Colorectal liver metastases

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Summary

Each year in the UK, between 12–14 000 people develop liver metastases from colorectal cancer. These metastases will contribute to the death of the patient in about 80% of cases. Treatments aimed at these tumours are best administered when the tumour is small. Current investigative methods allow tumours as small as 0.5 mm to be detected, and should be offered to all colorectal cancer patients at risk of developing liver metastases. Surgery remains the only curative treatment for these tumours, but, unfortunately, only 20% of those who have tumour excision will survive five years. In those patients unsuitable for surgery, chemotherapy with fluoropyrimidines produces the best tumour response. This may be administered systemically or regionally, via a catheter placed within the hepatic artery. The latter approach reduces systemic toxicity, but may produce hepatotoxicity. The results of other forms of systemic chemotherapy currently undergoing clinical trials are awaited. The vast majority of patients will benefit from suitable palliative treatment delivered either locally or systemically. With the wide range of treatments now available for liver metastases, these patients are best assessed in a unit with a special interest in the problem.

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Colorectal cancer is the second most common cancer in the UK with an incidence of approximately 28 000 new cases per year.¹ It is cured by surgical excision of the primary tumour in approximately 50% of cases, but further dissemination or local recurrence develops in the remaining 50%, usually within one to five years of primary tumour excision. The liver is involved in approximately 80% of patients who develop recurrent colorectal cancer.² This results in jaundice, abdominal pain, ascites and eventually death in most patients who develop liver metastases. Control of liver metastases therefore poses a significant challenge in improving both the quality and duration of survival in a substantial proportion of patients who develop colorectal cancer.

Natural history of colorectal metastases

It is thought that the predilection for liver metastases in colorectal cancer arises because of the portal venous drainage from the colonic or rectal primary tumour to the liver. Liver metastases develop within the liver during the period of primary tumour growth prior to diagnosis.³ These are frequently undetected (occult) at the time of primary tumour removal, and subsequently grow until they reach a size when approximately 30% of the liver is replaced.⁴ The diagnosis is usually subsequently made following the development of either abdominal pain or a mass which is investigated. The average survival from diagnosis of colorectal liver metastases in untreated patients is of the order of seven months,⁵ but there is considerable variation depending on the growth rate of the tumour – some patients survive for three to five years from diagnosis of liver metastases.⁶ Factors which correlate with survival after liver metastasis diagnosis in untreated patients are physical symptom score, serum alkaline phosphatase, extent of disease within the liver on computed tomography (CT) scan, Duke's stage of primary tumour and the presence of extra-hepatic disease, for example, hepatic lymph node or lung involvement, or local recurrence.^{4,6}

Detection of colorectal liver metastases

CLINICAL DETECTION

Clinical detection is possible only after growth of the disease within the liver. At greater than 30% replacement of the liver, the patient develops right upper quadrant abdominal pain and a palpable abdominal mass of metastases within the liver can frequently be felt on examination.⁵ Jaundice, ascites and lymphoedema suggest a terminal phase of the disease. Treatment of colorectal liver metastases is usually more effective when the treatment is started before the appearance of clinical signs or symptoms.

CARCINOEMBRYONIC ANTIGEN

Carcinoembryonic antigen is released by the primary tumour into the serum in approximately 70% of patients with colorectal cancer.⁷ There is usually a fall in serum levels after primary tumour removal, even in the presence of occult liver metastases. However, as the occult liver metastases grow, carcinoembryonic antigen can be detected in the serum in 70–80% of cases, and this rise in serum levels can usually be detected three to six months before the development of significant clinical symptoms.⁸ Serum levels of lactic dehydrogenase, alkaline phosphatase and bilirubin may also become abnormal with colorectal liver metastases, but are not as sensitive an indicator as a rise in serum carcinoembryonic antigen.⁹

ULTRASOUND SCAN

Ultrasound scan is capable of detecting metastases of greater than 1 cm diameter within the liver.¹⁰ Abdominal ultrasound has the advantage of being widely

Investigations used to diagnose liver metastases
<ul style="list-style-type: none">● serum carcinoembryonic antigen● ultrasound scan● hepatic perfusion index
Investigations used to determine extent of metastases
<ul style="list-style-type: none">● CT scan ± portography● intraoperative ultrasound scan● magnetic resonance imaging

Figure 1 CT portogram (A) reveals the metastasis more clearly than a plain CT (B) as the metastasis does not take up the contrast

Figure 2 An MRI scan showing a colorectal liver metastasis in the right lobe (A). This is seen more clearly when intravenous contrast (gadolinium) is given (B), as the metastasis does not take up the contrast

available, relatively inexpensive and noninvasive. It is therefore an ideal screening investigation for patients who have undergone excision of primary colorectal carcinoma and are at high risk for the development of liver metastases.

COMPUTERISED TOMOGRAPHY OF THE LIVER

Conventional CT scanning of the liver is less operator-dependent than ultrasound scanning and is capable of detecting some lesions of less than 1 cm diameter in the liver, particularly within the right lobe.¹¹ In addition, CT can be used to calculate the extent of disease within the liver which is useful in determining both prognosis and the effect of treatment on tumour size.¹² The accuracy of CT scanning in the detection of liver metastases can be increased by contrast enhancement of the liver parenchyma.¹³ This technique, known as CT portography, is performed by catheterisation of either the splenic or superior mesenteric artery via a femoral puncture and subsequent injection of iodine-based contrast (in the CT scanning suite). The contrast passes into the portal circulation and thence to the liver. As the liver parenchyma is supplied predominantly by the portal vein and the tumour receives its blood supply from the hepatic artery, metastases appear as darker lesions within the brighter surrounding parenchyma which has taken up the contrast (figure 1).¹³

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) is at least as sensitive in the detection of liver metastases as CT.¹⁴ The sensitivity of MRI may be improved by the use of suitable contrast agents, eg, gadolinium, Mn DPDP (figure 2).¹⁵

INTRA-OPERATIVE ULTRASOUND

This is carried out at the time of laparotomy or laparoscopy.¹⁶ An ultrasound probe is passed over the surface of the liver and each segment is assessed for areas of altered echogenicity (usually increased) which are suggestive of small metastases. Lesions as small as 5 mm in diameter can be identified¹⁷ and, using the ultrasound probe as a guide, a needle biopsy can be directed into the suspicious area. Liver metastases can be diagnosed in 10–25% of patients assessed by intra-operative ultrasound at the time of primary tumour resection.^{18,19} This approaches the estimate for the true prevalence of liver metastases at the time of primary tumour resection²⁰ and suggests that the majority can be diagnosed in this way.

HEPATIC PERFUSION INDEX

In the normal liver, hepatic artery blood flow constitutes 20–30% of total liver blood flow with the remainder coming via the portal vein.²¹ It has been shown that, in the presence of colorectal liver metastases, the ratio of arterial to portal blood flow increases. This ratio is known as the hepatic perfusion index and can be calculated if the hepatic arterial and total liver blood flows are known (figure 3). These can be measured by scintigraphy using 99m technetium-labelled colloid,²² or by using duplex colour Doppler ultrasound.²³ Leveson *et al*,²¹ using blood flow scintigraphy, and Leen *et al*,²³ using duplex colour Doppler ultrasound in patients with known colorectal liver metastases, have suggested a high sensitivity for these techniques in detecting patients with liver metastases.

Treatment

RESECTION OF LIVER METASTASES

The only curative treatment for liver metastases is surgical resection. This is technically feasible in 20% of all patients with liver metastases.² However, of those patients undergoing resection, only 20–25% will survive for five years.²⁴ Overall, it is estimated that about 2% of all patients developing primary large bowel cancer can be cured by surgical resection of liver metastases. Patients with less than four metastases within the liver,²⁵ those with a unilobar distribution of disease,²⁴ and patients with no evidence of disease outside the liver on CT scan of the chest and abdomen should be considered for metastasis resection. Additional good prognostic criteria are an observation interval during which extra-hepatic disease does not develop, and the absence of primary tumour lymph node involvement (Duke's A or B) (figure 4).

Recovery after major liver resection is slowed by reduced protein synthesis following resection of large volumes of parenchyma. Appreciation of the segmental nature of the liver has allowed segmental liver resection of metastases to be carried out whilst sparing parenchyma (figure 5).²⁶ The peri-operative mortality following liver metastasis resection should be less than 5%.²⁷ The main complication is sepsis which occurs in about 30% of patients following liver resection.²⁸

Figure 3 Hepatic perfusion index using technetium-labelled sulphur colloid. Regions of interest are drawn around the left kidney and the right lobe of the liver. The time at which the renal curve (arterial inflow only) reaches a peak (Tp) divides hepatic arterial (G1) and portal venous (G2) inflow phases. Hepatic perfusion index= $G1/(G1+G2)$ (normal range: 0.1–0.4, mean 0.25)

Figure 4 The liver before (A) and after (B) resection of a solitary metastasis in the right lobe

Patients suitable for liver metastases resection	
<ul style="list-style-type: none">• <4 metastases• unilobar disease• no extrahepatic disease

Figure 5 The liver is divided into eight segments according to its blood supply

Unfortunately, recurrent disease develops in approximately 60–80% of patients undergoing resection of metastatic liver disease.²⁵ The recurrence is confined to the liver in one third of cases but in the remainder extra-hepatic disease also develops. Further resection of liver-only recurrence is feasible and does appear to prolong high-quality survival.²⁹ It has been suggested from animal studies³⁰ that the release of hepatocyte growth factors induced by liver resection might stimulate the growth of residual occult liver metastases.

OTHER LOCAL TREATMENTS

Ultrasound-guided techniques for local destruction of unresectable metastases are available.

Cryotherapy

At laparotomy a probe cooled with liquid nitrogen to a temperature of -196°C is inserted into individual metastases using ultrasound guidance.³¹ This forms an ice-ball which destroys tumour cells. As the ice-ball is limited by the size of the probe, large metastases need multiple passes to be frozen, although in these larger tumours some cells may escape.

The technique may be complicated by haemorrhage from ‘cracking’ of the liver, and disseminated intravascular coagulation has been reported. However, these complications can be minimised by careful technique.

Laser treatment

This may be performed without laparotomy on an out-patient basis. Ultra-thin fibres are guided percutaneously into the metastases and the Neodymium-YAG laser used to destroy them.³² Information about any possible therapeutic benefit is not yet available.

Intrahepatic ethanol injection

Ethanol is toxic to tumour cells and may be injected directly into the tumour using ultrasound guidance. A response has been reported in patients with single, small and unresectable metastases.³³ The main difficulty is that liver metastases are normally scirrhous, and direct injection is difficult.

CHEMOTHERAPY

Colorectal liver metastases cannot be controlled in the majority of patients by either liver resection or other local treatments alone, and chemotherapy forms an important part of the treatment. Colorectal carcinoma is usually sensitive to fluorinated pyrimidines, and this can be modulated by the addition of thymidilate kinase inhibitors such as folinic acid.³⁴ In addition, there are some studies to suggest that colorectal cancer is sensitive to platinum agents, eg, oxaliplatinum³⁵ and to topoisomerase 1 inhibitors.³⁶ Chemotherapy can be administered either regionally via the hepatic artery, or systemically.

Systemic chemotherapy

The fluorinated pyrimidine 5-fluorouracil, when administered systemically as a single agent, results in a 10–15% tumour partial response rate.^{37,38} The combination of 5-fluorouracil with other cytotoxic agents has not been shown to improve the response rate.³⁹ Improved response rates are achieved by combining 5-fluorouracil with the thymidilate kinase inhibitor folinic acid, when a response rate in the order of 25% has been reported.³⁴ Systemic 5-fluorouracil with folinic acid has been reported to provide a significant survival benefit when compared with systemic 5-fluorouracil alone.⁴⁰ The side-effects of systemic chemotherapy with 5-fluorouracil/folinic acid include stomatitis and diarrhoea. This occurs to a mild extent in 70% of all patients treated but is of sufficient severity to require a cessation or reduction in treatment in only 30% of patients.⁴¹ Tomudex (ZD 1694) is a specific inhibitor of thymidilate synthetase which has been recently developed. Early results⁴² suggest that it is as effective as 5-fluorouracil/leucovorin, but less toxic. Irinotecan (CPT11) is a DNA topoisomerase 1 inhibitor which has recently undergone Phase II trials in patients with advanced colorectal cancer. It has achieved partial response rates of 20–25%,²⁶ but is associated with diarrhoea, nausea and leukopenia. Oxaliplatinum is a third generation platinum-based compound which is presently in Phase II trials. Response rates of 10% have been reported,³⁵ although this may be increased to 40% when oxaliplatinum is combined with 5-fluorouracil and folinic acid.⁴³

OTHER FORMS OF SYSTEMIC TREATMENT

Isotope-labelled monoclonal-antibody-directed radiotherapy has been attempted but has not proved very successful. Riva *et al*⁴⁴ demonstrated a 27%

Figure 6 Devices used for regional chemotherapy infusion. A subcutaneous pump (right) and an external infusion device (left)

Systemic chemotherapy
<ul style="list-style-type: none">• simple• best response 20–30%• moderate cost• severe systemic toxicity in 30%

Regional chemotherapy
<ul style="list-style-type: none">• complex• best response 40–50%• initially expensive• no systemic toxicity

response rate with ¹³¹I-labelled anti-carcinoembryonic antigen monoclonal antibodies, but this efficacy is limited by nontumorous, nonspecific uptake of antibody. Regional infusion of the capillary permeability agent histamine appears capable of doubling the tumour/normal uptake ratio⁴⁵ of antibody, but this technique has yet to be used in clinical practice. The use of a monoclonal anti-idiotypic antibody induces an antitumour response by both cellular and nonspecific mechanisms.⁴⁶ This has been shown to improve median survival (12 *vs* four months) in patients with advanced rectal disease.⁴⁷

As tumours cannot develop beyond a few millimetres in size without developing an arterial blood supply,⁴⁸ interest has been focused on inhibiting angiogenesis. Such an approach would avoid the toxicity of many cytotoxic agents. In an animal model, the anti-angiogenic agent TNP-470 has shown good activity in liver tumours.⁴⁹ Anti-angiogenic agents would not be expected to produce tumour shrinkage, and the use of ‘response’ to measure the effect of treatment is probably inappropriate. On-going clinical trials with anti-angiogenic agents in various types of cancer⁵⁰ are therefore assessing prevention of further tumour growth as the endpoint of treatment.

REGIONAL CHEMOTHERAPY

Regional administration of chemotherapy into the liver via the hepatic artery results in a greater concentration of drugs being taken up within the liver where there is a high first-pass extraction of the drug, and reduced systemic toxicity. A catheter is inserted surgically into the gastroduodenal artery and thence into the hepatic artery to allow infusion chemotherapy directly into the liver. Previous studies have suggested that colorectal liver metastases derive their blood supply predominantly from the hepatic artery rather than from the portal vein. Thus, drug uptake into liver metastases is greater if it is administered via the hepatic artery than if it is given through the portal vein. The 5-fluorouracil analogue floxuridine has a high first-pass extraction on passing through the liver and has been administered regionally to the liver via the hepatic artery using a totally implantable pump.⁵¹ A pump is placed subcutaneously below the right costal margin and can be refilled by insertion of a needle through the skin into a subcutaneous permeable port (figure 6). Floxuridine is delivered by continuous slow infusion, usually over a two-week period and is followed by a rest period with insertion of saline for a further two weeks, and the cycle then repeated. This approach produces the highest tumour partial response rate reported with chemotherapy, in the order of 50% (figure 7),⁵² and this is associated with improvement in patient survival and a well-sustained quality of life.^{53,5} Although this approach has been shown to be effective in controlling disease within the liver, death is more likely to occur from progression of extrahepatic disease.⁵ In order to reduce the growth of extrahepatic metastases while liver metastases are controlled, a combination of regional with systemic chemotherapy is now being evaluated.

Regional chemotherapy has a lower incidence of side-effects than systemic chemotherapy, but when side-effects do occur they involve the liver, which is the site of direct infusion. High doses of floxuridine are toxic to hepatocytes and may produce a chemical hepatitis leading eventually to sclerosing cholangitis if treatment is not reduced. Occasionally, gastritis can occur when drug infused into the gastroduodenal artery finds a path directly into the wall of the stomach or duodenum. Care should be taken at the time of hepatic artery catheter insertion to ensure that inadvertent perfusion of the stomach or duodenum is avoided by ligating any collateral vessels.

SYMPTOM CONTROL

Liver metastases have usually involved more than one-third of the liver by the stage where they become symptomatic.⁵ The most typical symptoms produced by liver metastases are upper abdominal pain or discomfort, a general feeling of

Figure 7 A response of >50% following regional chemotherapy. Before (A), after (B) treatment

tiredness, nausea, and loss of appetite. These are frequently associated with loss of weight, abdominal and ankle swelling, and jaundice. The abdominal pain and loss of appetite can be relieved by analgesics – if necessary opiates – and oral corticosteroids. Tense uncomfortable ascites can be relieved by tapping, but this usually reaccumulates and tapping may need to be repeated. Jaundice can be produced by bile duct obstruction arising from adjacent hepatic artery lymph node enlargement. The obstruction can frequently be overcome by passing a stent at endoscopic retrograde cholangiopancreatography. This is very worthwhile if it can be achieved, because the jaundice can result in troublesome itching. The pruritus can also be relieved by prescription of antihistamine.

Conclusions

Liver metastases are common and are frequently the cause of death in large bowel cancer. They are best treated when the disease within the liver is small, at a time when temporary arrest of the progress of disease of the liver can result in prolonged survival with a normal quality of life. In order to identify disease at this stage, regular liver ultrasound examination is required, since these patients will usually be asymptomatic.

The range of treatment options varies from surgical resection, other means of local control, to regional and systemic chemotherapies. All these approaches to treatment may have a part to play in an individual case in slowing the progression of disease and sustaining quality of life. Each of these treatments has its own particular indications, and also morbidity. In order to provide the best possible palliation with the minimum complications, it is preferable if these patients are managed in units with a particular interest in the problem, where the benefits of various approaches can be combined while keeping morbidity to a minimum. Current treatments can now prevent the gradual and progressive development of gross hepatomegaly, ascites and jaundice in over 70% of patients. Therefore, suitably fit and motivated colorectal liver metastasis patients should be offered treatment.

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