Modern management of colorectal liver metastases

The liver is the most frequent site of metastases from colorectal cancer.

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Colorectal cancer is one of the commonest malignancies worldwide. The liver is the most frequent site of metastasis from colorectal cancer and overall close to 50% of patients will develop liver metastases during the course of the disease. In one-third of patients, the liver metastases are synchronous, i.e. present at the time of diagnosis, while in two-thirds metastases are metachronous, presenting later. Surgical resection is the only established curative treatment in patients with colorectal liver metastasis. The rationale for resection is based on the recognition that colorectal tumour cells initially spread haematogenously via the portal circulation, making the liver the first site of metastasis in most patients. Liver resection has been shown to extend survival; without surgical resection, 5-year survival is rare and median survival is less than 12 months. Five-year survival after liver resection and chemotherapy now exceeds 40%.

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Although isolated liver metastases from colorectal primaries occur more frequently than with other gastrointestinal tumours, less than 10% of all patients with colorectal metastases are suitable for a liver resection.

Liver resection for metastatic disease is considered only if:

- the primary colon carcinoma has been completely resected and there is no residual or recurrent local tumour
- there are no systemic or extrahepatic intra-abdominal metastases
- the patient will tolerate a major abdominal operation
- complete resection of the liver metastases (with added ablation if required) is feasible.

The most important determinants of survival after resection are adequate tumour clearance and lack of residual extrahepatic disease. There is now good evidence that added combination chemotherapy produces a useful survival benefit in resectable tumours.

Two major factors, however, continue to plague the management of patients with colorectal liver metastases. Only 1 in 10 patients who develop colorectal liver metastases is a candidate for liver resection (because of the contraindications listed above) and in those who have had a resection, two-thirds will subsequently develop recurrent disease, either in the remnant liver or elsewhere, due to previously undetected micrometastases.

The prognosis in patients with colorectal liver metastases has improved considerably in the past decade due to substantial advances in chemotherapy, surgical resection and ablative therapy. Decision making has also become more complex because of the increased number of treatment options available. All patients who are found to have colorectal liver metastases should therefore be evaluated by a multidisciplinary team comprising surgeons, oncologists, radiologists and pathologists to co-ordinate optimal treatment. Some patients may require several different radiological investigations to accurately stage the extent of disease and to plan the feasibility of operative intervention, while most patients need chemotherapy which has become an integral component of modern therapy, either before or after the liver resection. A number of new and innovative strategies have been developed to increase resectability rates. These include neo-adjuvant chemotherapy to downstage tumours, portal vein embolisation with staged liver resections, and tumour ablation using microwave energy.

Preoperative evaluation

Preoperative evaluation and investigation of patients who may be suitable candidates for resection of colorectal liver metastases is focused on:

- evaluation of the patient's fitness for operation
- confirmation of the diagnosis
- meticulous staging to rule out extrahepatic metastatic disease
- defining the feasibility of a curative liver resection by determining the number and anatomical segmental location and intrahepatic vascular and biliary structural relationships of the liver secondaries
- assessment of liver function and the volume of the anticipated future liver remnant after complete curative resection.

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Evaluation of fitness for operation

Careful evaluation of the patient's general health and capacity to tolerate a major liver resection is essential to ensure a favourable outcome. In addition to a detailed cardiopulmonary evaluation and the assessment of associated medical co-morbidity, meticulous appraisal of the patient's liver function is crucial. History, physical examination and routine laboratory studies with complete blood count, liver function tests and coagulation

studies are required to screen for underlying liver dysfunction, because impaired hepatic function results in higher complication rates and may limit the extent of liver resection. Careful preoperative assessment and interdisciplinary consultation between anaesthetist, surgeon and intensive care staff are necessary in high-risk patients or those undergoing a major liver resection.

Imaging

Accurate staging and anatomical localisation of secondary cancer deposits both within and outside the liver in patients with colorectal cancer is crucial to ensure optimal treatment. Radiological imaging is the cornerstone of preoperative assessment of a patient with colorectal liver metastases and for operative planning.

Ultrasound is inexpensive and widely available as a good initial screening investigation of the liver, showing the number, size and distribution of approximately 90% of liver metastases. Duplex ultrasound can further help define the relationship of secondaries to portal structures, hepatic veins and the inferior vena cava. This can be followed by computed tomography (CT) if not precluded by the ultrasound findings and, when appropriate, magnetic resonance imaging (MRI) scanning.

CT scanning, particularly multidetector helical CT, plays a pivotal role in imaging patients for hepatic resection. CT offers good detail resolution and approximately 90% sensitivity in detecting colorectal liver metastases, although under 10 mm it becomes less sure. Liver metastases are classically best seen as hypodense rounded lesions in the portal venous phase of the CT (Fig. 1). A CT scan also provides information regarding the anatomical characteristics of the metastatic lesions and their relation to lobar architecture and major vascular structures. In addition, CT allows detection of diffuse hepatic steatosis, which may imply poor liver function. CT angiography (CTA) is not routine but can depict arterial anatomy.

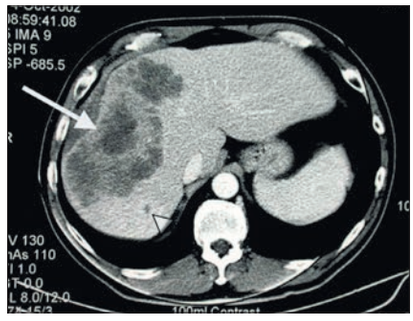

Fig. 1. Portal venous phase CT scan of the liver showing a large hypodense umbilicated colorectal secondary (arrow) and a small satellite lesion (arrowhead).

MRI provides a good alternative to CT in detecting metastases and defining relationships to hepatic vasculature, and can be improved by using liver-specific contrast agents. However, the limited access to MRI in most institutions tends to reduce its application. MR cholangiopancreatography (MRCP) is a useful supplementary tool, with MR angiography (MRA) an alternative to CTA.

A more recent addition to the imaging armamentarium is whole-body positron emission tomography (PET) (Fig. 2). The most common tracer in PET scanning is fluoro-18-deoxyglucose (FDG)-PET, a glucose analogue, which accumulates in glucose-avid cancer cells. The combination of CT and FDG-PET increases sensitivity and accuracy of localisation, permitting better selection of surgical therapy for patients likely to benefit. The main limitation of PET scanning is the reduced sensitivity in detecting sub-centimetre metastases, mucinous secondaries and metastases treated with neo-adjuvant chemotherapy.

Besides demonstrating detailed intrahepatic anatomy relevant to liver resection, preoperative cross-sectional imaging may also help to identify associated intrinsic parenchymal liver disease such as cirrhosis, portal hypertension, steatohepatitis or recurrent extrahepatic tumour. This requires careful searching for hepatic low densities, atrophy, nodularity, splenomegaly, ascites, varices, omental caking, peritoneal nodules and porta hepatis or aortocaval lymphadenopathy.

Fig. 2. Fused PET/CT scan showing uptake in a liver secondary tumour (arrow).

In selected patients, laparoscopy provides crucial information which may avoid unnecessary laparotomy. Rapid recourse to percutaneous biopsy of a liver mass without careful diagnostic evaluation and consideration of long-term treatment implications is inappropriate. Preoperative biopsy is seldom indicated or beneficial in the assessment of colorectal liver metastases and may result in tumour seeding, dissemination and decreased survival. It is strongly discouraged.

Although the likelihood of lung metastases is low, it is prudent to remember that chest radiographs and CT scans of the lungs, when clinically indicated, may avoid unnecessary further investigation by demonstrating widespread metastases. High-quality cross-sectional imaging is also critical to assess response to preoperative therapy and definitive surgery. Patients should be routinely re-imaged after any course of systemic therapy, preferably within 4 weeks of planned resection.

Preoperative treatment

Chemotherapy

Modern chemotherapy regimens including oxaliplatin and irinotecan in addition to 5-fluorouracil and leucovorin have achieved improved response rates in colorectal liver metastases, with significant reduction in disease bulk in almost 50% of patients and a median survival approaching 2 years. New biological agents, such as those targeting epithelial and vascular endothelial growth factor pathways (bevacizumab, cetuximab), have also added significant survival benefit. By downsizing tumours and rendering them resectable, chemotherapy has contributed to the improvement in survival of more patients with advanced metastatic disease.

Liver resection

The foremost difficulty when operating on the liver is that it is a solid parenchymal organ with an abundant blood supply and few external defining landmarks to orientate or identify the internal anatomy, which

makes resection a technically challenging procedure. This fact has made major liver surgery the province of only a small number of specialist surgeons.

The major advances in liver resection have been improvements in metabolic, haemodynamic and respiratory support, as well as in technology and surgical technique. Detailed knowledge of liver segmental anatomy is a fundamental prerequisite (Fig. 3). The use of vascular inflow control to reduce intraoperative blood loss, intraoperative ultrasound, ultrasonic dissection, argon beam coagulation and fibrin glue has reduced postoperative morbidity and mortality. Anatomical resection follows segmental liver anatomy. The overriding principle is to stay within the anatomical plane while obtaining optimal tumour clearance to preserve inflow and outflow vessels to the residual segments.

Most liver resections proceed in a systematic and orderly fashion and are divided into several distinct stages:

- laparotomy and exploration
- intraoperative ultrasonography to confirm and map intrahepatic tumour deposits and delineate vascular and biliary anatomy
- liver mobilisation
- inflow control
- outflow control
- parenchymal transection
- haemostasis and suture of small bile ducts at the resection margin before closing the abdomen.

Open liver resections are usually performed via an inverted chevron bilateral subcostal incision. After visual inspection and careful palpation of the liver, a meticulous search of the peritoneal cavity is undertaken for small intra-abdominal serosal, peritoneal and omental metastases (Fig. 4). The site of the primary colonic resection is assessed for local recurrence, as are the mesentery, coeliac axis and porta hepatis for metastatic adenopathy. The diaphragm, the paracolic gutters and the pouch of Douglas are examined, looking for peritoneal deposits.

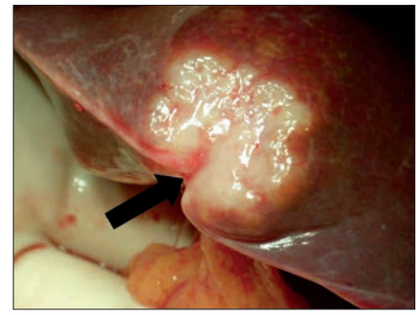

Fig. 4. Typical pale umbilicated colonic liver secondary (arrow).

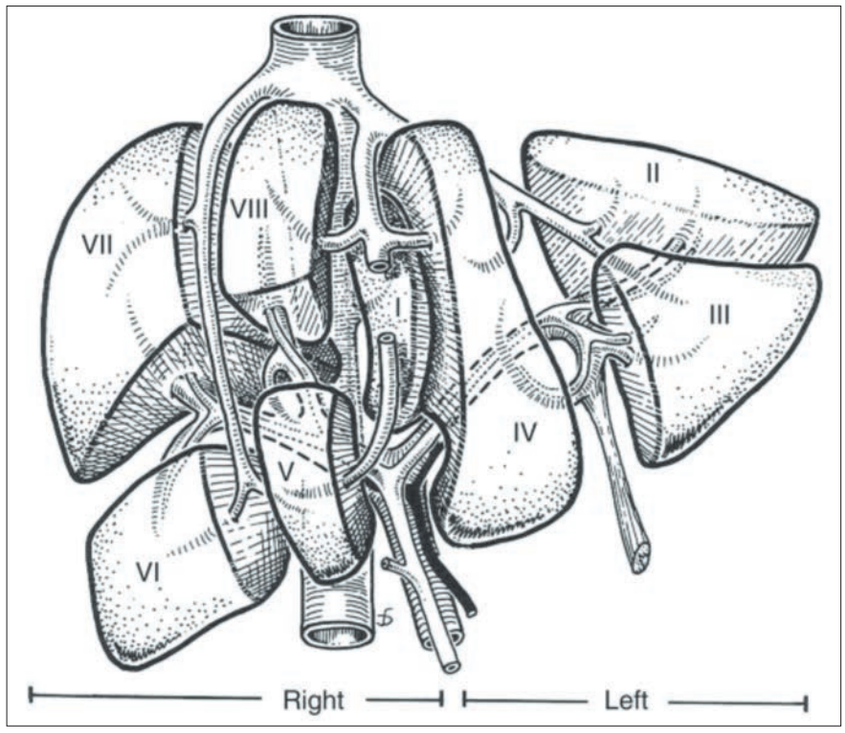

Fig. 3. Diagram showing the segmental anatomy of the liver from I to VIII.

Once extrahepatic recurrence has been excluded, a careful intraoperative ultrasound evaluation is performed by an experienced operator. Ultrasonic evaluation of the number, size and relationship and proximity of intrahepatic metastases to arterioportal, biliary and hepatic venous structures is reconciled with the preoperative imaging.

Major liver resection using modern operative techniques can routinely be performed without blood transfusion.

Following exploration and intraoperative ultrasound, the liver is mobilised by dividing the ligamentum teres, falciform, triangular and coronary ligaments. Dissection of the porta hepatis is undertaken to identify the branches of the hepatic artery, portal vein and biliary system of the segment(s) or lobe(s) to be resected. These are individually temporarily occluded. Glisson's capsule is then incised along the resection line, and the hepatic parenchyma is divided with a cavitron ultrasonic surgical aspirator (CUSA) (Fig. 5) to expose the larger ducts and vessels, which are individually ligated and divided.

The goal of surgery for liver metastases is removal of all metastases with tumour-free margins of at least 1 cm. Parenchymal transection is continued posteriorly until the major hepatic veins are identified, sutured and divided. Blood flow to and from the remaining segments is carefully preserved. Viability and adequate perfusion of the remnant liver are confirmed visually. Oozing from the resection margin is controlled with diathermy or fine monofilament sutures and the cut surface is sealed using an argon beam and the

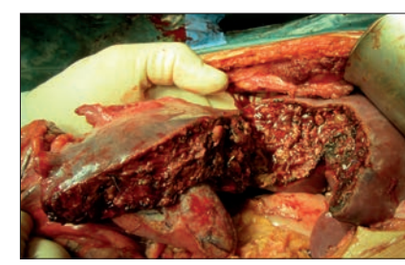

Fig. 5. Right hepatic lobectomy in progress.

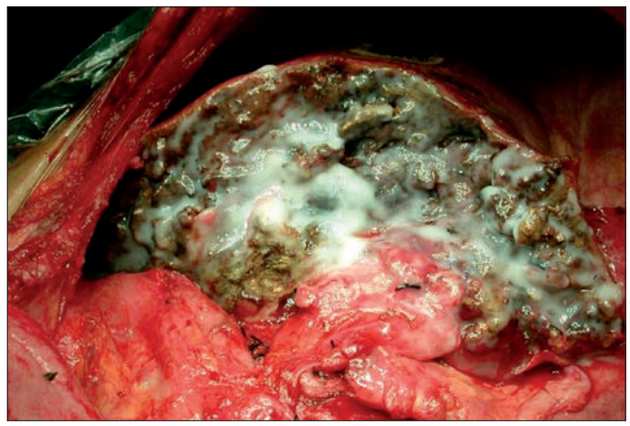

Fig. 6. Completed right hepatic lobectomy showing fibrin glue 'Tisseel' sprayed on the resection margin to prevent bile leaks.

application of a fibrin tissue sealant ('Tisseel') (Fig. 6). Before closing the abdomen, silastic suction drains are positioned near the liver resection margin and are removed several days later depending on the volume and type of drainage.

It is not necessary to proceed doggedly along the above-outlined sequence of events for resection. The type of resection is guided by the number and location of lesions, and by the need to attain a tumour-free margin. The surgeon may have to be flexible and improvise or modify the procedure depending on the operative findings. Anatomic resections are favoured over non-anatomic wedge resections due to better margin width and overall survival. Blood flow into the liver can be controlled to provide a dry operative field by intermittently cross-clamping the hepatoduodenal ligament ('Pringle manoeuvre') for 20-minute periods using a vascular clamp.

Major liver resection using modern operative techniques can routinely be performed without blood transfusion. Mortality of elective liver resections is now less than 3% in specialist centres. Long-term survival depends on the stage of the disease and tumour biology. The larger the hepatic resection, the greater the probability of postoperative complications. Particular care is taken postoperatively to avoid hypoglycaemia, coagulopathy and hypoalbuminaemia. The most frequent major complications are blood or bile collections and intra-abdominal sepsis in the resection cavity after partial hepatectomy. Ultrasound-guided percutaneous catheter drainage of perihepatic collections and endoscopic stenting of biliary leaks can avoid reoperation.

The liver has a unique regenerative capacity to restore normal mass and function after partial resection through DNA synthesis and mitosis. After partial hepatectomy, the residual tissue hypertrophies until the original mass has been restored, whereafter growth stops. The mechanisms which control regeneration are complex and subtle. The process is highly efficient after resection of normal liver, with the human liver initiating regeneration within 3 days and reaching its original size by 3 months. Patients with cirrhosis may have insufficient hepatocyte function to meet the increased metabolic demands after major resection with significantly reduced hepatic regeneration, making them vulnerable to post-hepatectomy liver failure.

Radiofrequency, and more recently microwave ablation (MWA), are newer developments in the therapeutic armamentarium using localised heat of up to 100^{0}C to eliminate viable liver secondaries. Both can be applied by ultrasound or CT guidance percutaneously or with intraoperative ultrasound as an adjunct to resection in patients with bilobar disease. The limitations are size (lesions must be <3.5 cm in diameter), position (not near vital structures) and number (not more than 4 secondaries). Alcohol injection into liver secondaries is no longer used and arterial chemo-embolisation, despite anecdotal successes, is not proven.

Follow-up after resection

Patients who have undergone hepatic resection of colorectal metastases should be followed up carefully to identify early recurrence that may be amenable to repeat resection or ablation for cure. Most patients undergo serial physical examination, serum CEA and CA 19-9 levels, chest X-ray, and CT of the upper and lower abdomen every 3 - 6 months for the first 2 years and then every 6 months for the following 5 years.

Conclusion

The treatment of colorectal liver metastases is in rapid evolution. Optimal management is complex and requires a multidisciplinary team approach for the best outcome. At present, 10% of all patients with colorectal liver metastases are candidates for curative liver resection. Liver resection combined with chemotherapy can be performed safely, with mortality rates of under 3% and 5-year survival rates over 40%. The Achilles heel of surgical treatment is recurrent disease, which unfortunately occurs in two-thirds of patients after liver resection. A variety of supplementary liver-directed therapies exist to treat unresectable, incurable patients with adequate palliation, survival benefit and morbidity rates.

In a nutshell

- 50% of patients with colorectal cancer develop liver metastases during the course of their disease.
- Adequate tumour clearance and absence of extrahepatic disease determine survival after resection.
- Accurate evaluation and staging by a multidisciplinary team is essential to ensure appropriate treatment.
- Recurrent disease is the Achilles heel of liver resection for colorectal secondaries.
- 5-year survival after liver resection and chemotherapy exceeds 40%.
- Preoperative biopsy of liver lesions is not indicated and is associated with a worse prognosis.