Malignant liver tumours

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Abstract

The liver is commonly affected by malignant tumours, both primary and secondary. The majority of liver tumours are diagnosed radiologically and MRI and CT scan are accurate at detecting even small tumours. Hepatocellular carcinoma (HCC) is the most common primary tumour and often presents on the background of liver cirrhosis. The curative options for HCC are liver resection and transplant. However non-curative management such as radiofrequency ablation (RFA) and trans-arterial chemoembolization (TACE) can prolong survival in patients not suited to curative management. Cholangiocarcinoma is a less common malignancy but unfortunately has poorer outcomes. It affects the bile ducts and treatment relies on resection of the affected liver and biliary tree, requiring reconstruction of the biliary drainage system. Postoperative morbidity is high and long term survival is often short. Colorectal liver metastases (CLM) are the most common liver tumours. With improvements in preoperative chemotherapy and surgical techniques such as portal vein embolization (PVE) and two stage resections, curative resection with good long term outcomes are often achieved.

Keywords Chemotherapy; cholangiocarcinoma; colorectal liver metastases; hepatocellular carcinoma; radiofrequency ablation (RFA); resection; trans-arterial chemoembolization (TACE)

Introduction

The liver is commonly affected by malignancy and represents 5.7% of all cancer cases.[1] Both primary and secondary tumours can affect the liver. The most common primary liver tumours are hepatocellular carcinoma and cholangiocarcinoma. The most common secondary tumour is a metastasis from colorectal cancer. This review will summarize the salient issues pertaining to the most common liver malignancies.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver tumour and one of the most common tumours worldwide representing 7.9% of all malignancies.[2] In northern Europe the incidence is <5 per 100,000 people. In areas of high incidence such as China and South East Asia HCC is reported in 20 per 100,000 people. Its incidence is increasing in the Western world but decreasing in areas with traditionally high levels of HCC.[2]

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Presentation

The majority of HCCs are picked up incidentally with no symptoms being evident. Symptoms include right upper quadrant pain or fatigue or weight loss. Most often symptoms are related to underlying liver disease, as HCC commonly presents on a background of cirrhosis. As symptoms are often mild or absent, presentation is often late and patients are often unresectable at the time of presentation.[3] As a result of this, ultrasound surveillance programmes are recommended for patients who are at risk of developing HCC, namely cirrhotic patients or chronic hepatitis B or C carriers.[3]

Risk factors for HCC

HCC presents on the background of underlying chronic liver disease in around 80% of cases.[3] It is important to establish the cause of the underlying liver disease as this can have implications for outcome and definitive management.

Chronic viral liver disease is an important precursor to HCC, namely hepatitis C virus (HCV) and hepatitis B virus (HBV), which together are present in 70% of all HCC cases.[3] Hereditary heamochromatosis, alcoholic liver disease and autoimmune disease are also significant risk factors.[3]

The presence of cirrhosis from any cause is a risk factor for developing HCC with an annual risk of 1–6%.[3] However, patients with HCV and HBV related cirrhosis are more at risk of developing HCC than other aetiologies.[3]

Diagnosis

Routine modalities for diagnosis and assessment of surgical approach are ultrasound, CT scanning and MRI scanning. Alpha-fetoprotein is often raised in HCC, has a sensitivity of 41–65% and a specificity of 80–94%[4] and is used as a tumour marker to aid diagnosis and monitor disease progression.

Often imaging is the only method of diagnosis and certain criteria are applied to contrast studies to help confirm the diagnosis. CT scanning that employs an arterial and venous phase of the scan of the intravascular contrast is important. This is because HCCs are only supplied by arteries whereas the liver receives blood supply from both the arterial system and the portal venous system. This anatomical distinction allows for radiological characterization.

When contrast is shown up in the arterial system the tumour will be brighter than the surrounding liver because the blood in the portal venous system will not show up with contrast. In the venous phase, the contrast will be in the portal venous system, enhancing the liver parenchyma and not the arteries supplying the tumour. This phase, known as the 'washout' phase, will show the tumour to be less bright than the surrounding tissue and is diagnostic for HCC.[5] MRI employing contrast that is taken up by hepatocytes and excreted via the biliary system allows for accurate assessment of pathology with rate of uptake indicative of cell involvement. This has allowed for a reduction in biopsy related diagnoses.

CT and MRI scanning have high sensitivities for diagnosing HCC. However, the specificity is not as high so there are instances of false positives. Because of this, particularly for small tumours both CT and MRI should be performed to provide the best chance of correctly diagnosing the lesion.[4]

Obtaining a biopsy of the tumour to confirm diagnosis prior to treatment is not normally indicated due to the ability to diagnose HCCs with CT and MRI scanning in the majority of cases. If these modalities are not diagnostic and there is a specific concern regarding the diagnosis, a biopsy may be performed. The concern with this approach is seeding of tumour during the procedure although reported instances of this occurring are low.

Treatment

The curative options for treatment of HCC are liver resection or liver transplantation. Radiofrequency ablation (RFA) or microwave ablation involve burning the HCC and may be curative if the lesion is very small, though for many patients with background liver cirrhosis there is a high chance of further lesions developing elsewhere within the abnormal liver. Trans-arterial chemoembolization (TACE) involves delivering chemotherapy directly to the tumour but does not result in cure. The choice of treatment depends on several factors, most notably the size and number of tumours, progression of disease, underlying liver disease, patient comorbidity and functional status as reported by the Barcelona Clinic Liver Cancer classification system (Figure 1).

Liver resection: surgical resection is indicated in patients with good liver function. Tumours must be positioned within the liver to allow curative resection while leaving a remnant liver of sufficient size. In patients without cirrhosis, liver resection for HCC results in a 5-year survival rate of 50%;[6] 50% of patients with non-cirrhotic liver will recur within 2 years.[6] Re-resection is often indicated in these patients with similar long-term outcomes to primarily resected patients.[6]

The majority of HCCs develop on the background of cirrhosis.[4] When assessing treatment options grading of the Child-Pugh score is important (Table 1) to quantify the underlying degree of hepatic compensation. Further assessment should be made to exclude portal venous hypertension, including detailed CT scanning to determine splenomegaly and ascites and oesophagogastroscopy to exclude oesophageal varices.[4] Portal hypertension is considered a contraindication for hepatic resection in patients with cirrhosis.[4]

The regenerative capacity of patients with higher Child-Pugh scores is compromised resulting in higher rates of liver failure and postoperative mortality. The 5-year survival rates for patients with cirrhosis who undergo resection for HCC is 45%; however, the recurrence rates have been reported as high as 80%.

In non-cirrhotic patients resection of up to 75% of the liver can be performed and an expected future liver remnant (FLR) of 25% would be expected to function adequately and regeneration would be expected to satisfactorily replace the resected liver.[7]

Should the FLR be anticipated to be less than 25% the options to permit surgical resection include portal vein embolization. This involves occlusion of the portal vein branch supplying the affected hemiliver in order to induce ischaemia and therefore atrophy to the affected segments and hypertrophy of the disease free segments in anticipation of resection of the atrophied portion of liver. In patients who are cirrhotic an FLR of up to 40% is required.[7]

Liver transplantation: is considered for HCC when the underlying liver disease is more advanced and the HCC size and number are more. The Milan criteria for liver transplant for HCC were developed to aid identification of patients are suitable for transplantation. These criteria stipulate that on imaging, the tumour should be either single and <5 cm in diameter or up to three nodules all <3 cm and without vascular invasion.[8] Pathological analysis of the explanted liver from those who have undergone transplantation can show if an individual was actually beyond the Milan criteria. That these individuals often have good long-term

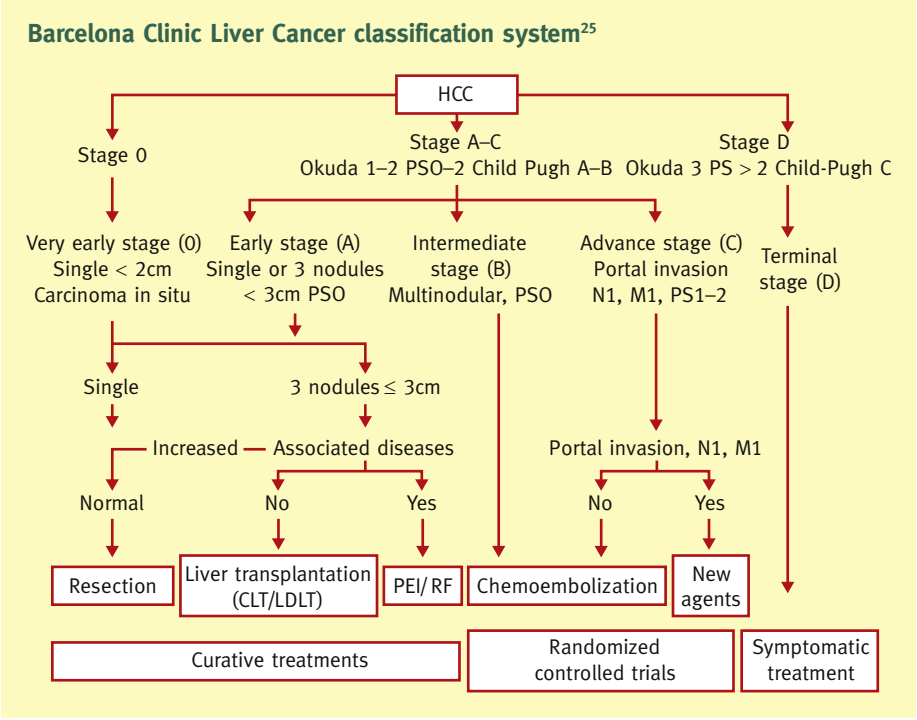

Figure 1

Child-Pugh scoring system

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Grade 1–2	Grade 3–4
Bilirubin, mg/dL	<2	2–3	>3
Albumin, g/dL	>3.5	2.8–3.5	<2.8
Prothrombin time			
Seconds over control	<4	4–6	>6
INR	<1.7	1.7–2.3	>2.3

CPT classification: Child A: score 5–6 (well compensated); Child B: score 7–9 (significant functional compromise); Child C: score 10–15 (decompensated)

Table 1

outcomes has encouraged the modification of the original Milan criteria to include more advanced disease. There is difficulty in the allocation of a limited supply of organs between unwell patients with liver failure and those with HCC. Given there can be no guarantee of a donor liver becoming available, HCC patients are often treated on the waiting list with an alternative modality such as ablation or chemoembolization (see below).

Radiofrequency/microwave ablation: is a potential treatment option for HCC, especially in patients who are not fit enough to tolerate resection or transplant. It involves passing a needle directly into the tumour through the skin, or directly at open or laparoscopic surgery. Radiofrequency or microwave energy is administered to heat the tumour and kill tumour cells. It is not a curative procedure but provides improvement in long term outcomes in patients who would not be able to tolerate curative procedures.

TACE: is the standard of care for patients with intermediate HCC as described by the Barcelona Clinic Liver Cancer group. TACE involves the injection of a chemotherapeutic agent and then a further agent that embolizes the artery feeding the tumour thus attempting tumour necrosis via reduction in blood supply and a cytotoxic effect. TACE, although a palliative treatment option, has been shown to offer improved survival in patients with unresectable HCC when compared to supportive treatment alone.[9] A further application for TACE is to control tumour growth while patients are awaiting transplantation to prevent tumour progression beyond transplant criteria or downsize tumours to allow transplantation.

Sorafenib: is a biological agent that inhibits several protein kinases which are upregulated in HCC. It has been shown to modestly improve survival compared to supportive treatment (10.9 months versus 7.9 months[10]) and is recommended in the BCLC pathway for non-operable HCC in patients with relatively preserved liver function. However, the survival benefit must be considered in the light of the significant side effects, namely hand and foot skin reaction and diarrhoea.

Although, with the exception of sorafenib, systemic chemotherapy has traditionally not been associated with improvements of outcome, in some instances systemic regimens may be beneficial to patients with advanced HCC. However, expert, multidisciplinary care is required to ensure optimal management is adhered to in order for patients to benefit from the emerging evidence.

Cholangiocarcinoma

Cholangiocarcinoma is cancer of the bile ducts and is a relatively rare malignancy accounting for 2% of all malignancies reported worldwide. However, it is important for liver surgeons because it is the second most common primary liver malignancy.[11] Approximately 1500 people a year die in the UK from cholangiocarcinoma.[11]

There are several established risk factors for developing cholangiocarcinoma although these only account for around one-third of cases.[11] The most common predisposing risk factor for cholangiocarcinoma is primary sclerosing cholangitis (PSC). Between 5% and 10% of people with PSC develop cholangiocarcinoma.[11] Other risk factors include chronic cholangitis, increasing age and inflammatory bowel disease.

Cholangiocarcinoma most commonly presents in the sixth decade.[11] It usually presents incidentally with deranged LFTs, as obstructive jaundice or as repeated episodes of cholangitis.

It is important to clarify the anatomical classification of cholangiocarcinomas. Depending on their location they are described as either intrahepatic, hilar or distal extrahepatic. Each tumour is managed differently depending on location. This article will focus on intrahepatic and hilar cholangiocarcinomas.

Diagnosis

Intrahepatic cholangiocarcinoma is commonly diagnosed via non-invasive imaging techniques. Tissue diagnosis can be obtained when diagnosis is in doubt.

Ultrasound is a common imaging modality that is often used as a screening tool when abnormal LFTs are encountered. Its main function is to assess if there is a dilated biliary system and can be useful in diagnosing gallstones that could potentially exclude malignant disease.

CT scanning is often the secondary imaging modality used and has an acceptable sensitivity for diagnosing cholangiocarcinomas. It is also able to assess the remaining abdominal and pelvic organs to assess the presence of extrahepatic disease.

However, MRI scanning is the critical imaging modality for assessing cholangiocarcinomas and can give increased detail to the operating surgeon regarding resectability. It gives detailed images of the vascular and bile duct tumour involvement to clarify if a resectional approach can be attempted. Bile duct anatomy and involvement is specifically assessed by MRCP which has replaced ERCP. MRCP is not only less invasive but also is able to accurately diagnose malignant causes of bile duct obstruction to a greater degree than ERCP.

Prior to resection, distant metastases need to be excluded. CT scanning of the chest, abdomen and pelvis is the most effective method for performing this. If peritoneal metastases are suspected, laparoscopic staging of the abdominal cavity may be indicated to exclude locally advanced and non-resectable disease. Fifty per cent of patients have positive lymph node involvement and up to one fifth have peritoneal deposits at the time of presentation.[11]

Treatment

The only treatment option for a potential cure is surgical resection and often a radical surgical approach is required. Only one-third of patients are found to be resectable at presentation[11] and often those who make it to laparotomy are subsequently found to be irresectable at operation.

Excision of the affected biliary tree is performed along with the involved liver parenchyma. Hilar cholangiocarcinoma resection will require radical bile duct excision of the biliary tree down to the common bile duct at the superior border to the pancreas. The biliary system then requires to be reconstructed by means of a Roux-en-Y hepatico-jejunosotomy. Such procedures are technically challenging, prolonged and often result in poor postoperative outcomes.

Prior to treatment it is important to manage any biliary obstruction with biliary drainage. For intrahepatic tumours a stent can be places into the biliary system that will remain postoperative via percutaneous transhepatic cholangiography. For distal and hilar tumours a stent can be placed via ERCP to relieve any obstruction.

Cholangiocarcinoma surgery has notoriously poor outcomes.[12] The recurrence rate is reported as up to 56%. Complete resection of cholangiocarcinoma is associated with 5-year survival rates of between 20% and 40% for perihilar cholangiocarcinoma.[12] Intra-hepatic cholangiocarcinoma has been associated with a 5-year survival of 61% but the majority of centres report between 20% and 40%.[12]

The differences in surgical technique when resecting hilar cholangiocarcinomas in particular, compared to other resections include the decision to perform a lymphadenectomy. This has not been associated with improved overall survival but does reduce recurrence rates.[12] It is also recommended that the caudate lobe be resected routinely in resection of cholangiocarcinoma as this is associated with better long term results.[13]

Following resection there is currently no evidence supporting adjuvant chemotherapy. A large trial (the BILCAP trial) is expected to clarify this issue over the next 12 months.

Colorectal liver metastases

The most common tumour encountered in the liver and the most common hepatic secondary is a metastasis from a colorectal primary. Colorectal cancer is the third most common newly diagnosed cancer in the UK. Between 2008 and 2010, 58 new cases per 100,000 men and 37 new cases per 100,000 women were diagnosed in the UK (Cancer Incidence and Mortality, 2012);[14] 25% of these patients present with synchronous liver metastases and a further 25% develop metachronous liver metastases over their follow up period post-colonic resection. Of these 15% will go on to have resection of the liver metastasis.[15]

Presentation

Colorectal liver metastases (CLM) are either found at the time of staging of the primary colon cancer (synchronous tumours) or found at a later stage (metachronous). CLM will often be asymptomatic and are found on staging or follow up CT scan. Occasionally they will be symptomatic with right upper quadrant pain, obstructive symptoms or present with weight loss or fatigue. During follow up, suspicion can be aroused by an increase in the tumour marker CEA on surveillance bloods.

Diagnosis

CT scanning is the preliminary investigation of choice to determine if CLM are evident. The sensitivity of CT scanning has been reported as 74.4%.[16] Other techniques used are MRI scanning and FDG PET scanning. PET scanning relies on the increased metabolic activity of malignant cells to 'take up' the FDG isotope to a greater degree than non-malignant cells. All three modalities have a comparable sensitivity and specificity for diagnosing CLMs when looking at all tumours.[16] MRI scanning has been reported to have a greater sensitivity for detecting tumours that are less than 1 cm in diameter.[16] In practice, CT scanning and MRI scanning are often both performed to allow a detailed characterization of the tumour or tumours and allow a surgical approach to be planned.

Staging

Another consideration is the staging of the disease. Colorectal cancer does not only metastasize to the liver but also to the lungs, brain, bone and peritoneum. Should there be evidence of extra-hepatic involvement then consideration should be made as to the benefit of hepatic resection. PET scanning is often performed in concert with CT scanning of the chest, abdomen and pelvis to exclude or confirm extrahepatic disease which may prevent or alter surgical management.

The presence of extrahepatic disease has traditionally been considered as contributory to poor outcomes and potentially a contraindication to resection. A large meta-analysis recently has recently reported that patients with extrahepatic disease, most notably pulmonary metastases, had disease-free survival and 5-year survival rates comparable to published data on patients undergoing liver resection without extrahepatic disease.[17] Therefore it is recommended to consider resection on patients even with certain extrahepatic disease at presentation.

Treatment

Chemotherapy: the use of chemotherapy before and/or after liver resection has gone through some significant developments over recent years. Eighty per cent of patients with CLM are unresectable at the point of presentation.[15] The use of chemotherapeutic agents to convert irresectable to resectable disease has significantly improved long-term survival rates for these patients with a reported 5-year survival rate of 46% for patients who received cetuximab-based chemotherapy regimens to covert their tumour to resectable disease.[18]

However, controversy exists regarding the benefit of chemotherapy for primarily resectable tumours. Perioperative chemotherapy has been shown to provide a benefit to patients who underwent liver resection for primarily resectable disease in terms of an increased recurrence free survival.[19] However, when these patients were followed up further their overall survival was no different.[19]

Resection: resectability is dependent on the removal of affected liver parenchyma to leave two contiguous segments with corresponding inflow, outflow and biliary drainage. Resectability also relies on the complete removal of all tumour without leaving any residual tumour.

Complete resection of the CLM can result in a long-term cure for patients. The reported 5-year survival rates can vary between institution but a frequently reported figure of 45% is accepted.[20]

The numbers of hepatic resections performed per year has increased over the past decade.[20] This means that surgical resection is being performed on patients who would have previously been deemed irresectable. The potential reasons for this are not only the introduction of effective chemotherapy as described above, but also the increased surgical expertise and techniques available.

A major cause of postoperative morbidity and mortality is post-resectional hepatic failure due, often to a small residual liver remnant volume. A method to mitigate against this is to perform a portal vein embolization to promote hypertrophy of the future liver remnant. This technique has been shown to provide overall and disease free survival rates similar to patients who underwent the same extensive resection but who did not require PVE.[7]

Two-stage hepatectomy, whereby initially deemed irresectable disease due to the extent of the disease, is being taken in stages. This means one hemiliver is being cleared of disease, either with or without portal vein ligation or embolization, and then, after a period of several weeks to allow hypertrophy of the cleared hemiliver, the second stage of resection is performed to clear the remaining hemiliver. This technique has increased over the last decade and a recent meta-analysis[21] showed a median survival of 36 months and a 3-year disease-free survival of 20%, which is certainly superior to systemic chemotherapy alone and is comparable to primarily resectable disease.[21]

Also, the intention to re-resect patients who have initially recurred has contributed to the overall survival of patients with colorectal metastases. The most recent evidence, comprising the largest series assessing patients re-resected following recurrence of their disease, found 3 and 5 year survival rates to be 76% and 45% respectively.[22]

RFA: 85% of all patients with colorectal liver metastases are unresectable at the time of presentation. For patients with unresectable disease, a median survival of just under 2 years can be achieved with palliative chemotherapy.[23] However, some tumours are amenable to radiofrequency ablation that may be used as an alternative or adjunct to palliative chemotherapy.

Not all disease distributions are suitable for RFA. Large and multiple tumours are often contraindicated and tumours close to the capsule and near to the large hepatic vessels are not suitable due to the dissipation of the radiowave causing damage to surrounding structures. When compared to chemotherapy OS rates for RFA are variable but the only RCT comparing RFA and chemotherapy with chemotherapy alone in unresectable tumours found a significantly increased 3 year DFS of 27.6% for combined treatment compared to 10.6% in the chemotherapy alone arm.[24]

Follow up

Follow up after liver resection for CLM consists of radiological, clinical and haematological assessment. Scanning is normally started from 6 month postoperatively, until 12 months and then annually thereafter. This, in combination with regular CEA and clinical assessment, allows close follow up.

Conclusion

The liver is a common site for malignancy. The outcomes of surgery for malignant tumours are improving. When tumours are initially thought to be irresectable a variety of techniques exist which can convert initially irresectable tumours into tumours that can be managed with curative intent. A number of less invasive techniques exist to prolong survival without undergoing major surgery. ◆

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