (Acute Physiological and Chronic Health Evaluation) score is an indirect marker of associated comorbidities and has direct bearing on the postoperative morbidity and mortality. Preoperative biopsy and pathological confirmation may cause tumor seeding and adversely impact both the survival and the local control, and therefore should be avoided.

The use of several clinicopathological factors which are predictive of local control and survival has recently been highlighted. The one scoring system which is formally reproducible was devised by Fong et al. and includes the presence of positive nodal status of the primary tumor, CEA level more than 200 ng/ml, tumor size more than 5 cm, disease-free interval of less than 1 year between the primary and the liver metastasis, and multiple hepatic lesions. These risk factors, though helpful in prognostication, should not be used for denying the patients the benefits of resection.

Diagnostic imaging

Historically, CT scans played a crucial role in selecting patients for hepatic resection; however, as many as 40% of the cases turned out to be unresectable on laparotomy and the sensitivity was low, at 53%. The use of multidetector helical CT scans improved resolution and has increased the sensitivity of detecting CRLM to 70%–90%. Liver metastases appear as hypodense lesions in the portal phase. Additional advantages of CT scan include its ability to provide anatomical details of CRLM and its relation to segmental, lobal architecture and its proximity to vascular structures. Limitations of CT scan include low sensitivity in detecting extrahepatic disease and subcentimeter hepatic lesions.

Magnetic resonance imaging (MRI) with the use of the contrast agents (gadolinium-super paramagnetic iron oxide) has shown a sensitivity of 70%–80% and offers no unique advantage over the CT scan. Positron emission tomography using fluoro-18-deoxyglucose (FDG-PET) has recently emerged as a supplemental modality in the diagnosis of hepatic metastasis. A recent metaanalysis has reported the sensitivity and specificity of FDG-PET at 88% and 96%, respectively, for detecting hepatic metastasis and 90% and 95% for detecting extrahepatic disease. The results of FDG-PET scan are particularly impressive for detecting extrahepatic disease and have the potential to change the overall management plan in 20%–25% of the patients.

Combination CT and FDG-PET increases the sensitivity from 75% to 89%. The combination is considered the gold standard as it allows the surgically directed therapies to patients likely to benefit the most. The limitation of FDG-PET includes its reduced sensitivity in detecting subcentimeter lesions, mucinous lesions, and lesions which have been subjected to chemotheraphy. Its reported sensitivity drops to 60%–70% when the patients are exposed to neoadjuvant chemotherapy. Additionally, it has poor anatomical and spatial resolution. It remains to be seen if the uptake of FDG can predict the response to chemotherapy or provide prognostic information, as seen in other solid tumors.