

Surgical Management of Colorectal Metastases to the Liver

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Abstract

Liver metastases develop in 50% to 60% of patients with colorectal carcinoma. Surgical resection offers a good five-year survival rate and the only chance of cure. In this article, the natural history and risk factors for the development of colorectal liver metastases are discussed, followed by the diagnostic work-up towards surgical resection. Various issues pertaining to surgical management, such as patient selection, timing of resection, perioperative mortality and morbidity, prognostic factors, adjuvant and neoadjuvant therapy and repeat resection are reviewed.

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Key words: Adenocarcinoma of colon, Hepatic metastases, Liver resection, Neoadjuvant therapy, Treatment

Introduction

Colorectal carcinoma is the second commonest cancer in both males and females in Singapore, accounting for about 15% of all cancer cases.¹ The liver is the most common site of distant metastases from colorectal cancer. At the time of presentation of a colorectal primary, about 25% of patients will have synchronous liver metastases, and 50% to 60% will develop metastases over their lifetime. In patients who have undergone potentially curative resection of the colorectal primary cancer, and who subsequently develop recurrent disease, almost 80% of the recurrence occurs in the liver.² The management of colorectal metastases to the liver is, therefore, a significant clinical problem.

Risk Factors

The strongest risk factor for the development of liver metastases is the stage of the primary tumour, i.e. the depth of invasion of the tumour and the number of lymph nodes involved. Sixty per cent of patients with Duke's C primary tumour will develop liver metastases.³ Venous involvement correlates with the stage of the primary tumour and is thus unlikely to be an independent prognostic factor.⁴ It is also interesting to note that colorectal metastases rarely develop in cirrhotic livers.

Natural History

Not unexpectedly, patients with untreated liver metastases have poor survival, as the presence of liver metastases represents a biologically aggressive tumour and the loss of

local control. In reported series, the median survival of these patients ranges from 4.5 months to 19 months.^{5,6} Generally, death occurs in less than two years, and five-year survival is rare (less than 1%).

The actual survival will of course depend on the burden of metastatic tumour. In a retrospective review of 113 patients, the one-year survival was 5.7% in patients with widespread liver disease, 27% in those with liver metastases localised to a segment or lobe, and 60% in those with a solitary liver metastasis.⁷

Diagnosis

Synchronous liver metastases are those diagnosed within six months of the diagnosis of the primary colorectal cancer, while metachronous liver metastases are those diagnosed after six months. Patients diagnosed with colorectal cancer will usually undergo an ultrasound (US) and/or computed tomography (CT) of the liver, performed as part of the staging process, when liver metastases may be detected. Liver metastases may also be detected during laparotomy for resection of the colorectal primary, either by direct visualisation for surface lesions, manual palpation, intraoperative US (IOUS) or laparoscopic US for deep lesions.

For patients who have had resection of the colorectal primary and are on follow-up, liver metastases are often detected incidentally by US or CT of the liver as part of the investigations for a raised or rising carcino-embryonic antigen (CEA) level. Less often, patients with a large

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tumour or extensive metastases may present with symptoms of abdominal pain and distension.

Imaging Studies

The role of imaging is three-fold: (1) detection of the lesion and assessment of tumour burden/volume, (2) characterisation of the liver nodules, and (3) assessment of extrahepatic disease or involvement.

Liver metastases are often first diagnosed with US or CT. While US is non-invasive and inexpensive, it is operator-dependent. Its sensitivity ranges from 35% to 68%, and a specificity as high as 97% has been reported.⁸⁻¹⁰ Liver metastases from colorectal primaries are often hyperechoic on US, although some may be hypoechoic when there is extensive tumour necrosis. In comparison to US, CT has a higher sensitivity. On intravenous contrast-enhanced CT, liver metastases appear as hypodense lesions, classically with rim enhancement due to compression of the adjacent normal liver parenchyma. The appearance of liver metastases on CT in a patient with colorectal carcinoma is usually sufficiently diagnostic without the need for further imaging studies or biopsy.

CT arterial portography (CTAP) is generally regarded as the most sensitive imaging technique for the detection of liver metastases, especially those smaller than 1 cm in diameter. CTAP is, however, an invasive, time-consuming, technically demanding and costly study, with possible false-positive results due to artefactual lesions. Although previously routinely employed prior to surgical resection to detect multifocal small tumours, the high false-positive rates that precluded surgery for potentially curable patients, and the improvements in imaging techniques with triphasic CT and magnetic resonance imaging (MRI), have made CTAP obsolete.

MRI is as sensitive as triphasic CT (if not more so) in the detection of liver tumours, and is superior to CT in the characterisation and differentiation of liver tumours. Currently, because of cost constraints, MRI is only employed when there is a need to better characterise doubtful lesions on standard triphasic liver CT.

In the work-up of patients for resectability of liver metastases, it is important to determine the existence of extrahepatic metastases, as the presence of this will contraindicate curative resection for liver metastases. Imaging studies commonly performed include a basic chest radiograph augmented by CT thorax for lung metastases, radionuclear bone scan for bone metastases, and CT of the brain for intracranial spread.

In addition to preoperative diagnosis and work-up, imaging has a special role to play during surgery in the form of IOUS. The sensitivity and specificity of surgical palpation for liver metastases is only 60% and 88%

respectively, compared to IOUS with a sensitivity and specificity of 82% and 92% respectively.¹⁰ IOUS is now routinely performed in most centres prior to surgical resection to detect small metastases that may have been missed in preoperative imaging studies, as well as an adjunct to liver resection by demonstrating the relationship of the tumour to major vascular and biliary structures.

Treatment

The optimal treatment for colorectal metastases to the liver is surgical resection. However, only about 10% to 20% of patients are suitable for potentially curative resection. The reasons for non-resectability include (1) extrahepatic disease, (2) extensive liver metastases, (3) inability to obtain a resection margin, (4) insufficient residual liver resection, and (5) overall poor state of the patient. For unresectable disease, treatment options include systemic chemotherapy and various loco-regional ablative therapies, such as hepatic arterial infusion (HAI) of chemotherapeutic agents, radiofrequency ablation (RFA) and cryotherapy.

Surgical Resection

There is actually no randomised trial comparing surgery with chemotherapy, or surgery with supportive treatment. However, surgical resection has been and remains the only treatment modality that offers substantial five-year survival and a chance of cure. For patients with potentially curative resection, various series have reported overall five-year survival rates of 25% to 40%, with a disease-free five-year survival of 15% to 30%, and 10-year survival of 22% to 26%.¹¹⁻¹⁹ Chemotherapy, on the other hand, modestly improves median survival up to 12 to 18 months, with cure being unlikely.^{20,21}

It may be suggested that the better survival after surgical resection is due to patient selection bias. Although there is no prospective randomised trial that compares the survival of untreated colorectal metastases with those that are resected, there are, however, several comparative studies that showed better survival after surgical resection. In one study, there was no five-year survival in the 921 patients judged unresectable (median survival, 6.9 months) or in the 62 patients judged resectable but did not undergo surgery (median survival, 14 months). In comparison, there was a 38% five-year survival in the group of 183 patients who underwent potentially curative liver resection.²² All patients with liver metastases from colorectal cancer who are medically fit should therefore be evaluated for the feasibility of surgical resection.

Patient Selection for Surgical Resection

In the late 1970s, only solitary liver metastases from colorectal cancer were deemed resectable. During the 1980s, resection of multiple liver metastases became

increasingly acceptable. Hence, three contraindications to resection of liver metastases were proposed: 1) the presence of four metastases or more, 2) extrahepatic disease and 3) a projected achievable resection margin of less than 1 cm.²³ Today, in most established hepatobiliary units where there is acceptable mortality and morbidity rates, the number of lesions is no longer a contraindication to resection.

The ability to achieve R0 resection (i.e., absence of gross residual disease and clear resection margins all around the specimen), while maintaining adequate liver reserve, remains the most important criteria in patient selection for surgery. Patients with incomplete resections had poor survival similar to those without resection.²⁴ However, although a clear resection margin is important, recent studies have shown that the exact width of the resection margin has actually little effect on patient survival.^{25,26}

Five or even 10-year survivals have been reported in patients with four or more liver metastases resected, although this is generally lower than patients with less than four metastases. In one study, for example, the five-year survival of 68 patients with more than four metastases was 24%, compared to 31% in those with two or three tumours (140 patients) and 47% in solitary metastases (240 patients).²⁷ In another study, however, the 10-year survival of patients with four or more nodules (29%) was better than those with two or three nodules (16%), and similar to those with a solitary nodule (32%).¹⁹ Most surgeons will, therefore, not exclude patients with four or more metastases from undergoing liver resection, provided that a clear margin can be obtained.

To benefit from resection of liver metastases, the primary tumour must be controlled. The presence of extrahepatic disease, except for direct invasion of adjacent structures, must be excluded, as this will generally preclude curative liver resection. The only possible exception is isolated lung metastases, as long-term survival has been reported in selected patients undergoing combined, staged liver and lung resections.²⁸⁻³⁰

Thus, the current absolute contraindications for resection of liver metastases from a colorectal cancer primary are the inability to achieve R0 resection and the presence of extrahepatic disease, except for direct invasion of adjacent structures and solitary lung metastases.

Timing of Liver Resection

There is ongoing controversy regarding the timing of liver resection for colorectal metastatic disease. The presence of liver metastases implies a loss of local control and the possibility of widespread disseminated disease. In view of this concept, some have advocated a “test of time” approach before liver metastases are resected. Advocates argue that this would avoid unnecessary non-curative

resections by allowing time for microscopic metastases to grow to a detectable size and, within this period, a curable tumour is unlikely to become unresectable. The time to wait is, however, unclear and varies between a few weeks to six months. Others recommend early resection, as the existing liver metastases may become the source of lymphatic or hematogenous spread (tertiary tumour).

There is also debate on whether synchronous liver metastases should be resected simultaneously as the resection of the colorectal primary. Combined resection has been reported to be safe without added morbidity or mortality. Furthermore, there was no difference in the survival between combined and delayed resections.³¹⁻³³ Most surgeons will, nevertheless, prefer delayed resection because different incisions are needed for good exposure for colorectal and liver resections. Our preferred practice is to defer resection of synchronous liver metastases to allow for microscopic liver metastases to declare themselves, so as to avoid unnecessary non-curative resection. Meanwhile, the patients will usually undergo systemic chemotherapy, generally oxaliplatin and 5-fluorouracil (5-FU) with folinic acid, which is needed anyway for systemic disease control. The presence of the unresected liver metastases can thus also provide a measurable indicator for tumour response to chemotherapy and help guide overall management strategy.

In metachronous liver metastases (i.e., secondary tumours detected six months after diagnosis of the primary), the patient would have had adjuvant chemotherapy for the primary disease if indicated, and there would have been “test of time” for the development of liver lesions. Prior to curative resection in this setting, the patient would need to have local recurrence excluded by a colonoscopy and CT of the abdomen/pelvis, and the absence of extrahepatic metastases confirmed by imaging studies (chest X-ray, CT brain and thorax, and radionuclear bone scan). As long as there is no evidence of extrahepatic disease, our practice has been to perform resection as soon as liver lesions are detected in a metachronous setting.

Perioperative Mortality and Morbidity

With better understanding of the anatomy of the liver and improvements in surgical technique and perioperative care, liver resection has become safer.¹¹⁻¹⁹ Perioperative mortality in most hepatobiliary centres is less than 5%, with most deaths due to infection, perioperative haemorrhage or liver failure. The overall morbidity rate in most series is reported to be about 20%. The most common complications are pulmonary, mainly pneumonia and pleural effusion.

Prognostic Factors after Surgical Resection

Several factors have been found by multivariate analysis in several studies to be significant in predicting recurrence and survival after resection of liver metastases. The most

important factors are the (1) stage of primary cancer, (2) volume of metastatic tumour and (3) presence of extrahepatic disease. Other factors include the (1) time interval between primary diagnosis and development of metastases, (2) tumour grading, (3) involvement of the resection margin and (4) number of metastases.

Prognostic scoring systems have also been proposed by several authors to help improve patient selection for liver resection.^{12,34,35} Fong et al¹⁸ proposed a clinical risk score comprising five factors: (1) nodal status of the primary tumour, (2) disease-free interval from primary to diagnosis of liver metastases <12 months, (3) number of metastases >1, (4) preoperative CEA level >200 ng/mL and (5) size of largest tumour >5 cm, assigning one point for each criterion. The total score was found to be highly predictive of outcome ($P < 0.0001$). The actuarial five-year survival was 60% for patients with 0 point, 40% to 44% for those with 1-2 points, 20% to 25% for those with 3-4 points and 14% for those with 5 points.

Adjuvant Therapy

Despite R0 curative resection, 60% to 70% of patients will still develop recurrent disease.^{11,18} Adjuvant treatment for post-curative liver resection has thus been proposed to reduce the high recurrence rate and to improve survival. Various studies using HAI of chemotherapeutic agents and/or systemic chemotherapy have been published. In a randomised study of adjuvant therapy using HAI with 5-FU and folinic acid versus surgery alone, there was no benefit but significant toxicity was seen in the patients receiving chemotherapy.³⁶ An intergroup prospective randomised trial organised by the Eastern Cooperative Oncology Group (ECOG) comparing adjuvant HAI of floxuridine combined with intravenous continuous infusion of 5-FU versus surgery alone showed that adjuvant therapy reduced the risk of recurrence, but resulted in no benefit in terms of overall survival.³⁷ In another randomised study, adjuvant HAI using floxuridine combined with systemic 5-FU and folinic acid was compared to systemic 5-FU and folinic acid only. Combined treatment resulted in a decrease in the hepatic recurrence rate and an improved two-year overall survival.³⁸

From these studies, it appears that HAI alone is not sufficient as adjuvant treatment, while HAI combined with systemic chemotherapy can reduce the risk of recurrences after surgery for liver metastases. The latter strategy, however, results in a significant increase in side effects. The availability of floxuridine and the high cost of infusion pumps also limit the widespread use of HAI. Currently, the role of adjuvant therapy after curative liver resection has not been proven.

Neoadjuvant Therapy

Neoadjuvant therapy may be used to improve survival and recurrence rates after potentially curative resection. It is, however, more frequently used to downstage unresectable tumours to improve the resectability rate. Most of these studies are retrospective. In a large study of 701 patients with initially unresectable liver metastases, 13.5% of patients subsequently underwent potentially curative resection, with no perioperative mortality and a complication rate of 23%. The overall five-year survival was 35% from the time of resection and 39% from the onset of chemotherapy.³⁹ The survival was thus similar to that reported for *a priori* surgical candidates. Similar results were reported in several other, albeit smaller, studies.⁴⁰⁻⁴²

Repeat Resection of Recurrent Liver Metastases

Of the 60% to 70% of patients who develop recurrent disease after resection of colorectal liver metastases, one third will be isolated to the liver. Due to low mortality and morbidity with liver resections in established hepatobiliary units, repeat resections in patients with isolated liver recurrence is being performed more frequently.⁴³ The survival benefit of repeat liver resections has been demonstrated in several retrospective studies as well as a recent bi-institutional prospective study of 126 patients.⁴⁴⁻⁴⁹ In the latter study, repeat liver resection was safe (30-day mortality 1.6%, complications 28%) and effective (34% five-year survival, 37 months median survival). In addition, it was shown that patients with a low tumour load (small numbers and size) are best candidates for repeat resection.

After resection of recurrent isolated liver metastases, subsequent liver recurrence occurs in 50% to 60% of patients. A third resection is sometimes possible, with reported five-year survival of 17% and apparent cure for some patients.^{44,50}

Conclusion

Surgical resection remains the treatment of choice for resectable liver metastases from colorectal cancer, with an operative mortality of less than 5% and five-year survival of up to 40%. The main criterion in patient selection is the ability to completely remove all tumours safely with an adequate resection margin. Selected initially non-resectable metastases may be down-staged to resectable tumours through neoadjuvant chemotherapy. It is foreseeable that surgery with adjuvant chemotherapy (HAI and/or systemic chemotherapy) may be validated as the best treatment for resectable liver metastases. Large prospective trials evaluating new regimens and new treatment modalities should be conducted to further improve the treatment outcome of liver metastases from colorectal cancer.

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QUESTIONS

1. Colorectal cancer metastases
 - a) develop in 25% of cases.
 - b) are most commonly confined to the liver.
 - c) are most likely with advanced local primary disease.
 - d) are considered synchronous if these occur within six months.
2. With isolated liver metastases,
 - a) the median survival without treatment is 14 months.
 - b) chemotherapy increases median survival to five years.
 - c) surgery offers potential five-year survival.
 - d) actual survival is dependent on tumour load/burden.
3. The following statements about the role of imaging for metastatic disease are true:
 - a) Ultrasound is not a useful first-line screening test.
 - b) A properly performed contrast-enhanced CT is usually adequate for diagnosis.
 - c) CTAP is required prior to surgical resection.
 - d) IOUS forms an integral part of imaging assessment for liver resection.
4. Non-resectability of liver metastases can be due to
 - a) extrahepatic disease.
 - b) extensive liver metastases.
 - c) insufficient liver reserve.
 - d) unskilled surgeon.
5. With liver resection for colorectal metastases,
 - a) five- and 10-year survivals are possible.
 - b) extrahepatic metastases are not a contraindication.
 - c) adjuvant chemotherapy is of proven value.
 - d) neoadjuvant chemotherapy may improve resectability.

ANSWER SHEET

Continuing Professional Development:
Surgical Management of Colorectal Metastases to the Liver

Question 1

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 2

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 3

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 4

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 5

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

For answers, log on to the *Annals* website at: <http://www.annals.edu.sg/>