Malignant liver tumours

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Abstract

The liver is commonly affected by both primary and metastatic malignancy. The surgical management of liver tumours must be carefully considered to ensure good oncological outcomes and to avoid serious complications of liver surgery. Primary tumours of the liver include hepatocellular carcinoma and cholangiocarcinoma. The resectability of primary liver tumours is dependent on thorough preoperative staging. Primary liver tumours pose a major global health burden, particularly in Asia and in countries affected by epidemic viral hepatitis. Metastatic disease commonly affects the liver and often hepatic resection in such circumstances provides the best chance of prolonging life and disease free survival. This review discusses recent advances, in addition to the epidemiology, diagnosis and management of both primary and secondary liver tumours.

Keywords Cholangiocarcinoma; epidemiology; HCC; hepatobiliary cancer; hepatocellular carcinoma; imaging; liver metastasis; liver tumour; management

The liver is an organ which is commonly affected by both primary and secondary tumours. Secondary tumours are the most common malignancies to affect the liver, particularly if arising from colorectal, breast, pancreatic, ovarian or lung primary cancers.[1] Primary tumours of the liver are less common, yet still make up 6% of the total burden of cancer disease worldwide.[2] Primary liver tumours include hepatocellular carcinoma, cholangiocarcinoma and sarcoma. This review aims to discuss the epidemiology, diagnosis and treatment of the commonest liver malignancies.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is the sixth most common, worldwide. In the UK, HCC is relatively uncommon, with an incidence of 9.4 per 100,000 population.[3] In China, SE Asia and areas of Africa, the incidence of HCC is estimated to be as high as 20 per 100,000. Although the incidence is increasing in the Western world, it is currently decreasing in high incidence areas.

Presentation

Many asymptomatic HCCs are picked up incidentally or through screening. Symptomatic patients may present with right upper quadrant pain, weight loss, jaundice, bruising from clotting abnormalities and loss of appetite. More often, patients will have symptoms of underlying liver disease, as HCC is often a consequence of cirrhosis and hepatitis. Nevertheless, presentation is typically late and treatment with curative intent may not be possible. For patients with a high risk of developing HCC, particularly those with severe inflammation and fibrosis, 6-monthly ultrasound surveillance with α-fetoprotein (AFP) testing is recommended to identify early lesions.

Risk factors

The main risk factor for the development of HCC is the presence of chronic liver disease (Table 1). Chronic viral hepatitis is a major cause, with the hepatitis B and hepatitis C viruses contributing towards 80–90% of all HCC cases. Patients with cirrhosis of the liver from any cause have an elevated annual risk of developing HCC versus the normal population, independent of the underlying aetiology. However, cirrhosis due to viral hepatitis carries a far higher annual risk of 2–8%, with hepatitis C infection the greatest risk. Infection with both hepatitis B and C viruses increases the risk of developing HCC when compared to infection with only one virus. Obesity is a key risk factor for the development of non-alcoholic fatty liver disease (NAFLD) which predisposes to the development of HCC; recent studies identifying a 1.5-fold higher risk of HCC.[4] Those with diabetes are also noted to be at a higher risk of developing HCC. Patients with NAFLD or steatohepatitis are at a similarly heightened risk. Individuals of Asian descent have been found to be at an increased risk of developing HCC. Other risk factors predisposing individuals to the development of HCC include alcohol-related cirrhosis, auto-immune diseases (e.g. primary biliary cirrhosis), Wilson disease and hereditary haemochromatosis. Any patient with an HCC should be investigated for underlying liver disease.

Diagnosis

At present, diagnosis and staging of HCC is conducted using a multi-modal approach. Unlike other solid tumours, imaging enables a definitive diagnosis of HCC to be made without the requirement of tissue biopsy.

Ultrasonography is useful for screening patients at risk, for initial characterization of lesions and for intraoperative assessment. On ultrasound, small HCCs often appear hypoechoic compared to surrounding parenchyma. Larger HCCs are more heterogeneous due to necrosis, fatty changes, tumour thrombus and neovascularization. In the presence of cirrhosis, HCC may be difficult to identify on ultrasonography from the already disrupted cirrhotic liver parenchyma. Arterial phase contrast greatly assists in identifying HCCs.

Computed tomography (CT) has a high sensitivity and specificity for detecting HCC larger than 1 cm in diameter. CT must include arterial and venous contrast phases to allow radiological characterisation. In the arterial phase, the tumour will be brighter than the surrounding liver (tumour enhancement). In the venous phase, the tumour will characteristically appear less bright than the surrounding tissue (tumour washout).[5]

Magnetic resonance imaging (MRI) has become increasingly important in diagnosing HCC. MRI, employing contrast that is taken up by hepatocytes or Kupffer cells and excreted via the biliary system (rather than MRI using extracellular contrast

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Risk of developing hepatocellular carcinoma by predisposition

	Alcohol	Hepatitis B	Hepatitis C
Risk with no cirrhosis (per 100 person years)[7]	0.01	0.1—0.7 (asymptomatic carrier) 0.1—1.0 (for chronic hepatitis)	0.0—1.8 (for chronic hepatitis)
Risk with compensated cirrhosis (per 100 person years)[7]	0.2—1.8	2.2—4.3	3.7—7.1

Table 1

agents), allows for accurate assessment of pathology with the rate of uptake dependent on the degree of cell differentiation. This has allowed for a reduction in biopsy related diagnoses. MRI and CT in combination increases the sensitivity and specificity for detecting HCC lesions less than 2 cm in diameter. Lesions less than 1 cm in diameter are usually regarded as 'indeterminate'. For those patients who have indeterminate lesions, surveillance is prudent. It is possible for imaging to only detect larger lesions and miss smaller satellite lesions in the liver, which may lead to incorrectly staged disease.

Serum biomarkers are also used in the diagnosis of HCC. AFP is typically raised in HCC, has a sensitivity of 41—65% and a specificity of 80—94% and is used as a tumour marker to aid diagnosis and monitor disease progression. Serum AFP performs poorly in early disease; however, in late stage disease, a raised AFP has a high sensitivity and specificity. Specificity reaches 100% in patients with AFP levels over 200 IU/ml. Despite this, AFP can be raised in other tumours (e.g. germ-cell tumours) and raised in patients with cirrhosis, thus limiting its utility alone. Des-γ-carboxyprothrombin (DCP) is an abnormal form of prothrombin, which is produced by abnormal areas of the liver (i.e. HCC). DCP is also found in patients who are vitamin-K deficient. Although not commonly used in the UK or USA, DCP is a useful biomarker in those with cirrhosis and can distinguish HCC from cirrhosis. If a falsely elevated DCP level is suspected, vitamin-K can be administered and the DCP level repeated; if HCC is present the DCP level will remain elevated even after vitamin-K supplementation.

If these modalities are not diagnostic and there is a specific concern regarding the diagnosis, a biopsy may sometimes be indicated. There is a risk of seeding tumour out-with the liver, rendering a potentially curable patient incurable, although reported instances of this occurring are low.

Treatment

There are several treatment options available for HCC, dependent on the stage of the disease and health of the patient. The main curative approaches for HCC are liver resection or liver transplantation. For small lesions, radiofrequency ablation (RFA) or microwave ablation (MWA) may also be curative and avoid the necessity for major resection. Locoregional chemotherapy is often used in patients for whom liver transplantation or resection are not possible. Locoregional chemotherapy can be delivered to the liver by transarterial chemoembolization (TACE). Systemic chemotherapy with sorafenib is also a possibility. Deciding on the best treatment plan depends largely on the stage of disease, functional status, co-morbidities and presence of any background liver disease. The Barcelona Clinic Liver Cancer (BCLC) classification system in Figure 1 provides a useful guide to treatment decision making.

Liver resection: surgical resection is indicated in patients with good liver function. Tumours must be located within the liver to allow curative resection while leaving a sufficiently sized liver remnant. If at any point there is an insufficient functional liver remnant following hepatectomy, postoperative liver failure may ensure, which is associated with a high mortality rate. In patients without cirrhosis, liver resection for HCC results in a 5-year survival rate of 50%, however half of patients with background non-cirrhotic liver will develop recurrence within 2 years. Re-resection is often indicated in these patients with similar long-term outcomes to primarily resected patients.[6]

Most HCCs develop on the background of cirrhosis. When assessing treatment options, grading using the Child-Turcotte-Pugh score is important (Tables 2 and 3) to quantify the underlying degree of hepatic compensation. Further assessment should be made to exclude portal venous hypertension, including CT to determine splenomegaly and ascites, and oesophagogastroscopy to exclude oesophageal varices. Portal hypertension is considered a relative contra-indication for hepatic resection in patients with cirrhosis.

The regenerative capacity of patients with higher Child-Turcotte-Pugh scores is compromised, resulting in higher rates of liver failure and postoperative mortality. Five-year survival rates for patients with cirrhosis who undergo resection for HCC is 45%, however recurrence rates as high as 80% are reported.

In non-cirrhotic patients, resection of up to 75% of the liver can be performed. Determining the expected function of the future liver remnant (FLR) is difficult and the focus of current research. In patients with cirrhosis, great care must be taken prior to any resection to ensure sufficient residual liver volume to avoid potentially catastrophic post-hepatectomy liver failure.

Should the FLR be anticipated to be insufficient, one option that may facilitate subsequent surgical resection is portal vein embolization (PVE). This involves introduction of an embolic agent (i.e. cyanoacrylate, microspheres, coils or PVA) into the portal vein branches supplying the affected lobe to induce ischaemia and therefore atrophy of the affected segments. In response to this, the disease-free segments of liver hypertrophy. This then allows for resection of the atrophied portion of liver, which would previously not have been possible.

Liver transplantation: liver transplantation is considered for HCC when resection is not possible. To assist in the selection of

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