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Early detection of liver cancer key to improving outcomes

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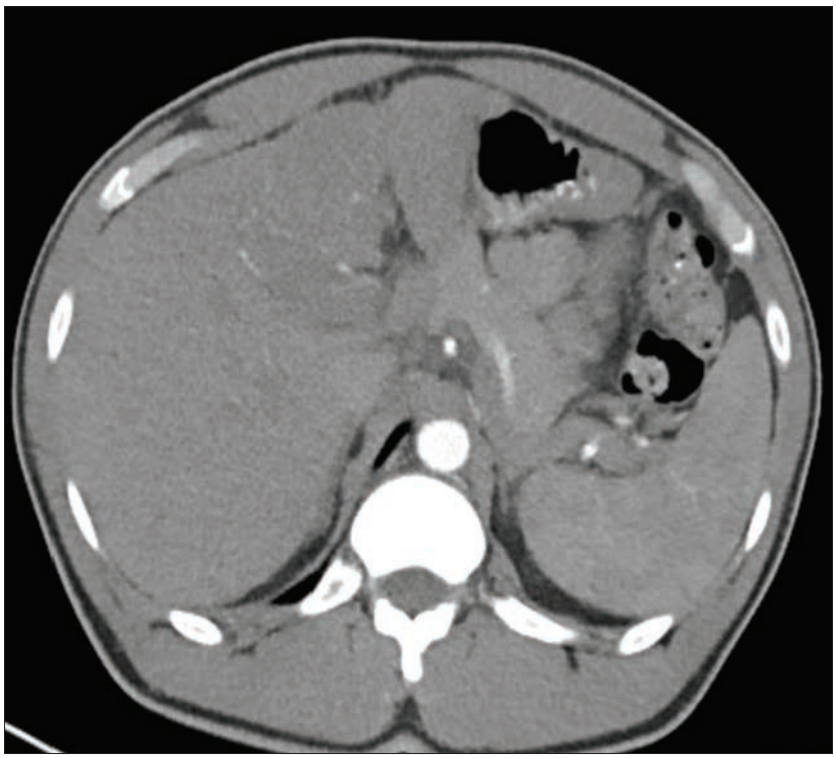

Hepatocellular carcinoma in the left lobe of the liver

How do patients present in primary care?

How should patients be assessed?

What are the treatment options?

LIVER CANCER IS THE SIXTH MOST PREVALENT CANCER[1] AND THE THIRD MOST COMMON CAUSE of cancer deaths worldwide with approximately 800,000 deaths globally per annum.[2] In the UK, it is the eighteenth most prevalent cancer, the eighth most common cause of cancer deaths in males and eleventh most common in females.

Hepatocellular carcinoma (HCC), which arises from the liver cells, accounts for approximately 90% of liver cancer cases. Other primary liver cancers include intrahepatic cholangiocarcinomas (CC), arising from the bile ducts within the liver, which account for 9-10% of cases alongside rarer angiosarcomas and hepatoblastomas. HCC remains a challenge as it is commonly diagnosed late in its course, often in patients with other comorbidities, and only has limited treatment options leading to a poor five-year survival.

In the UK, there are on average 5,900 new cases of HCC each year.[3] Worldwide, countries with higher rates of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV), which are significant risk factors for HCC, such as Sub-saharan Africa and East Asia, have a higher incidence of the disease with around 15 per 100,000 compared with 3 per 100,000 in western countries.

The average five-year survival for HCC is 13.1% in the UK,[4] however, for non-cirrhotic patients who are eligible for liver resection the five-year survival rate is 42%.[5] This compares with an overall five-year survival rate of 17.4% in the USA.[6] Survival rates in the UK have been improving with one-year survival rates in men increasing from 36.1% (2010-14) to 37.3% (2011-15), the largest improvement in survival rate in any type of cancer in males.[4]

RISK FACTORS

In 90% of cases HCC occurs in the context of chronic liver disease with cirrhosis, particularly in those with chronic HBV or HCV. Other major risk factors include excessive alcohol consumption, obesity and aflatoxins. In Africa and East Asia, approximately 54% of cases are attributable to HBV whereas in western countries, HBV accounts for 20% and HCV is a larger underlying cause. As the incidence of non-alcoholic fatty liver disease (NAFLD) rises in the UK this will lead to an increase in the number of HCC cases with NAFLD as the underlying cause.[7] In contrast to hepatitis related HCC, a large proportion of these cases occur in the absence of cirrhosis.[8]

Of those patients with a background of cirrhosis, in particular those with cirrhosis secondary to chronic viral hepatitis, 10-15% will go on to develop HCC within 20 years.

In the UK, NICE and the British Society of Gastroenterology (BSG) guidelines recommend surveillance with ultrasound scanning (USS) ± alpha fetoprotein (AFP) testing every six months for patients with established cirrhosis (apart from those receiving end of life care) to screen for early HCC.[9] While AFP can be helpful when significantly raised (> 400 ng/ml), levels below this may not be helpful in screening given the fact it is only raised in 10-20% of small tumours and smaller rises can be due to other causes. »

Table 1

The Child-Pugh classification

Measure	1 point	2 points	3 points
Total bilirubin µmol/L)	< 34	34-51	> 51
Serum albumin (g/L)	> 35	28-35	< 28
INR	< 1.7	1.7-2.3	> 2.3
Ascites	Absent (2)	Mild	Moderate-severe
Hepatic encephalopathy	None	Grade I-II	Grade III-IV

Child-Pugh score A = 5-6 Child-Pugh B = 7-9 Child-Pugh C = 10-15

Table 2

Eastern Cooperative Oncology Group (ECOG) performance status

Grade 0 Able to carry out normal daily activities
Grade 1 Able to carry out light work but restricted in strenuous activity
Grade 2 Able to self-care but unable to work, up and about > 50% of the day
Grade 3 Symptomatic, confined to bed or chair > 50% of the day
Grade 4 Confined to bed or chair, unable to manage any self-care

Screening at six-month intervals rather than annually, improves median survival in those diagnosed with HCC from 30 to 45 months.[10] Studies have shown that screening for HCC in patients with HCV related cirrhosis is cost effective when the annual risk of HCC is > 1.5%.[11]

In the UK, men develop HCC 2.1 to 5.7 times more frequently than women. Men living in deprived areas of England are most likely to be affected. The vast majority (90%) of cases present in those over the age of 50 with the highest incidence in the UK among those aged 85-89. Liver cancer is more prevalent among Asian and Black people than Caucasian people in the UK.[3]

PRESENTATION

In patients with underlying cirrhosis, presentation of liver cancer may occur with signs of liver decompensation. Early HCC is rarely symptomatic but as it advances, patients may present in primary care with upper or right-sided abdominal pain, jaundice, weight loss, early satiety or a palpable mass in the right upper quadrant.[12]

Patients may rarely also present with features of a paraneoplastic disease including erythrocytosis, hypoglycaemia, hypercalcaemia or diarrhoea.

Extrahepatic metastases are present at diagnosis in 10-15% of patients, with the most common sites being lung, intra-abdominal lymph nodes, bone and the adrenal glands.

In the UK, 39% of patients are diagnosed after emergency presentation, 28% after routine or urgent GP referral and 11% via two-week wait referrals.[13]

CC is frequently not diagnosed until the symptoms of biliary obstruction develop such as jaundice, pruritus and non-specific symptoms such as weight loss, nausea and fever.

DIAGNOSIS

When assessing a patient for whom liver cancer is a differential diagnosis, it is important to enquire about risk factors and exposure. The NICE guideline on referral for suspected cancer recommends an urgent direct access USS within two weeks for people presenting with an upper abdominal mass consistent with an enlarged liver.[14]

Diagnosis of liver cancer is largely based on laboratory tests and imaging, generally including USS, MRI and CT scanning which have roles in both detection and monitoring.

Blood tests

AFP is the most important serological marker. Levels > 400 ng/ml in a high-risk patient are considered diagnostic of HCC (specificity > 95%). AFP is positive in 60-80% of HCC cases. However, in small tumours, AFP is raised in only 10-20% of cases.

Liver function tests are likely to be abnormal in HCC and CC. There is ongoing research into other potential markers of HCC including plasma microRNA expression.[15] In CC, cancer antigen CA 19-9 may be raised.

Imaging

Diagnosis can be made through contrast-enhanced CT or MRI scan for lesions > 2 cm. If lesions do not fully meet diagnostic criteria or in non-cirrhotic patients, biopsy is recommended to confirm findings.[16]

USS has sensitivity varying from 25 to 79% and its limitations include operator dependence and the possibility of missing small tumours. Furthermore, it is unable to identify distal spread. Therefore, it is limited in its role for definite diagnosis. Any unusual lesion identified on USS should be followed up with more detailed imaging.

Cholangiocarcinoma

For diagnosis of CC, CA 19-9 is used alongside imaging and biopsy. Magnetic resonance cholangiopancreatography (MRCP) or contrast enhanced MRI can be used to identify the extent of the tumour and biliary anatomy further.

Endoscopic retrograde cholangiopancreatography (ERCP) is inferior for identification but can be used for obtaining a biopsy if differentiation from a benign stricture is required.

Staging CT chest, abdomen and pelvis should be performed for all patients with identified liver cancer to assess for metastatic disease.

TREATMENT

Currently, the Barcelona Clinic Liver Cancer (BCLC) staging system is used to categorise stages of HCC taking into account the number and size of tumours, the patient performance score and the severity of their liver disease (using the Child-Pugh score). There are five stages and treatment available is dependent on the stage. The BCLC provides prognostic information, (see tables 1 and 2, above, and table 3, p19).

Research is ongoing on the role of specific biomarkers such as phospho-ERK and genomic profiling to determine whether in the future, targeted therapy or immunotherapy could be used depending on the specific traits of the identified tumour.[17,18]

Hepatocellular carcinoma

Treatment options for HCC include the following.

Surgery: Liver resection (for stage 0 or A) is the treatment of choice in patients with HCC and non-cirrhotic liver. Eligible patients are those with a single HCC of any size or with two or three

nodules within Milan criteria depending on patient performance status, comorbidities and liver function/remnant volume, see table 4, below right. Those not eligible for resection but still stage 0 or A may be eligible for liver transplantation.

Portal vein thrombosis is a common complication of HCC that has often developed prior to diagnosis, this usually leads to liver decompensation precluding the option of surgical resection.

Percutaneous ethanol injection (PEI): Ethanol is injected percutaneously into the tumour which leads to coagulative necrosis within the tumour. It is most successful in smaller tumours but recurrence rates are high.

Radiofrequency ablation (RFA): High energy radio waves are used to induce a coagulative necrosis. RFA is also more successful when used with smaller tumours and is associated with a much lower recurrence rate.

Chemoembolisation: Embolisation of the artery supplying the tumour is carried out via transcatheter delivery of lipiodol or gel beads (known as TAE), or embolic or cytotoxic agents such as doxorubicin (known as TACE) causing local tumour ischaemia and delivery targeted chemotherapy. It is used in patients with stage B HCC, is not curative but slows tumour growth.

Chemotherapy: Chemotherapy has a limited role in HCC. The response rate to systemic doxorubicin is approximately 20% in patients without cirrhosis.

Biologic therapies: For advanced liver cancer (BCL stage C), NICE has approved sorafenib, an oral tyrosine kinase inhibitor. This functions by preventing tumour cell proliferation and angiogenesis.

It is estimated to extend life by three months in those patients with advanced HCC.

If this fails, patients may qualify to be trialled on lenvatinib or regorafenib which are approved by NICE but not funded within the NHS.[19,20]

Cholangiocarcinoma

In CC, treatment decisions are made according to the tumour, node, metastasis (TNM) system (see table 5, right).

Treatment options are surgery which can be of curative intent, such as resection or transplantation, palliative, or symptom relief such as biliary bypass or stent placement. Other options include radiotherapy or chemotherapy which can be neoadjuvant, adjuvant or palliative. »

Table 3

Treatment options according to Barcelona Clinic Liver Cancer disease stage

Stage	Features	Treatment options
Very early (0)	● Single < 2 cm ● Child-Pugh A ● PS 0	● Resection ● Ablation ● Transplant
Early (A)	● Single or 2-3 nodules < 3 cm ● Child-Pugh A ● PS 0	● Resection ● Ablation ● Transplant
Intermediate (B)	● Multinodular ● Child-Pugh A-B ● PS 0	● TACE
Advanced (C)	● Portal vein invasion ● Extra-hepatic spread ● Child-Pugh A-B ● PS 1-2	● Sorafenib
Terminal (D)	● Terminal stage ● Child-Pugh C ● PS 3-4	● Best supportive care

PS = performance status

Table 4

Milan criteria for liver transplantation

Single tumour < 5 cm or 2-3 tumours (none > 3 cm) and no vascular invasion or extrahepatic spread.

Table 5

TNM staging for cholangiocarcinoma

Feature	Scoring
Primary tumour (T)	**Tx** - cannot be assessed **T0** - no evidence of primary tumour **T1** - solitary tumour, no vascular invasion **T2** - solitary tumour with vascular invasion or multiple tumours all < 5 cm **T3a** - multiple tumours of any size **T3b** - single tumour or multiple tumours of any size involving a major branch of the portal or hepatic vein **T4** - tumours with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
Regional lymph nodes (N)	**Nx** - cannot be assessed **N0** - no regional node metastases **N1** - regional node metastasis
Distant metastases	**M0** - no distant metastasis **M1** - distant metastasis

key points

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Hepatocellular carcinoma (HCC) accounts for around 90% of liver cancer cases. Intrahepatic cholangiocarcinomas (CC) account for 9-10% of cases. In the UK, there are on average 5,900 new cases of HCC each year with an average five-year survival of 13.1%, although for non-cirrhotic patients who are eligible for liver resection the five-year survival rate is 42%.

Most cases of HCC occur in the context of chronic liver disease with cirrhosis, particularly in those with chronic hepatitis B or C. Other major risk factors include excessive alcohol consumption, obesity and aflatoxins. Overall, 10-15% of cirrhotic patients will develop HCC within 20 years. In the UK, NICE and the BSG guidelines recommend surveillance with ultrasound scanning ± alpha fetoprotein (AFP) testing every six months for patients with established cirrhosis (apart from those receiving end of life care) to screen for early HCC.

In patients with underlying cirrhosis, liver cancer may present with signs of liver decompensation. Early HCC is rarely symptomatic but as it advances, patients may present in primary care with upper or right-sided abdominal pain, jaundice, weight loss, early satiety or a palpable mass in the right upper quadrant. Patients may rarely also present with features of a paraneoplastic disease including erythrocytosis, hypoglycaemia, hypercalcaemia or diarrhoea. Extrahepatic metastases are present at diagnosis in 10-15% of patients, with the most common sites being lung, intra-abdominal lymph nodes, bone and the adrenal glands. CC is frequently not diagnosed until the symptoms of biliary obstruction develop. Patients presenting with an upper abdominal mass consistent with an enlarged liver should be referred for an urgent direct access ultrasound within two weeks.

AFP levels > 400 ng/ml in a high-risk patient are considered diagnostic of HCC. However, AFP is only positive in 60-80% of HCC cases and in small tumours AFP is raised in 10-20% of cases. Diagnosis can be made through contrast-enhanced CT or MRI scan for lesions > 2 cm. If lesions do not fully meet diagnostic criteria or in non-cirrhotic patients, biopsy is recommended to confirm findings. For diagnosis of CC, CA 19-9 is used alongside imaging and biopsy. Staging CT chest, abdomen and pelvis should be performed for all patients with identified liver cancer to assess for metastatic disease.

The Barcelona Clinic Liver Cancer staging system is used to categorise HCC taking into account the number and size of tumours, the patient performance score and the severity of their liver disease (using the Child-Pugh score). Treatment options are determined by the stage. Liver resection is the treatment of choice for HCC patients with a non-cirrhotic liver and for stage 0 or A HCC arising in a cirrhotic liver. For early tumours unsuitable for resection, treatment options are ablation or transplantation.

CONCLUSION

The management of HCC remains a significant challenge especially improving early detection and treatment. It still has poor five-year survival compared with many other cancers.

Research is currently underway looking at the effects of treatment with sorafenib earlier in the disease course, such as after surgery or TACE, or whether efficacy can be improved by combining it with chemotherapy.

A potential future agent is ramucirumab that works by blocking new blood vessel growth and can result in tumour shrinkage. It is already being used in other cancers such as stomach cancer, non small cell lung cancer and colorectal cancer.

Competing interests: None

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Useful information

British Society of Gastroenterology
www.bsg.org.uk

British Liver Trust
www.britishlivertrust.org.uk

Macmillan Cancer Support
www.macmillan.org.uk

GUTs UK
https://gutscharity.org.uk

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