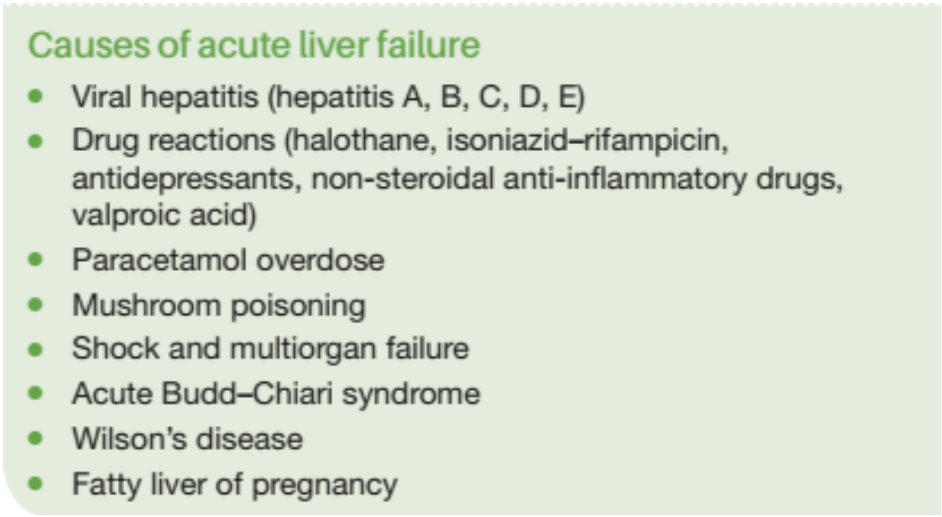
Acute liver failure

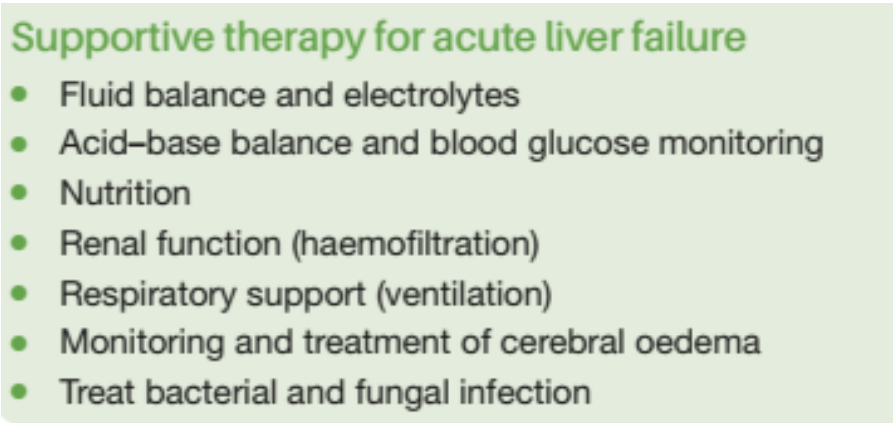
Causes of acute liver failure

In the early stages, there may be no objective signs, but with severe dysfunction the onset of clinical jaundice may be associated with neurological signs of liver failure (hepatic encephalopathy), consisting of a liver flap, drowsiness, confusion and, eventually, coma.



Treatment of acute liver failure

The overall mortality from acute liver failure is approximately 50%, even with the best supportive therapy.



Liver transplantation is appropriate for some patients with acute liver failure, although the short-term results are poor in comparison with liver transplantation for chronic liver disease and suitable donor livers are frequently unavailable during the brief window of opportunity before death from liver failure.

Chronic liver disease

Lethargy and weakness are common features irrespective of the underlying cause. These often precede clinical jaundice, which indicates impairment of the liver's ability to metabolise bilirubin. Progressive deterioration in liver function is associated with a hyperdynamic circulation involving a high cardiac output, large pulse volume, low blood

pressure and flushed warm extremities. Fever is a common feature, which may be related to underlying inflammation and cytokine release from the diseased liver or may be due to bacterial infection, to which patients with chronic liver disease are predisposed. Skin changes may be evident, including spider naevi, cutaneous vascular abnormalities that blanch on pressure, palmar erythema and white nails (leuconychia). Endocrine abnormalities are responsible for hypogonadism and gynaecomastia. The mental derangement associated with chronic liver disease is termed hepatic encephalopathy. This is associated with memory impairment, confusion, personality changes, altered sleep patterns and slow, slurred speech. The most useful clinical sign is the flapping tremor, demonstrated by asking the patient to extend his or her arms and hyperextend the wrist joint. Abdominal distension due to ascites is a common late feature. This may be suggested clinically by the demonstration of a fluid thrill or shifting dullness. Protein catabolism produces loss of muscle bulk and wasting, and a coagulation defect is suggested by the presence of skin bruising.

Features of chronic liver disease

- Lethargy
- Fever
- Jaundice
- Protein catabolism (wasting)
- Coagulopathy (bruising)
- Cardiac (hyperdynamic circulation)
- Neurological (hepatic encephalopathy)
- Portal hypertension
  - Ascites
  - Oesophageal varices
  - Splenomegaly
- Cutaneous
  - Spider naevi
  - Palmar erythema

Acute infections of the liver

Possible sources of infection are the following:

• *portal*, from an area of suppuration drained by the portal vein, usually diverticular sepsis or appendicitis;

• *biliary*, resulting from an ascending cholangitis;

• *arterial*, as part of a general septicaemia – this is unusual;

• *adjacent infections* spreading into the liver parenchyma, for example subphrenic abscess or acute cholecystitis.

Pyogenic liver abscess

Pyogenic liver abscess is a consequence of infection in either the portal territory, leading to a portal pyaemia (pyelophlebitis), or the biliary tree. Multiple abscesses are common. Common infecting organisms include *Escherichia coli*, *Streptococcus faecalis* and

Streptococcus milleri.
Clinical features The condition should be suspected in patients who develop rigors, high swinging fever, a tender palpable liver and jaundice. A previous history of abdominal sepsis, such as Crohn's disease, appendicitis or diverticulitis, may be obtained. The clinical course is often insidious, with a non-specific malaise for over a month before presentation and diagnosis.

Special investigations

• *Blood culture*, carried out before treatment is commenced, is often positive.
• *Ultrasound or CT* of the liver may identify and localize hepatic abscesses, as well as identifying the source of the pyaemia.

Treatment

The originating site of sepsis should be dealt with appropriately. A large liver abscess can be drained percutaneously under ultrasound guidance; smaller abscesses are treated by parenteral antibiotic therapy alone.

Portal pyaemia (pyelophlebitis) Infection may reach the liver via the portal tributaries
from a focus of intra-abdominal sepsis, particularly acute appendicitis or diverticulitis. Multiple abscesses may permeate the liver; in addition, there may be septic thrombi in the intrahepatic radicles of the portal vein, and infected clot in the portal vein itself. The condition has become rare since the advent of antibiotics .

Biliary infection Multiple abscesses in the liver may occur in association with severe suppurative cholangitis secondary to impaction of gallstones in the common bile duct. Clinically, the features are those of *Charcot's intermittent hepatic fever*10 – pyrexia, rigors and jaundice. (Rigors represent a bacteraemia and are commonly
due to infection in either the renal or biliary tract.) Urgent drainage of the bile ducts is performed, by either endoscopic sphincterotomy or percutaneous transhepatic drainage.

Amoebic liver abscess

This particular type of portal infection is secondary to an *Entamoeba histolytica* infection of the large intestine. From there, amoebae travel via the portal circulation to the liver, where they proliferate. The amoeba produces a cytolytic enzyme that destroys the liver tissue, producing an amoebic abscess, which is sterile, although amoebae may be found in the abscess wall. Computed tomography and ultrasound of the liver are the most valuable special investigations.

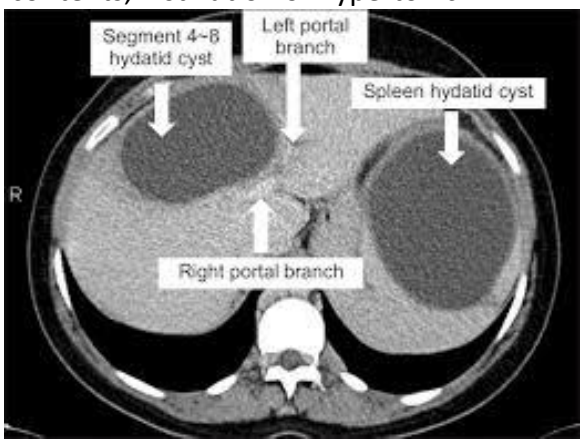
Treatment

The majority respond to medical treatment with metronidazole. Ultrasound-guided percutaneous drainage is required infrequently in non-responding cases. Often patients with clinical signs of an amoebic
abscess will be treated empirically with metronidazole (400–
800 mg t.d.s. for 7–10 days) and investigated further only if
they do not respond. Resolution of the abscess can be monitored using ultrasound.

Hydatid liver disease

This is a very common condition in countries around the Mediterranean and Middle East and Iraq. The causative tapeworm, *Echinococcus granulosus*, is present in the dog intestine, and ova are ingested by humans and pass in the portal blood to the liver. Liver abscesses are often large by the time of presentation with upper abdominal discomfort or

may present after minor abdominal trauma as an acute abdomen due to rupture of the cyst into the peritoneal cavity. Diagnosis is suggested by the finding of a multiloculated cyst on ultrasound and is further supported by the finding of a floating membrane within the cysts on CT scan **)**. Active cysts contain a large number of smaller daughter cysts and rupture can result in these implanting and growing within the peritoneal cavity. Liver cysts can also rupture through the diaphragm producing an empyema, into the biliary tract producing obstructive jaundice, or into the stomach. Clinical and radiological diagnosis can be supported by serology for antibodies to hydatid antigen, in the form of an enzymelinked immunosorbent assay (ELISA). Treatment is indicated to prevent progressive enlargement and rupture of the cysts. In the first instance, a course of albendazole or mebendazole may be tried. There are many reports that percutaneous treatment of hydatid cysts is safe and effective. Percutaneous treatment (PAIR) constitutes of an initial course of albendazole followed by puncture of the cyst under image guidance, aspiration of the cyst's contents, instillation of hypertonic saline in the cyst cavity and reaspiration. PAIR should only be attempted if there is no communication with the biliary tree. Failure to respond to medical treatment or percutaneous treatment usually requires surgical intervention. The surgical options range from liver resection or local excision of the cysts to deroofing with evacuation of the contents. Contamination of the peritoneal cavity at the time of surgery with active hydatid daughters should be avoided by continuing drug therapy with albendazole and adding peroperative praziquantel. This should be combined with packing of the peritoneal cavity with 20% hypertonic saline-soaked packs and instilling 20% hypertonic saline into the cyst before it is opened. A biliary communication should be actively sought and sutured. The residual cavity may become infected, and this may be reduced, as may bile leakage, by packing the space with pedicled greater omentum (an omentoplasty). Calcified cysts may well be dead. If doubt exists as to whether a suspected cyst is active, it can be followed on ultrasound, as active cysts gradually become larger and more superficial in the liver. Rupture of daughter hydatids into the biliary tract may result in obstructive jaundice or acute cholangitis. This may be treated by endoscopic clearance of the daughter cysts prior to cyst removal from the liver.



Liver cysts

These include simple hepatic cysts, choledochal cysts, cystadenoma of the liver, Caroli disease and parasitic cysts.

▌Non-parasitic hepatic cysts

Within the non-parasitic group there are a variety of clinical conditions that reflect underlying developmental defects of the liver parenchyma or bile ducts. Some cystic lesions follow trauma in which a central rupture has resulted in a collection of bile and serum and these cysts have no epithelial lining. Others are clearly similar to dermoid cysts found in other sites. Most of the remainder are lined by cuboidal or columnar epithelium, contain serous fluid and do not communicate with the biliary tract. These

are nowadays referred to as simple cysts and are multiple in 50% of cases. The cysts can grow to a large size and in so doing cause pressure atrophy of the surrounding hepatic parenchyma. They are generally regarded as developmental abnormalities from aberrant bile ducts. The ultrasound incidence of asymptomatic cysts is 1%, but symptomatic cysts are much rarer. Symptomatic cysts are much commoner in females (9:1) and huge cysts are almost exclusively found in women above the age of 50 years.

Clinical features and treatment

Most simple hepatic cysts are asymptomatic and only become apparent when the cysts reach sufficient size to exert pressure on adjacent viscera, producing non-specific symptoms of vomiting,upper abdominal pain and occasionally diarrhoea. Clinical examination reveals a non-tender smooth mass in the liver. Jaundice is very unusual and LFTs are usually normal. Plain film of the abdomen may show displacement of the colon or stomach but the diagnosis is best confirmed by ultrasonography.

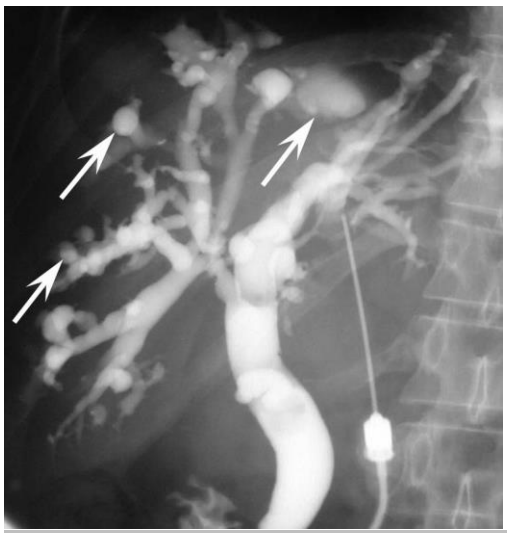
Other investigations including CT are not usually necessary. Complications are uncommon and include intracystic bleeding that causes sudden severe pain and increase in size, fistulation with the intrahepatic biliary tract or duodenum, bacterial infection, compression of the bile duct with obstructive jaundice and compression of the vena cava or portal vein.

▌Hepatic cystadenoma

This is rare and affects predominantly females. It forms a large multiloculated cyst filled with mucinous fluid the lesion is liable to complications, notably cholestasis due to compression of the bile duct, intracystic bleeding, infection, rupture and malignant degeneration to cystadenocarcinoma. Hepatic cystadenoma must be excised completely even when asymptomatic.

▌Caroli syndrome

This is not a single entity and covers a spectrum of disorders characterized by congenital multifocal dilatations of the segmental bile ducts. In 50% of cases Caroli syndrome is associated with congenital hepatic fibrosis, itself an inherited malformation (autosomal recessive). The clinical picture of Caroli syndrome is dominated by recurrent episodes of bacterial cholangitis.



Caroli disease. Percutaneous transhepatic cholangiogram shows multiple saccular dilatations of the intrahepatic bile ducts (arrows), mostly at the periphery of the liver, and fusiform dilatation of the common bile duct.

Liver neoplasms

Classification

Benign

• Haemangioma.
• Adenoma.
• Focal nodular hyperplasia.

Malignant

1 *Primary*:
a hepatocellular carcinoma (hepatoma);
b fibrolamellar carcinoma, uncommon variant of hepatoma affecting young adults and children;
c cholangiocarcinoma.

2 *Secondary* (most common):
a portal spread (from alimentary tract);
b systemic blood spread (from lung, breast, testis, melanoma, etc.);
c direct spread (from gallbladder, stomach and hepatic flexure of colon).

Surgical approaches to resection of liver tumours

Adequate exposure of the liver is an absolute prerequisite to safe liver surgery. A transverse abdominal incision in the right upper quadrant with a vertical midline extension to the xiphoid provides excellent access to the liver if adequate etraction of the costal margin is employed, using a costal margin retractor. If necessary the incision can be extended across the midline transversely in the left upper quadrant. Thoracoabdominal incisions are very rarely required. The procedure for complete mobilisation of the liver is described, although this will not be necessary in all cases. There are many variations in surgical technique.

Blood loss and transfusion

The reduction of blood loss during liver surgery has been one of the major achievements in the last 20 years, and resection is often possible without blood transfusion. Better understanding of the segmental anatomy of the liver, better patient selection for surgery and low central venous pressure anaesthesia (<10 mmHg) have all helped to reduce the need for blood transfusions. Better control of the coagulation cascade has been achieved using TEG, and the antifibrinolytic drug aprotinin has significantly reduced bleeding in patients with liver disease and an underlying coagulopathy. Oozing from the resected surface of the remnant liver can be reduced by the topical application of fibrin glue or fibrin-impregnated collagen fleece. The main alternative is use of an argon-beam coagulator. Intermittant temporary clamping of the portal vein and hepatic artery in the hepatoduodenal ligament (Pringle manoeuvre) can reduce blood loss during parenchymal transection. The optimal duration of the Pringle manoeuvre is unknown, but it can be applied intermittently, e.g. cycles of 15 minutes inflow occlusion followed by 5 minutes of reperfusion, until parenchymal transection is complete.

Ablation for liver tumours

Ablative therapies aim to destroy tumour by the direct application of energy to discrete lesions and can be perfomed percutaneously, laparoscopically or at open surgery.

surgery remains the gold standard treatment for resectable disease. Despite these concerns, ablation still has a role as an adjunct to resection. Patients with small volume resectable lesions who are not sufficiently fit to undergo liver resection should be considered for ablation, as should those with limited liver metastases who have insufficient liver volume to undergo resection. In addition, a combined resection/

ablation approach has also been advocated. Radiofrequency ablation (RFA) is the most widely used ablative technique and relies on direct current transmission through tissue to generate heat and ablation of the tumour

Benign liver tumours.

Benign Liver Tumors

Haemangiomas

These are the most common liver lesions, and the reported incidence has increased with the widespread availability of diagnostic ultrasound. They consist of an abnormal plexus of vessels, and their nature is usually apparent on ultrasound.

If diagnostic uncertainty exists, CT scanning with delayed contrast enhancement shows the characteristic appearance of slow contrast enhancement due to small vessel uptake in the haemangioma. Often, haemangiomas are multiple. Lesions found incidentally require radiological confirmation of their nature and no further treatment. The management of 'giant' haemangiomas is more controversial. Occasional reports of rupture of haemangiomas have led some to consider resection for large lesions, especially if they appear to be symptomatic.

Hepatic adenoma

Adenomas are benign liver tumours seen almost exclusively in women aged between 25 and 50 years. These well-defined and vascular lesions are classically associated with use of the oral contraceptive pill, and are generally solitary. The majority are found incidentally on imaging, although up to one-third may present with pain because of rupture or bleeding. Adenomas are recognised as having malignant potential, with up to 10% developing into hepatocellular carcinoma. The risk of rupture and malignancy means that surgical excision is generally recommended if >5 cm in size, although some lesions may regress after discontinuation of the oral contraceptive pill.

Focal nodular hyperplasia

Focal nodular hyperplasia (FNH) is an unusual but not uncommon benign condition of unknown aetiology, in which there is a focal overgrowth of functioning liver tissue supported by fibrous stroma. Patients are usually middle-aged females, and there is no association with underlying liver disease. FNH does not have any malignant potential and once the diagnosis is confirmed, does not require any treatment or follow-up.

Primary Liver cancers:

Hepatocellular carcinoma

The majority of primary liver . There is wide variation in the geographical incidence of HCC, with >80% of cases occurring in Asia and sub-Saharan Africa, with an incidence of 99

per 100 000. By contrast, the incidence in Europe is considerably lower (approximately 5 per 100000). Chronic hepatitis B virus (HBV) infection accounts for >50% of cases of HCC worldwide. HBV as a risk factor for HCC is supported by strong evidence that HBV vaccination programmes have led to falls in the incidence of HCC in high-risk areas such as Hong Kong. Hepatitis C virus (HCV) increases the risk of HCC by 17 times, primarily by promoting end-stage liver disease. There is clear evidence that lifetime alcohol exposure correlates with the incidence of HCC. Hepatic metabolism of alcohol is thought to lead to the production of free radicals, causing intracellular oxidative stress eventually leading to a chronic inflammatory state. Because of the critical role of the liver in glucose metabolism, it is not surprising that obesity and diabetes mellitus (both of which involve impaired glucose handling) are significant independent risk factors for the development of HCC, and the global rise in obesity and diabetes is likely to lead to a significant increase in HCC developing on a background of hepatic non-alcoholic fatty liver disease (NAFLD).

Special investigations

• *Serum α-fetoprotein (AFP)* may be significantly raised, but it is neither sensitive nor specific for hepatocellular carcinoma and may rise in other diseases such as hepatitis C.

• *Cross-sectional imaging* with ultrasound and contrast-enhanced CT or MR will confirm the presence of a large tumour. Small tumours, 1 cm or less in diameter, are difficult to distinguish from regenerative nodules in the presence of cirrhosis.

• *Selective hepatic angiography* may distinguish regenerative nodules from small HCCs, or may reveal multifocal cancer.

Surgical resection for HCC

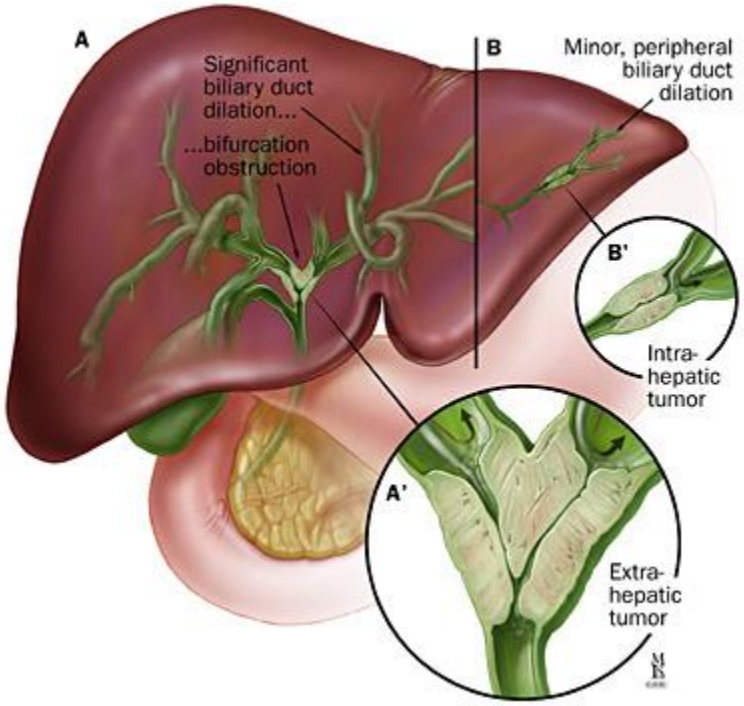
Only 20–40% of patients with HCC are considered candidates for surgical resection. surgical resection is increasingly considered the mainstay of treatment . Although tumour size, vascular invasion and multifocal disease are recognised as poor prognostic indicators, none is considered an absolute contraindication to surgical intervention. Multinodular lesions present a particular management challenge. In general, oncological contraindications to resection
now include:

(1) extrahepatic metastasis;
(2) multiple and bilobar tumours;
(3) involvement of the main bile duct;
(4) presence of tumour thrombus in the main portal vein/vena cava.

However, reasonable long-term outcomes from highly selected patients outside these contraindications have also been reported.

Cholangiocarcinoma

This is much less common (20% of primary tumours). It is an adenocarcinoma arising from the bile duct system that usually presents with jaundice and may complicate primary sclerosing cholangitis. Spread occurs directly through the liver substance and regional nodes with a fatal outcome. Some tumours present early and are amenable to resection, which usually involves an extended liver resection (see later in this chapter). For the more usual inoperable cases, it may be possible to relieve the jaundice at ERCP by passing a plastic or expanding metal stent upwards along the common bile duct through the growth into the dilated radicles above the obstruction or downwards by percutaneous intubation. This relieves the jaundice, often for many months.

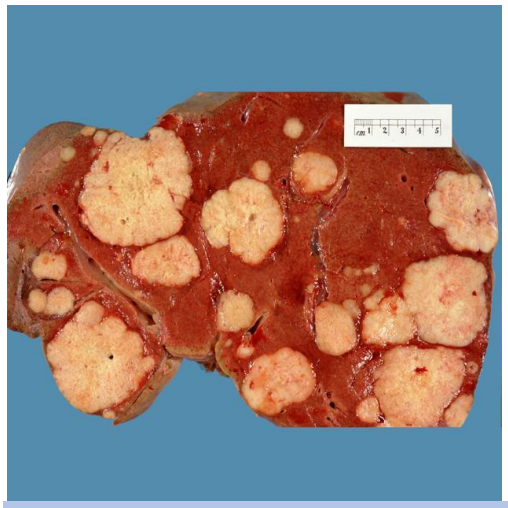


Metastatic liver tumours

Direct invasion of the liver may result from locally advanced cancers of the stomach, pancreas and hepatic flexure of the colon. More commonly, hepatic metastases are the result of vascular spread from the primary tumour via either the portal vein or hepatic artery. The liver is by far the commonest site of metastatic disease from gastrointestinal, bronchial and breast cancers. In part this is due to its dual blood supply. Although many of the secondary deposits appear necrotic on cut section, there is sufficient blood supply to allow multiple deposits to expand, and livers weighing in excess of 10kg at autopsy have been recorded. Although the histological picture normally reflects the primary tumour, there is a general tendency towards dedifferentiation. Hepatic metastases are often asymptomatic, but patients with widespread involvement or large superficial deposits may suffer abdominal and back pain secondary to stretching of the Glissonian capsule or haemorrhage and necrosis within the tumour. Although many patients appear physically well when liver metastases are first detected, as the disease progresses, malnutrition, jaundice, ascites and cachexia are inevitable. By the time liver metastases become symptomatic, there is usually massive involvement of the liver. Thus the objective of modern management is the detection of early asymptomatic disease in patients at risk of secondary hepatic deposits, especially with colorectal cancer, when the results of surgery or *in situ* ablation are better and can even be curative.

Colorectal cancer is the commonest gastrointestinal malignancy and the second commonest cause of cancer death in the Western world. is usually the first site of metastatic disease and may be the only site in 30–40% of patients with advanced cancer. At the time of initial diagnosis of colorectal cancer, 20–25% of patients will have clinically detectable liver metastasis. A further 40–50% will develop liver metastases, most commonly within the first 3 years of follow-up after resection of the primary tumour. The median survival of untreated colorectal liver metastasis (CRLM) is around 6–8

months, varying with the extent of disease at presentation. Although overall survival of patients with CRLM has improved with modern chemotherapy agents and median survival of 18–20 months can be achieved with the most aggressive protocols . A recent systematic review has shown that 30–40% of patients will achieve 5 year survival after liver resection and, although relapse may still occur between 5 and 10 years, 20% will still be alive at that point. Further relapse is unlikely after 10 years. Some tertiary referral centres have achieved 5 year survival in excess of 50% after liver resection in subgroups of patients with more favourable prognostic factors



Liver metastases (gross pathology)

Criteria for resection

In the past, the decision to resect CRLMs was relatively straightforward. Liver resection was considered appropriate only in patients who had one to three unilobar metastases, preferably presenting at least 12 months after resection of the primary tumour, whose disease was resectable with at least a 1cm margin of healthy liver tissue and who had no hilar lymphadenopathy or extrahepatic disease. More recently, with advances in surgical technique, preoperative and postoperative care and chemotherapy, indications for liver resection have expanded and even patients traditionally expected to have poor prognosis have been reported to have long-term survival following liver resection. .

CRLMs are nowadays considered resectable if (1) the disease can be completely resected, (2) two adjacent liver segments can be spared with adequate vascular inflow and outflow and biliary drainage and (3) the future liver remnant (FLR), calculated on preoperative CT scan with volumetry software, is adequate. The presence of bilateral metastases has also traditionally been considered as a contraindication to surgical treatment.

More recently, however, resections in two or more stages have been successfully performed for bilobar disease with good short- and long-term results. . Radiofrequency ablation or other techniques of *in situ* liver ablation have also been used in combination with resection surgery with the aim of increasing resectability and temporarily controlling disease progression. In this

clinical setting, PVE and two-staged resection can often be used together with PVE employed to induce hypertrophy of the future remnant following clearance of metastatic disease When assessing resectability, it is important to observe that a positive liver resection margin remains a predictor of poor prognosis.