Hepatobiliary tumours

Stephen D Ryder

Abstract

Hepatocellular carcinoma (HCC) and cholangiocarcinoma are the two major types of primary liver tumour. Both are increasing in incidence in the UK, in the case of HCC because of the increasing prevalence of chronic liver disease, particularly caused by alcohol and non-alcoholic fatty liver disease. They have a poor overall prognosis because of late presentation and the presence of underlying liver cirrhosis in patients with HCC. Patients usually present with a liver mass or jaundice. Assessment is primarily radiological by means of computed tomography and/or magnetic resonance imaging. Surgery remains the major curative option for both tumour types; liver transplantation and, rarely, resection are performed for HCC, and surgical resection for cholangiocarcinoma. However, only approximately 20% of these cancers present at a stage when surgery is possible. For non-surgical candidates with HCC, there are three potential treatment options: ablation, trans-arterial chemo-embolization and sorafenib or lenvatinib. Chemotherapy for cholangiocarcinoma is limited to gemcitabine-based systemic chemotherapy. Screening for HCC is a strategy that could potentially enhance early diagnosis.

Keywords BCLC staging; cholangiocarcinoma; gallbladder carcinoma; gemcitabine; hepatocellular carcinoma; MRCP; sorafenib

Key points

- Primary liver cancer (particularly hepatocellular carcinoma) is rising in incidence, reflecting the increase in liver disease in the population
- Surgery remains the only curative therapy, with liver transplantation an option for selected patients with hepatocellular carcinoma
- Most patient present with advanced disease for which only palliative treatment is possible
- Screening for hepatocellular cancer in people with established cirrhosis with 6-monthly ultrasound scanning can provide earlier diagnosis

Background

Two common malignant tumour types affect the liver and biliary tree: those derived from hepatocytes — hepatocellular carcinoma (HCC); and those derived from biliary epithelial cells — cholangiocarcinoma (CC) and carcinoma of the gallbladder. They are very different in their risk factors, presentation and treatment. Several benign liver lesions can cause diagnostic challenges but rarely cause clinical problems.

Epidemiology

The incidence of HCC follows that of the chronic liver disease it complicates. Most tumours (70–90%) occur in patients with cirrhosis, with some variation based on aetiology. There are around 3000 new cases per year in the UK (Figure 1). In the past, most cases of HCC were from a background of alcohol-related or viral cirrhosis, but this is changing with the increasing incidence in obese populations of non-alcoholic fatty liver, associated with an equally high risk of HCC.

Cholangiocarcinoma by contrast has no proven aetiological cause apart from in a minority of patients with underlying primary sclerosing cholangitis or choledochal cysts, or because of infection by liver flukes, *Clonorchis sinensis* or *Opisthorchis viverrini*; these are commonly seen only in South-East Asia. Cholangiocarcinoma is also increasing in incidence in Western populations (Figure 1),[1] but the reason for this is unknown. Gallbladder cancer is related to gallstones and calcification of the gallbladder (porcelain gallbladder).

Presentation

HCC presents as a liver mass or with decompensation of the underlying cirrhosis. Patients with cirrhosis are often entered into surveillance programmes, the most common of which involves 6-monthly ultrasonography scan. There is evidence that this can detect smaller tumours but the benefit of surveillance regimens on overall survival remains controversial. The first episode of decompensation of a patient with known cirrhosis should raise the possibility of underlying cancer, and imaging with ultrasound is indicated.

Cholangiocarcinoma presents with either jaundice (tumours affecting the central biliary tree) or a liver mass (peripheral tumours) that is often associated with systemic symptoms such as weight loss or upper abdominal pain. Gallbladder cancer also presents with upper abdominal pain and/or weight loss. Some cases are detected incidentally at or after routine cholecystectomy for presumed asymptomatic gallstones.

Gallbladder polyps may be detected incidentally on ultrasound or other imaging undertaken for non-liver indications. Gallbladder polyps <1 cm in diameter are almost always cholesterol crystals in the gallbladder wall and have no risk of malignancy. Polyps >1 cm carry a risk of neoplasia, and further imaging and cholecystectomy are usually recommended.

Diagnosis

Patients presenting with a liver mass should undergo serological testing and imaging. The tests depend on the clinical context. In a patient with cirrhosis who has a nodule detected on screening, serum α-fetoprotein (AFP) estimation and more detailed radiological assessment should be made using computed tomography (CT) or magnetic resonance imaging (MRI).[2] There are

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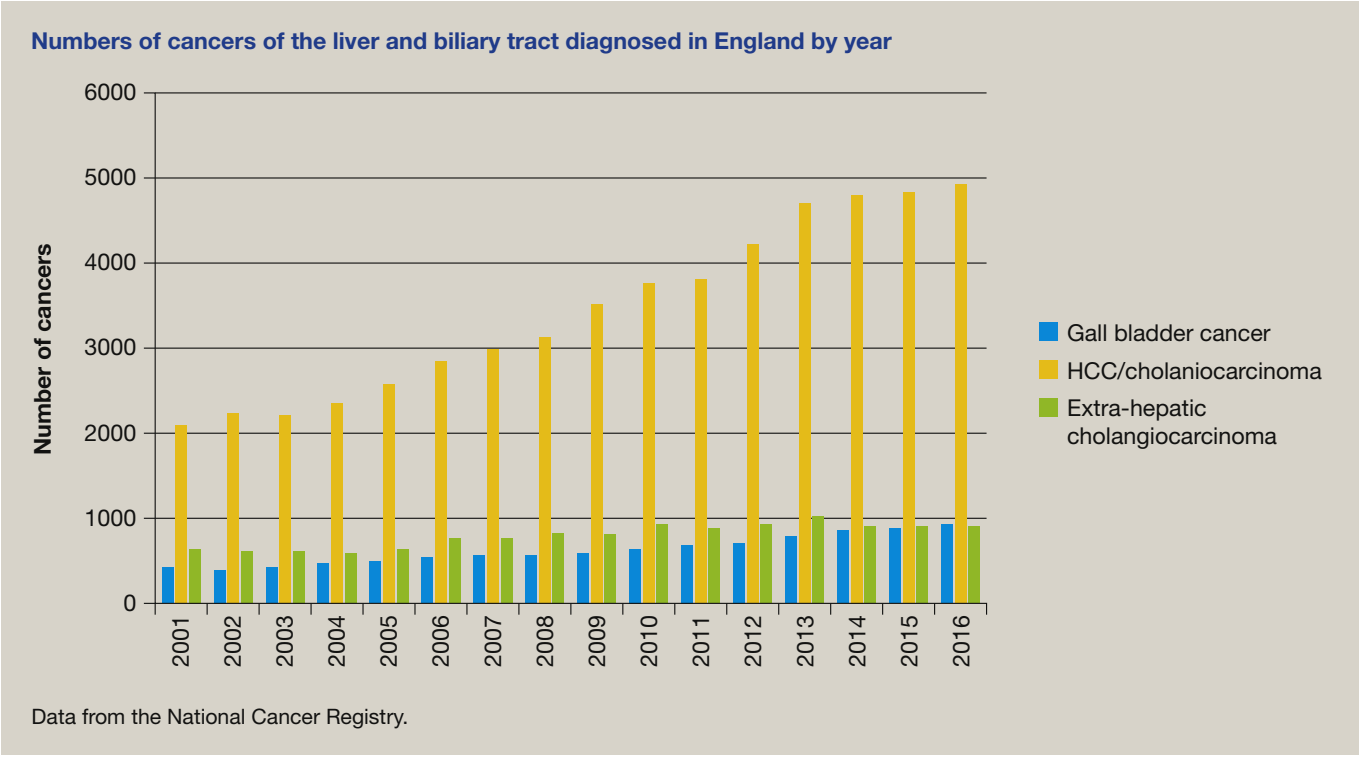


Figure 1

established radiological criteria for the diagnosis of a liver mass in this context, which involve arterial phase hypervascularity on triple-phase CT with washout of contrast in the portal venous phase. An AFP concentration >400 ng/ml in the context of a liver lesion in cirrhosis is diagnostic of HCC. Current guidelines do not require biopsy for diagnosis if the AFP or imaging is diagnostic, but a tissue diagnosis may be required before palliative treatments are undertaken. The differential diagnosis of a new liver mass in cirrhosis is limited to regenerative cirrhotic nodules, which can usually be distinguished by radiological assessment.

Cholangiocarcinoma presenting with jaundice should be assessed by the patient's performance status and then by imaging. Ideally, CT and MRI should be carried out before radiological or endoscopic biliary intervention, as staging is more accurate before such intervention. The key factors in radiological assessment are the presence of metastatic disease, vascular and biliary involvement. Radiological appearances are not diagnostic of cholangiocarcinoma.

If the patient is not jaundiced, measurement of serum cancer antigen (CA) 19-9 is helpful in the diagnosis but is often falsely (and sometimes grossly) elevated in obstructive jaundice from non-malignant causes. Cytology can be obtained from a biliary stricture on endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC), and a tissue diagnosis can be established in most patients preoperatively or just before palliative stenting. Immunoglobulin (Ig) G4-related disease can mimic the radiological signs of cholangiocarcinoma and should always be excluded by measuring the serum IgG4 concentration and/or by biopsy.

The differential diagnosis of a liver mass in a patient not known to have underlying liver disease can be more challenging. Liver metastases are frequently established by the presence of a primary mass on the initial CT scan, which should always include imaging of the chest and pelvis for this reason. Tumour markers can be helpful in giving a guide to the nature of the liver mass: AFP and CA19-9 are raised in HCC and cholangiocarcinoma, respectively, and serum carcinoembryonic antigen is often raised in metastatic colorectal cancer.

Peripheral cholangiocarcinoma presenting as a liver mass can be difficult to diagnose. CA19-9 is often elevated and can be useful, but all cases of hepatobiliary tumours or suspected tumours should be presented at a dedicated hepatobiliary multidisciplinary team (MDT) meeting, and decisions such as biopsy for diagnosis should be made by a specialist team.

A range of benign liver tumours can also present as an incidental liver mass in a patient who is usually symptom-free. These lesions have characteristic radiological appearances, and a firm diagnosis can usually be made without recourse to biopsy. In situations where doubt exist, such cases should be discussed at an hepatobiliary MDT meeting.

Hepatocellular carcinoma

Assessment

Two key factors determine the outcome for patients with HCC — the size and number of tumours within the liver and the severity of the underlying liver disease. Both should be assessed in order to plan treatment. The extent of the tumour is determined by radiological evaluation. The severity of liver disease should be established using the Child–Pugh score. The accepted overall assessment of HCC now follows the Barcelona Clinic Liver Cancer (BCLC) guidelines (Figure 2).

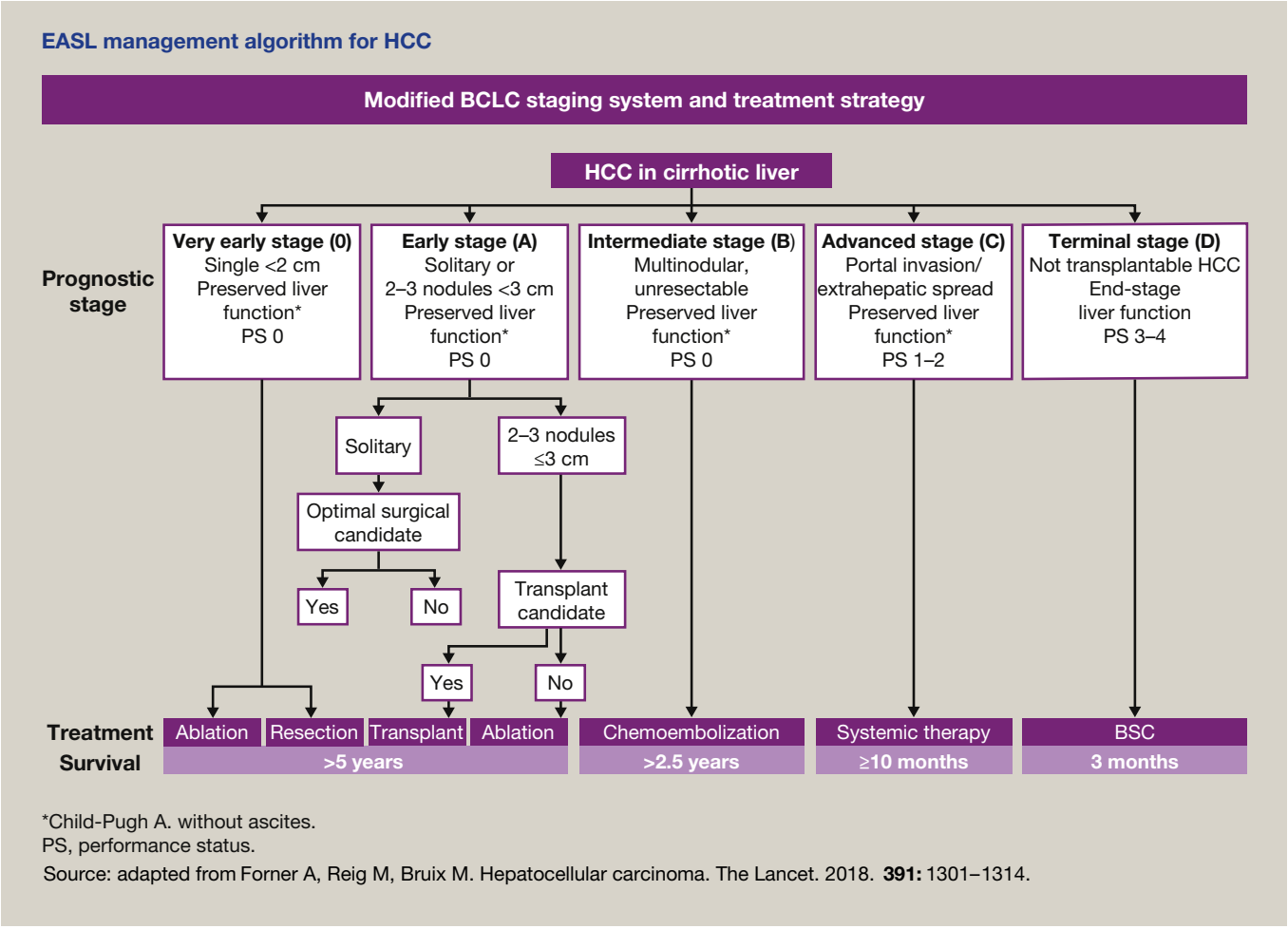


Figure 2

Treatment

There are two proven potentially curative treatments for HCC — liver transplantation and liver resection. The outcomes of treatment depend on the tumour stage and the severity of liver disease. The BCLC stage of the tumour dictates the best treatment (Figure 2).[2]

The Milan criteria[3] have stood the test of time; transplantation is recommended in patients who have a maximum of three tumour nodules, with the largest <5 cm in diameter, and no evidence of metastases. In this group, transplantation is usually curative and the prognosis does not differ significantly from that of transplantation for the underlying liver disease. In the UK, a raised AFP of >1000 ng/ml carries an increased risk of tumour recurrence after transplant and currently excludes patients from consideration.

Liver resection is the treatment of choice for HCC arising in a non-cirrhotic liver. In cirrhosis, the presence of portal hypertension is a contraindication to resection, and the morbidity and mortality for resection in cirrhosis in the absence of portal hypertension are higher than for resection of colorectal liver metastases. Such surgery should occur only in specialist units.

In ablative treatment (radiofrequency, microwave), a probe is placed into the liver tumour and generated heat is used to destroy the tissue. It is an effective treatment option and can be considered as an alternative to resection and (occasionally) liver transplantation for patients with one or two tumour nodules <2 cm in diameter. It requires a general anaesthetic but has a low complication rate.

The optimal treatment has to be determined on an individual basis by the hepatobiliary MDT;[1] each patient's situation differs — for example, a peripheral HCC in cirrhosis may be removed laparoscopically at low risk even in the presence of portal hypertension. Patients can have more than a single modality of treatment; for example ablation followed by local tumour recurrence can be an indication for resection or transplantation. The major risk with resection and ablation is the development of a second tumour in the cirrhotic liver, which occurs in up to 50% of patients within 5 years of initial treatment; continuing surveillance is therefore essential.

Palliative treatments for HCC include hepatic trans-arterial chemo-embolization (TACE) and sorafenib (a multikinase inhibitor). TACE is a radiologically delivered form of targeted chemotherapy usually doxorubicin (Adriamycin®). This is delivered by selective cannulation of the feeding branch of the hepatic artery, followed by direct injection of doxorubicin mixed with Lipiodol® (an oily radiological contrast dye) or by beads impregnated with doxorubicin. The Lipiodol® or beads provide effective devascularization of the tumour in addition to the

chemotherapeutic effect. This is generally a safe procedure in patients with preserved liver function.

Response rates are determined by tumour size and number, but there is evidence of significant survival benefit in patients with small tumours and those with a radiological response. Assessing response radiologically is not straightforward as this relies on both tumour size and vascularity (RECIST criteria). Portal vein thrombosis and extrahepatic disease are the major tumour-related contraindications to TACE, and Child–Pugh stage B or C patients are unlikely to be able to tolerate treatment with TACE without incurring a significant risk of further decompensation of their cirrhosis.

In patients with segmental portal occlusion, targeted (selective internal) radiotherapy can be performed. This is a highly interventional radiologically delivered therapy with radioactive spheres, injected into intrahepatic arteries after occlusion of any hepatic vascular shunts. This technique can produce radiological responses and overall survival similar to TACE.

Sorafenib, an oral multikinase inhibitor, has been shown to improve overall survival in advanced HCC by around 12 weeks. Lenvatinib acts as a multiple kinase inhibitor. It inhibits the three main vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3, as well as fibroblast growth factor receptors (FGFR) 1, 2, 3 and 4, platelet-derived growth factor receptor (PDGFR)-α, c-Kit and the *RET* proto-oncogene.

Lenvatinib has recently been shown to be non-inferior in terms of survival compared with sorafenib,[4] and unlike sorafenib produces a radiological response, with tumour shrinkage in 20–40%. Its adverse effect profile is different. The most common any-grade adverse events in the non-inferiority trial were hypertension (201 (42%)), diarrhoea (184 (39%)), decreased appetite (162 (34%)), and decreased weight (147 (31%)) for lenvatinib, and palmar–plantar erythrodysaesthesia (249 (52%)), diarrhoea (220 (46%)), hypertension (144 (30%)) and decreased appetite (127 (27%)) for sorafenib. It is now approved by the National Institute for Health and Care Excellence as an alternative to sorafenib.

Survival

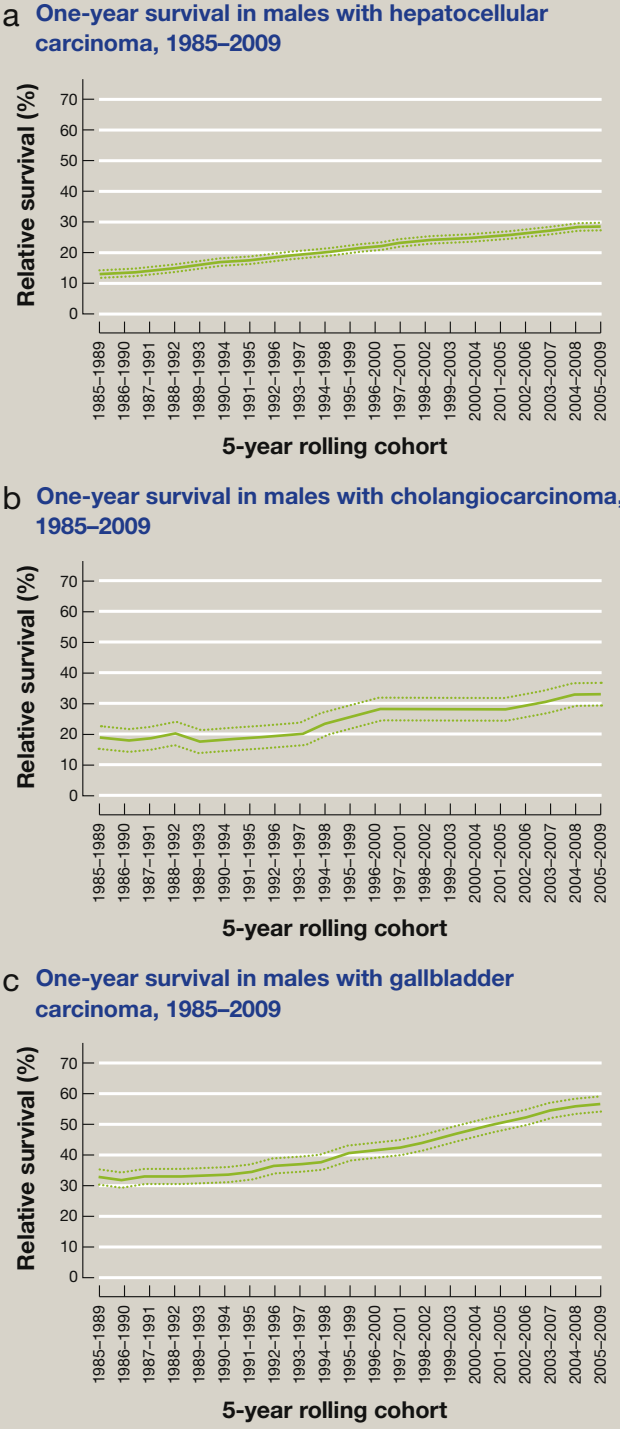
Overall survival for HCC remains poor (Figure 3), reflecting the late presentation of this cancer and the frequent presence of cirrhosis. In the UK, there are 3000 cases per year, with a 5-year mortality of 75%. Patients who have undergone potentially curative treatment have a much better survival; after transplant within the Milan criteria, the 5-year survival is >80%. The risk of second tumour development means a lower (40%) 5-year survival after surgery or ablation.

Cholangiocarcinoma

Assessment and treatment

For cancers of the biliary tract, surgery remains the only curative therapy.[5] Surgical classification of cholangiocarcinoma (Bismuth classification) remains valid; only a small proportion of tumours are operable at diagnosis and survival rates, although improving, remain low (Figure 3)

- Bismuth I – tumour of the common hepatic duct, not reaching the junction.



Survival from liver and biliary tract cancers in England. Source: Upper Gastrointestinal Site Specific Cancer Clinical Reference Group. One year survival rates for patients diagnosed with cancer of the oesophagus, stomach, primary liver, gallbladder, biliary tree and pancreas in England 1985–2009. http://www.ncin.org.uk/publications/.

Figure 3

- Bismuth II – tumour of the common hepatic duct, reaching the junction.
- Bismuth III – tumour of the common hepatic duct and left or right hepatic duct.
- Bismuth IV – tumour of the common hepatic duct and left and right hepatic duct.

This classification guides the feasible surgical options; Bismuth III or IV tumours are resectable only if liver resection is carried out in addition to biliary tract removal. The presence of vascular involvement is the other major barrier to curative resection; the presence of a mass at the hilum on CT is usually a negative factor.

There is no current role for adjuvant chemotherapy in cholangiocarcinoma. Palliative chemotherapy can be given with gemcitabine-based regimens, with a tumour response rate of around 40%. However, many patients present with advanced disease and poor performance status, so that this approach is not possible.

Palliation of jaundice in patients with inoperable cholangiocarcinoma affecting the major bile ducts can be challenging. In general, for inoperable tumours affecting the hepatic hilum, the best palliative approach is usually percutaneous cholangiography with insertion of metal stents. Drainage of the left and right lobe probably has the best long-term stent patency rate, although draining one lobe of the liver is often adequate to palliate the jaundice. Some form of drainage is essential if chemotherapy is to be offered, as a serum bilirubin of >90 micromol/litre is a contraindication to treatment. If the segmental ducts are involved within the liver, successful palliation is unlikely.

PTC is a relatively high-risk procedure: every patient has pain after the procedure, and a serious complication rate of around 10% is expected from bleeding or biliary leaks. The mortality after PTC is around 30% at 30 days, usually from the underlying cancer rather than as a result of the procedure. However, although it has no effect on overall survival, it is successful in the relief of troublesome symptoms such as pruritus, and usually improves quality of life in this palliative phase.

For tumours of the common bile duct and common hepatic duct below the bifurcation, ERCP is the preferred approach, both to obtain a tissue (cytological) diagnosis and to place palliative stents, as it is safer than PTC. Removable metal stents have better long-term patency rates than plastic stents and should be preferred if the patient's performance status is good.

Gallbladder cancer

Assessment and treatment

The diagnosis of gallbladder cancer can be challenging. An acute presentation with biliary pain and imaging showing gallbladder wall thickening can be caused by cholecystitis, and there are no imaging characteristics that are diagnostic in the absence of metastatic disease. Biopsy is often required in this setting.

If imaging suggests a locally operable gallbladder cancer, this should be treated with open cholecystectomy; some surgeons recommend local lymphadenectomy or associated liver resection, but an MDT should make such decisions.

Incidental gallbladder cancer found after cholecystectomy is not uncommon and accounts for most of the long-term survivors (Figure 3). If the resection margin is clear, it is usual to recommend no further action. If the margin is involved, laparotomy with resection of the gallbladder bed is usually offered.

Chemotherapy has low response rates in gallbladder cancer and overall survival remains poor. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 53 year old man presented with fatigue and upper abdominal discomfort. He had previously been found to have chronic hepatitis C. He had continued to work as a bricklayer.

Investigations

- Bilirubin 9 μmol/litre (1–22)
- Albumin 43 g/L (37–49)
- INR 1.0. (<1.4)
- CT and MR scans showed a liver with irregular outline, intraabdominal varices and splenomegaly and a 2x2cm mass with arterial enhancement and washout in the portal venous phase in the right lobe of the liver.
- Alpha-fetoprotein1200 kU/litre (<10)

What is the next most appropriate step?

A. percutaneous biopsy of the lesion
B. contrast ultrasound scan
C. assess for therapy for hepatocellular carcinoma
D. refer for palliative care
E. transjugular biopsy of the lesion

Question 2

A 45 year old man presented with a 2 x 2 cm hepatocellular carcinoma on the basis of characteristic imaging and a markedly raised alpha fetoprotein (1200kU). He had previously been found to have chronic hepatitis C infection and there was evidence of compensated cirrhosis (Child Pugh class A) with significant portal hypertension. He had a good performance status.

What is the most appropriate therapy?

A. Liver transplantation
B. Liver resection
C. Radiofrequency ablation (RFA)
D. Hepatic arterial chemo-embolization (TACE)
E. Levantinib

Question 3

An 80 year old woman presented with a short history of painless jaundice. Clinical examination was normal apart from the jaundice.

Investigations

- Bilirubin 150 μmol/L (1—22)
- US and CT scan showed bilateral intrahepatic duct dilatation with a normal common bile duct and no radiological mass lesion.

What is the next best step?

A. Endoscopic retrograde cholangiopancreatography (ERCP)
B. Percutaneous transhepatic cholangiogram (PTC)
C. Magnetic resonance (MRCP) and MR scan liver
D. Cancer antigen (CA) 19.9 estimation
E. Exploratory laparotomy