

Improving the detection and treatment of liver cancer

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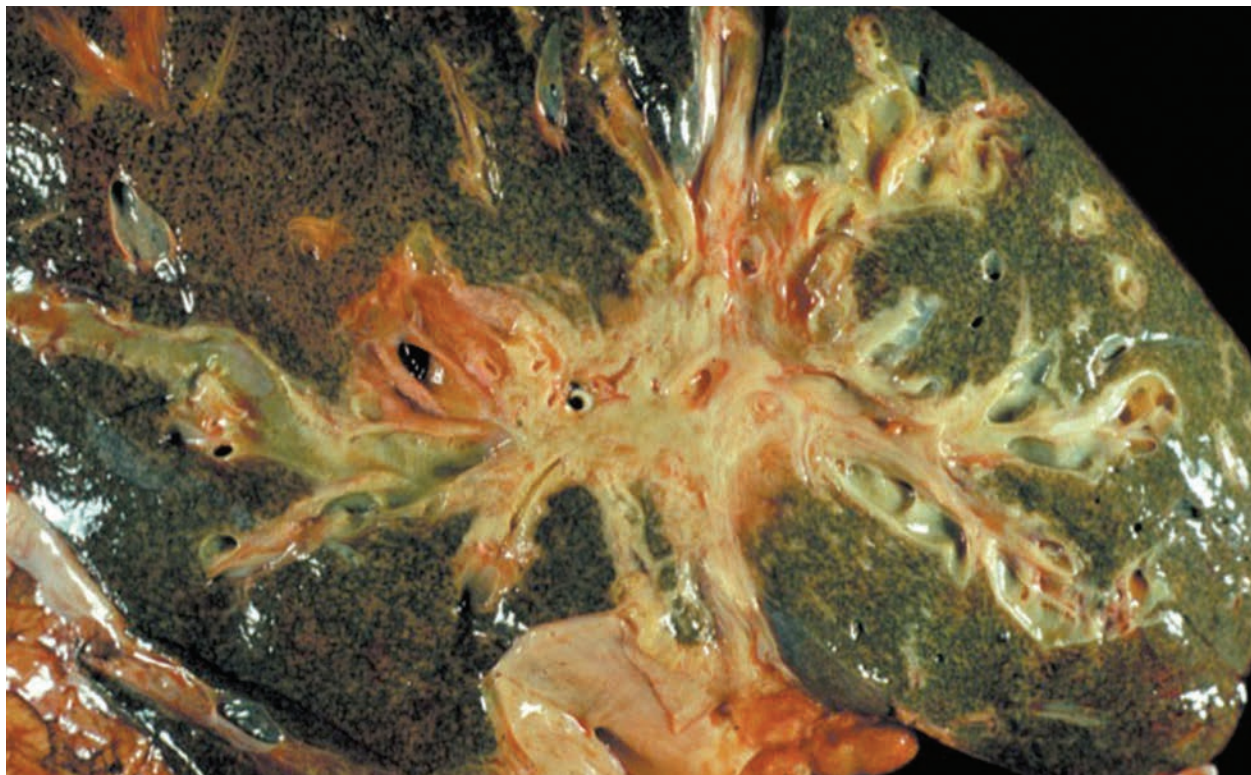


FIGURE 1
Post-mortem
liver section
showing a hilar
cholangiocarcinoma
with a plastic stent
in situ, and upstream
duct dilatation

What are the risk factors for liver cancer?

How should diagnosis be made?

What are the treatment options?



LIVER CANCER IS THE SIXTH MOST COMMON CANCER WORLDWIDE WITH AN ESTIMATED

750,000 new cases every year.¹

The majority (75-90%) of all primary liver tumours are hepatocellular carcinomas (HCC), arising from the liver parenchyma. Other primary liver cancers include cholangiocarcinomas (CC), which make up 10-25% of liver cancers, see figure 1, above. These tumours arise from cells lining the biliary tree. Angiosarcomas and hepatoblastomas are very rare primary liver tumours.²

CCs may arise from the intra- or extrahepatic bile ducts. Management of intra- and extrahepatic lesions varies considerably. This article will

focus on the management of HCC and intrahepatic CC.

The incidence of liver cancer varies significantly worldwide. Chronic viral hepatitis and in particular hepatitis B virus (HBV) remains the most important risk factor for the development of HCC.³ Areas with high prevalence such as SE Asia, China and sub-Saharan Africa see the highest rates of HCC.

The prevalence of CC also varies globally. The highest rates are seen in Thailand where liver fluke infestation is endemic. In the UK the incidence of CC is 1-2 cases per 100,000 population, but rates are increasing⁴ and in the mid-1990s CC overtook HCC as the most common cause of liver cancer-related death.⁵

Over the past decade survival in

liver cancer has been steadily improving as a result of developments in surgery, transplantation and the introduction of a number of novel local, ablative and molecular targeted therapies, as outlined below.

PRESENTATION

Symptoms that have been associated with HCC include fatigue, weight loss, abdominal pain, pruritus and jaundice, which may also be caused by the underlying liver disease. However, HCCs are often relatively asymptomatic until late in the disease. Unlike CC where 70% of tumours occur sporadically, in HCC 90% of cases are associated with one or more risk factors, see table 1, p22. Hence most high-risk individuals are followed up >>

Table 1

Risk factors for hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC)

Hepatocellular carcinoma	Cholangiocarcinoma
Age > 60 ³	Age > 60 ⁶
Male sex ³	Male sex ⁶
Chronic viral hepatitis (B and C). Worldwide approximately 54% of cases of HCC are attributable to hepatitis B and 31% to hepatitis C. ³	Primary sclerosing cholangitis (PSC) - (5-35% lifetime risk of CC) ⁸
Co-infection with HIV further increases the risk of HCC ⁷	
Cirrhosis (chronic viral hepatitis, haemochromatosis, ⁹ alpha-1-antitrypsin deficiency ¹⁰ and non-alcoholic fatty liver disease). ³ One third of cirrhotic patients will develop an HCC during their lifetime ¹¹	Chronic inflammation secondary to hepatolithiasis, choledocholithiasis and cholangitis ¹²
Excessive alcohol consumption ^{3,13}	Bile duct adenoma and biliary papillomatosis ¹²
Smoking ^{13,14}	Rare congenital cystic diseases such as choledochal cysts and Caroli's disease ¹²
Haemochromatosis - 45% of patients develop an HCC, the majority are already cirrhotic ⁹	Parasitic infections (liver fluke e.g. <i>Clonorchis sinensis</i> and <i>Opisthorchis viverrini</i>) and chronic typhoid carriage, common in SE Asia ¹²
Aflatoxin B ¹⁵	Cirrhosis ¹²
Diabetes, obesity and fatty liver ^{13,16}	Chronic hepatitis (B and C) ¹²
Anabolic steroids ¹⁷	Inflammatory bowel disease without PSC ¹²
Primary biliary cirrhosis (PBC) - risk is greater in men than women ¹⁸	Toxins such as thorotrast, digoxins, nitrosamines and vinyl chloride ¹⁹
BRCA1/BRCA2/EGF gene ^{20,21}	Obesity, diabetes, fatty liver disease, alcohol and smoking ¹²

as part of a surveillance programme and are diagnosed via this pathway.^{12,22}

Currently the European Association for the Study of the Liver (EASL) recommends HCC surveillance in the following groups:

- Cirrhotic patients, Child-Pugh stage A and B (see table 2, p23)
- Cirrhotic patients, Child-Pugh stage C (see table 2, p23) awaiting liver transplantation
- Non-cirrhotic HBV carriers with active hepatitis or a family history of HCC
- Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis

The British Society of Gastroenterology (BSG) and EASL recommend that surveillance should be performed by abdominal ultrasound every 6 months.^{23,22}

In addition, the BSG guidelines, published 10 years ago, recommend that surveillance ultrasound should be combined with measuring serum alpha fetoprotein (AFP).²⁴

Classical symptoms of CC include jaundice, dark urine, clay-coloured stools and pruritus and occur as a result of progressive bile duct obstruction by the tumour.^{25,26}

Screening and vaccination of individuals at high risk of HBV is

recommended by the WHO and EASL. It is also recommended that children born to mothers who are HBsAg positive should be vaccinated against HBV at birth to prevent transmission.^{27,28}

DIAGNOSIS

Blood tests

AFP is the most widely used and tested biomarker for the diagnosis of HCC. As a diagnostic tool AFP is only useful when it is found to be markedly elevated; an AFP > 400 ng/ml is considered to be diagnostic (normal range 10-20 ng/ml). In surveillance for

FIGURE 2
CT and MRI in a patient with a large hepatocellular carcinoma in the left lobe of the liver

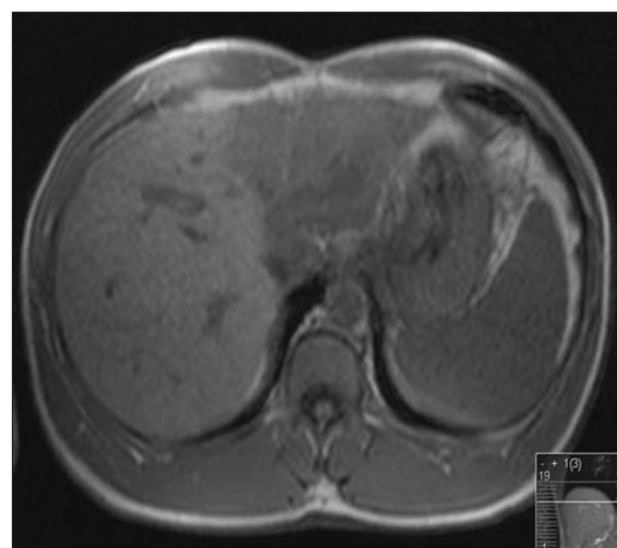
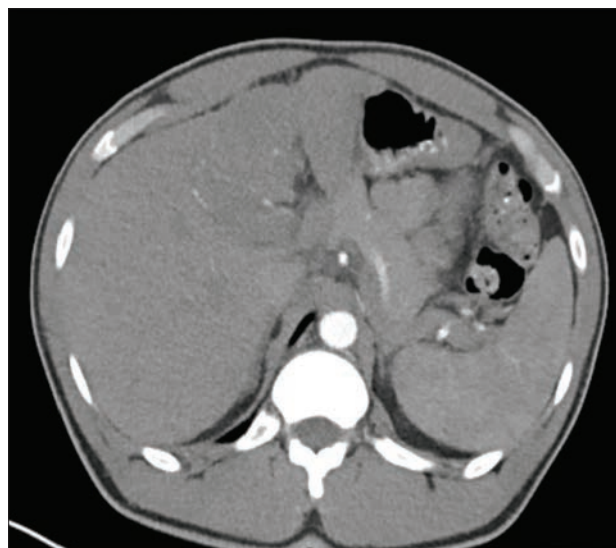


Table 2

Child-Pugh classification and its interpretation

Child-Pugh classification			
Measure	1 point	2 points	3 points
Total bilirubin (μmol/L)	< 34	34-50	> 50
Serum albumin (g/L)	> 35	28-35	< 28
PT/INR	< 1.7	1.7-2.3	> 2.3
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grade I-II	Grade III-IV
Interpretation of the Child-Pugh classification			
Points	Class	Three-year survival ³⁶	
5-6	A	73%	
7-9	B	59%	
10-15	C	46%	

HCC in high-risk groups the current BSG guidelines recommend undertaking an AFP six monthly in combination with an abdominal ultrasound.²⁴ However, only 10-20% of small tumours will have an abnormal AFP level and its overall role in surveillance is debated.^{24,29}

In suspected CC, CA 19-9 is used frequently in combination with imaging or other diagnostic tools. However, its overall sensitivity and specificity for diagnosis and surveillance are too low to be recommended in clinical practice.³⁰

Routine liver function tests are usually abnormal in both cancers.³⁰

Ultrasound

Abdominal ultrasound is the most widely available imaging technique for the liver. Sensitivity is 58-89% for detecting HCC and CC in high-risk groups. However, the test is operator dependent, may miss small tumours and cannot define distal spread.

Cross-sectional imaging

Contrast-enhanced CT or MRI is considered the optimal imaging technique for suspected HCCs. These tumours demonstrate unique radiological criteria taking up contrast during the arterial phase and producing washout during the venous phase.³¹ The American Association for the Study of Liver Disease (AASLD) has recommended that these findings are diagnostic of HCC and in nodules > 2 cm histological confirmation is not required.³²

For CC contrast-enhanced MRI/MRCP (magnetic resonance cholangiopancreatography) is recommended to delineate biliary anatomy, tumour extent and parenchymal disease.

A staging CT (chest, abdomen and

pelvis) is undertaken in both tumours to assess for evidence of metastatic disease, see figure 2, p22.

Liver biopsy

Although the need for liver biopsy in HCC is debated because of the small risk of tumour seeding and post-procedure bleeding (<1:1,000), it remains a particularly useful investigation in lesions which do not meet diagnostic radiological criteria. EASL guidelines on the management of HCC recommend a targeted liver biopsy of nodules > 2 cm without diagnostic radiological criteria and of lesions 1-2 cm in which two different forms of imaging do not demonstrate typical radiology findings.²³

A liver biopsy allows differentiation between benign, premalignant nodules and early HCC so correct surveillance intervals can be defined and treatments instigated.³³

Cholangiography

MRCP has been shown to be superior to endoscopic retrograde cholangiopancreatography (ERCP) for differentiating between CC and benign biliary strictures.³⁴ However, ERCP allows for tissue acquisition, essential for patients undergoing chemotherapy and/or radiotherapy, and stent placement to relieve obstructive jaundice when present.

The development of new diagnostic adjuncts such as cholangioscopy have enabled targeted biopsies which improve the diagnostic accuracy.³⁵

TREATMENT

Treatment of primary liver tumours is dependent on a number of factors such as the stage of the tumour, the position of the tumour, involvement of major vessels and the general health of the patient including the presence

of cirrhosis which is defined using the Child-Pugh scoring system, see table 2, above.

To decide on the most appropriate treatment option for HCC, several staging criteria have been developed but the Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy is most frequently applied, see figure 3, p25. CC staging is based on the tumour node metastasis system.

Surgery

In patients with primary liver tumours and Child-Pugh A cirrhosis or a normal liver, resection is the first-line treatment. Perioperative mortality is 2-3% and five-year survival can be up to 80% in well selected patients.³⁷ Neoadjuvant therapies have not been shown to improve prognosis. Currently only 5% of patients diagnosed with HCC in the UK are suitable for surgical resection. If tumours recur following surgery they can be restaged and managed in accordance with the BCLC algorithm.³⁸

Transplantation

Historically liver transplantation for HCC has been associated with low survival rates (20-36%) which limited its use in liver cancer. However, following the introduction of the Milan criteria, see table 3, p24, which restricted the indication for transplantation to small HCCs, survival improved dramatically.³⁷

HCC is now one of the most common reasons for liver transplantation in many transplant centres worldwide. The upper limit of tumour size for transplantation is controversial and several expanded criteria such as UCSF, see table 3, p24, have been proposed, but without impact on overall survival.

Transplantation is not routinely recommended for CC but there is



emerging evidence that when combined with neoadjuvant therapy, it can be associated with up to a 70% five-year survival in highly selected patients.^{41,42}

Chemotherapy

Recent randomised trials of chemotherapy in HCC have shown response rates of less than 20%, with limited improvements in survival.^{43,44} Chemotherapy is therefore rarely used for HCC and not recommended in European guidelines for the management of HCC.²³ However, in locally advanced and metastatic CC the ABC-01 and ABC-02 randomised trials showed that 24 weeks of cisplatin plus gemcitabine improved overall survival from 8.1 to 11.7 months ($P < 0.001$).^{45,46} There is emerging evidence that neoadjuvant chemotherapy may also be able to downstage some unresectable CC patients to resectability.⁴⁷

Biologic therapies

Sorafenib is an oral multi-tyrosine kinase inhibitor which inhibits blood vessel development and tumour cell proliferation by inhibiting the Raf cascade, vascular endothelial growth factor and platelet-derived growth factor receptors in tumour cells. It has been shown to improve survival from 7.9 to 10.7 months ($P < 0.001$) in patients with advanced HCC.⁴⁸ However, because of its high cost, the

treatment is currently not approved by NICE.⁴⁹

Local and ablative treatments

Local and/or ablative therapies are considered to be first-line treatment in patients with early HCC who are not suitable for surgical resection or transplantation, see table 4, below. In intrahepatic CC they can be used similarly to HCC but because of the rarity of intrahepatic CC fewer large

Table 3

Criteria for transplantation in hepatocellular carcinoma

Milan criteria³⁹

- Single tumour < 5 cm or
- 2-3 tumours none exceeding 3 cm and
- No vascular invasion and/or extrahepatic spread

UCSF criteria⁴⁰

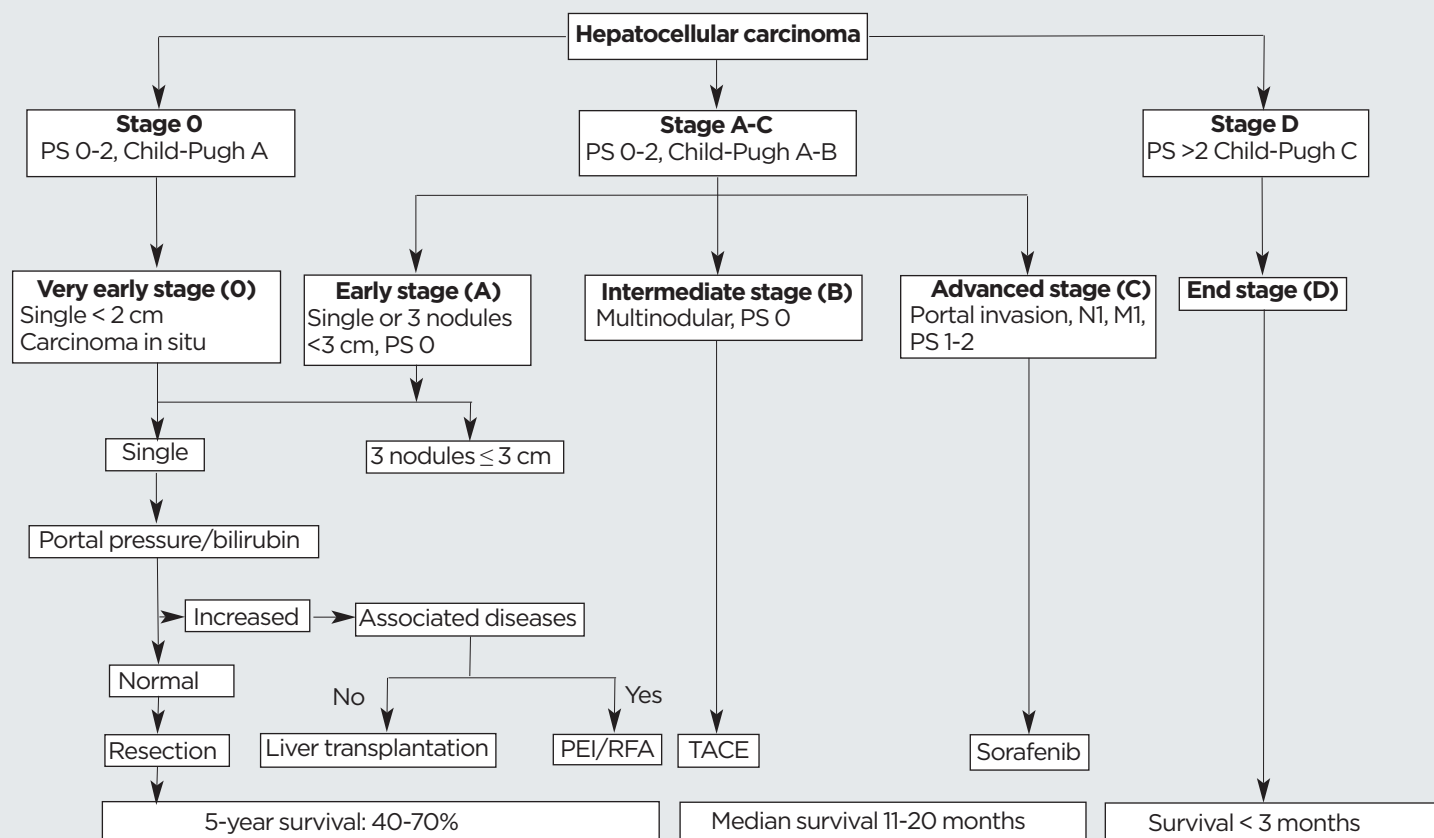
- Single tumour < 6.5 cm or
- 2-3 lesions, none exceeding 4.5 cm, with total tumour diameter < 8 cm
- No vascular invasion and/or extrahepatic spread

Table 4

Local and ablative therapies

Procedure

Percutaneous ethanol injection (PEI)	PEI was the first ablative technique described. Following an injection of ethanol into the tumour, dehydration and protein denaturation are induced leading to a coagulative necrosis. PEI can successfully ablate most small tumours, but recurrence rates are high (43%). ⁵⁰ Five-year survival following PEI is 47-53%. ^{51,52}
Radiofrequency ablation (RFA)	RFA uses high energy radiowaves to induce a coagulative necrosis. When compared with PEI, RFA is equally successful at ablating small HCCs but is associated with a much lower recurrence rate (2-18%). ^{53,54} This treatment has been approved by NICE. ⁵⁵ In hilar and distal CC, RFA has been used in combination with self-expanding metal stents (SEMS) to improve biliary drainage and prolong stent patency. ⁵⁶
Microwave ablation	This therapy, approved by NICE, uses microwaves to ablate small HCC tumours. ⁵⁷ When the treatment was compared with RFA it was found to be inferior. However, it may be preferable in tumours adjacent to large vessels. ⁵⁸
Cryoablation	The injection of liquid nitrogen into the tumour causes the destruction of tumour cells through freezing. Its use has been limited by the infrequent but serious complication of cryoshock which results in multiorgan failure following the procedure. ⁵⁹
Photodynamic therapy (PDT)	Light-activated laser therapies have been used successfully to ablate small HCCs. Phase III studies to evaluate this therapy are in progress. ⁶⁰
High-intensity focused ultrasound (HIFU)	HIFU is a novel ablative technique that has been used to treat small HCC in a few centres. ⁶¹ Larger studies are needed to evaluate this treatment
Transarterial embolisation (TAE)	The procedure involves the embolisation of the feeding artery of the tumour through the transcatheter delivery of lipiodol or gel beads
Transarterial chemoembolisation (TACE)	This treatment involves the transcatheter delivery of embolic and cytotoxic agents (e.g. doxorubicin) which causes local tumour ischaemia and targeted chemotherapy. It is the most commonly used treatment for unresectable HCC. Although a partial response is seen in up to half of patients and tumour progression halted in many, an overall improvement in survival has not been observed. ⁶² A recent Cochrane review of TACE and TAE stated there was currently insufficient evidence to recommend or refute either treatment. ⁶²
Radioembolisation/Selective internal radiation therapy (SIRT)	Cohort studies have reported the use of yttrium-90 containing beads, to embolise the feeding tumour artery and provide local radiation therapy. A tumour response was seen in 35-50% but a fifth developed liver toxicity. ⁶³⁻⁶⁵

Figure 3**Barcelona Clinic Liver Cancer staging and treatment algorithm³⁸****PS: World Health Organization Performance Status Classification**

Grade 0: able to carry out normal daily activities

Grade 1: able to carry out light work

Grade 2: able to self care but unable to work

Grade 3: symptomatic and in bed or chair more than half of the day

Grade 4: bedridden requiring complete care

TNM Classification

T: Primary tumour (T0-T4)

N: Regional lymph nodes (N0-N1)

M: Distant metastasis (M0-M1)

studies have been conducted to evaluate these treatments.

CONCLUSION

Most patients with HCC are diagnosed with advanced disease. Current guidelines recommend high-risk groups should be surveyed every six months by abdominal ultrasound with or without measurement of serum AFP.

Recent advances in surgery and extension of transplant criteria have meant more patients are now amenable to curative therapy. There have been significant advances in the development of targeted therapies, which individually or in combination, can prolong survival and have the potential to downstage patients so they are eligible for curative treatment.

Treatments are now available for all patients at any stage of liver cancer and should be tailored to account for the degree of liver dysfunction and other comorbidities.

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key points

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Liver cancer is the sixth most common cancer worldwide with an estimated 750,000 new cases every year.

The majority (75–90%) of all primary liver tumours are hepatocellular carcinomas (HCC), arising from the liver parenchyma. Other primary liver cancers include cholangiocarcinomas (CC), which make up 10–25% of liver cancers. These tumours arise from cells lining the biliary tree.

Chronic viral hepatitis, and in particular hepatitis B virus (HBV), remains the most important risk factor for the development of HCC. In the UK the incidence of CC is 1–2 cases per 100,000 population, but rates are increasing and in the mid-1990s CC overtook HCC as the most common cause of liver cancer-related death. Over the past decade survival in liver cancer has been steadily improving as a result of developments in surgery, transplantation and the introduction of a number of novel local, ablative and molecular targeted therapies.

Symptoms that have been associated with HCC include fatigue, weight loss, abdominal pain, pruritus and jaundice, which may also be caused by the underlying liver disease. However, HCCs are often relatively asymptomatic until late in the disease, and 90% of cases are associated with one or more risk factors. Patients with risk factors should undergo surveillance by abdominal ultrasound every six months. Classical symptoms of CC include jaundice, dark urine, clay-coloured stools and pruritus and occur as a result of progressive bile duct obstruction by the tumour.

Alpha fetoprotein (AFP) is the most widely used and tested biomarker for the diagnosis of HCC. As a diagnostic tool AFP is only useful when it is found to be markedly elevated. Sensitivity of abdominal ultrasound is 58–89% for detecting HCC and CC in high-risk groups. Contrast enhanced CT or MRI is considered the optimal imaging technique for suspected HCCs, where nodules are greater than 2 cm histological confirmation is not required. Liver biopsy remains a particularly useful investigation in lesions which do not meet diagnostic radiological criteria.

Treatment of primary liver tumours is dependent on a number of factors including the stage of the tumour, the position of the tumour, involvement of major vessels and the general health of the patient including the presence of cirrhosis. In patients with primary liver tumours and Child-Pugh A cirrhosis or a normal liver, resection is the first-line treatment. Liver transplantation for HCC is limited to small tumours and is not routinely recommended for CC. Chemotherapy is rarely used for HCC, but has been shown to improve survival in locally advanced and metastatic CC. Local and/or ablative therapies are considered to be first-line treatment in patients with early HCC who are not suitable for surgical resection or transplantation. In intrahepatic CC they can be used similarly to HCC.

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