Primary liver cancer

Types of primary liver cancer

The most common primary liver cancer is hepatocellular carcinoma. Other primary liver cancers include hepatoblastoma (which is much more common in children) and cholangiocarcinoma.

Epidemiology[1]

- Incidence rates for liver cancer in the UK are highest in people aged 85 to 89 (2016-2018). Each year 43% of all new liver cancer cases in the UK are diagnosed in people aged 75 and over (2016-2018).
- Since the early 1990s, liver cancer incidence rates have increased by 167% in the UK.
- In females, the most common specific type of liver cancer in the UK is intrahepatic bile duct carcinoma, in males the most common specific type of liver cancer in the UK is hepatocellular carcinoma (2016-2018).

Hepatocellular carcinoma

In most cases, hepatocellular carcinoma (HCC) develops in patients with chronic liver disease (70-90% of all patients).[2] HCC accounts for 90% of all liver cancers.[3] Tumours are multifocal in the liver in 75% of cases at diagnosis.[3]

The incidence of primary liver cancer is increasing in several developed countries and the increase will likely continue for some decades. This is due to infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), which peaked in the 1950s to 1980s. In some developing countries, the incidence of primary liver cancer has decreased, possibly as a result of the introduction of hepatitis B vaccine. The geographic variability in incidence of primary liver cancer is largely due to the distribution and the natural history of HBV and HCV.[4]

Epidemiology

- Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and the third leading cause of cancer-related death worldwide.[5]
- Incidence is highest in Asia and sub-Saharan Africa with as many as 120 cases per 100,000. It is relatively uncommon in Europe and North America.
- HCC usually occurs 20-30 years after the initial liver insult.
- The average age of development of HCC in the UK is 66 years.
- HCC is four to eight times more common in men.[3]
- HCC is the second most common hepatic malignancy in children (behind hepatoblastomas): it usually occurs in children with pre-existing liver disease (hepatic fibrosis and cirrhosis) - eg, secondary to metabolic liver disease, viral hepatitis, chemotherapy or total parenteral nutrition.

Aetiology[6]

Patients with cirrhosis have the highest risk of developing HCC.[2] 90-95% of people who develop HCC have underlying cirrhosis but non-cirrhotic HCC does occur. Cirrhosis may be due to:

- HBV or HCV infection:
    - Chronic HBV infection is the most common cause of HCC worldwide.
    - HCV is the most common cause of HCC in Europe.
    - There is a 3-5% per year risk of developing HCC if someone has either HBV or HCV infection.
    - Co-infection with both HBV and HCV increases the risk of HCC further.
- Alcoholism.
- Genetic haemochromatosis.
- Primary biliary cirrhosis.
- HCC may also be associated with a high concentration of aflatoxins, a group of mycotoxins produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus* in food. In sub-Saharan Africa and in Asia such high levels can occur due to fungal contamination of foodstuffs, including peanuts and grains.
- The metabolic syndrome, diabetes and smoking.[7] [8] [9]
- Rare associations include: androgenic steroids, primary sclerosing cholangitis, alpha-1-antitrypsin deficiency, oral contraceptives, porphyria cutanea tarda.

Presentation

It usually presents with symptoms of advancing cirrhosis and liver failure.[5]

Symptoms

- Pruritus.
- Splenomegaly.
- Bleeding oesophageal varices.
- Weight loss.

- Jaundice.
- Confusion and hepatic encephalopathy.
- Abdominal distension due to ascites.
- Right upper quadrant abdominal pain.

Signs

- Jaundice.
- Hepatomegaly.
- Ascites.
- Spider naevi.
- Peripheral oedema.
- Anaemia.
- Periumbilical collateral veins.
- Flapping tremor.

Metastases can develop in the lung, portal vein, periportal nodes, bone or brain.

Screening [3] [6]

- Patients at high risk for HCC should be offered entry into surveillance programmes. These patients include all cirrhotic HBV carriers, non-cirrhotic patients with high HBV DNA concentration, and patients with HCV-related or alcoholic cirrhosis.
- Surveillance should be performed using ultrasonography at 6- to 12-monthly intervals, associated or not with alpha-fetoprotein (AFP) determination, in order to detect early HCC amenable to curative surgical treatment.

However, the efficacy and cost-effectiveness of screening programmes for at-risk patients is unclear. Although HCC may be discovered at an earlier stage, there is a lack of curative treatment options in all patients with cirrhosis. Therefore, for some, earlier tumour detection may not lead to improvements in survival.

Possible screening tests include:

- AFP:
    - Alpha fetoprotein (AFP) is the most widely used biomarker for HCC surveillance and diagnosis.
    - The normal range for AFP is 10-20 ng/mL. The diagnostic sensitivity of AFP for detecting HCC is around 60%.[2]
    - A level of >400 ng/mL may be regarded as diagnostic for HCC by some.
    - **NB**: two thirds of HCC <4 cm have AFP levels <200 ng/mL and up to 20% of HCC do not produce AFP.
    - High levels of AFP may be seen in regenerating nodules in viral cirrhosis, so false positives may occur.
- Imaging:
    - The preferred imaging method for surveillance is ultrasound, which has a sensitivity of 60-80% and specificity of over 90%.[2]

Combining both ultrasound and AFP measurements seems to be better as a screening tool.

Diagnostic tests

- A focal liver lesion in someone with cirrhosis is highly likely to be HCC.
- If a >2 cm mass is detected on ultrasound and AFP is also raised, this is diagnostic. Further investigation is only needed to determine the best treatment. CT of the liver can look for local spread and CT of the thorax can look for metastases.
- MRI scanning with contrast or angiography with Lipiodol® injection with follow-up CT may also be used in assessment.
- If diagnosis is still in doubt, percutaneous fine-needle aspiration or biopsy may be needed. Some sources state that seeding of tumour in the needle tract occurs in 1-3% of cases.[10] However, controversy exists over these figures.

Other investigations

- AFP is elevated in 75% of cases. A level of >400 ng/mL may be regarded as diagnostic by some.
- LFTs may be consistent with cirrhosis.
- Check for clotting abnormalities.
- Albumin may be low.
- CXR may show a raised right hemidiaphragm or lung metastases.

Differential diagnosis

See also separate Benign Liver Tumours and Secondary Liver Cancer articles.

- Cirrhosis.
- Cholangiocarcinoma.
- Primary lymphoma of the liver.
- Metastatic carcinoma (30 times more common than HCC in Europe).

Staging [11]

A number of staging systems have been developed. Those that incorporate the state of liver function and the patient's clinical state (eg, presence of ascites, portal vein involvement, etc) as well as the tumour morphology, may be most useful.

- The Cancer of the Liver Italian Program (CLIP) enables an estimation of survival. A score between 0-2 is given for each of the four features listed below. The cumulative score ranging from 0-6 is the CLIP score:
    - Child-Pugh stage - the Child-Pugh-Turcotte (CPT) classification system - is a widely-used and validated way to estimate prognosis in those with cirrhosis. (Further details can be found in the separate related Cirrhosis article.)
        - Stage A = 0.
        - Stage B = 1.
        - Stage C = 2.
    - Tumour morphology:
        - Uninodular and extension less than 50% = 0.
        - Multinodular and extension less than 50% = 1.
        - Massive and extension greater than 50% = 2.
    - AFP:
        - Less than 400 = 0.
        - Greater than 400 = 1.
    - Portal vein thrombosis:
        - Absent = 0.
        - Present = 1.
- Estimated survival based on CLIP score: patients with a CLIP score of 0 have an estimated survival of 31 months; those with score of 1, about 27 months; with a score of 2, 13 months; with a score of 3, 8 months; and scores of 4-6, approximately 2 months.

- The Barcelona Clinic Liver Cancer (BCLC) staging and treatment approach is another tool that is used by many for management. The algorithm for this can be found in the Lancet reference.[2] The BCLC classification has been validated in different settings and establishes treatment recommendations for all stages of HCC.

Management

Treatment for primary liver cancer depends on the location and stage of the cancer and how well liver function is preserved. Treatment options include surgical resection, thermal ablation, systemic chemotherapy, transarterial chemoembolisation and selective internal radiation therapy. Liver transplantation may be appropriate for some patients.

In general, surgical resection or liver transplantation is the first option to treat early-stage HCC yielding the best outcomes, with a 5-year survival of 70-80%.[12]

In patients with primary liver cancer, surgical removal with curative intent may be possible.[13]

Before treatment of the primary tumour, any complications of cirrhosis or liver failure must be treated. These include ascites, encephalopathy or spontaneous bacterial peritonitis and oesophageal varices. See also separate Cirrhosis and Liver Failure articles.

Liver transplantation[14]

- Only a minority of people with HCC are suitable for transplantation.
- Because of limited donors, the 'Milan criteria' help to select transplantation candidates carefully.[8] Liver transplantation is most beneficial for individuals who are not good candidates for resection, especially those within Milan criteria (solitary tumour ≤5 cm and up to three nodules ≤3 cm).[2]
- For patients being considered for liver transplantation, a Model for End-stage Liver Disease (MELD) score is mandatory.[3]

See also the separate Liver Transplantation article.

Tumour resection

- Resection is the treatment of choice for hepatocellular carcinoma in individuals without cirrhosis.[2]
- In the short term, resection produces similar results to transplantation but, at three years, there is a higher chance of tumour-free survival after transplantation.
- Very good liver function is needed if resection is to be considered. This is because decompensation can occur after surgery.
- Also, the liver that is left behind after resection still has malignant potential and recurrence rates are 50-60% after five years.

Ablative therapy

Image-guided tumour ablation is now a standard treatment option for patients with early-stage HCC.[2]

- Alcohol (ethanol) injection - this is done percutaneously and has been carried out on small tumours in those with good underlying liver function. Larger lesions have been treated but with limited ablation success and high recurrence rates. Treatment is difficult in the posterior segments of the liver and needle tract tumour seeding is a risk, as well as bile duct injury. This may be the best treatment for those with small, inoperable HCCs.

- Radiofrequency ablation:
    - High-frequency ultrasound probes are placed into the tumour mass. This is a relatively new technique that produces tumour necrosis.
    - Radiofrequency ablation is an alternative therapy for hepatocellular carcinoma and liver metastases when resection cannot be performed or, in the case of HCC, when transplant cannot be performed in a timely enough manner.[15]
    - It may be more effective than ethanol injection for larger tumours but survival following radiofrequency ablation seems to be inferior to hepatic resection. More studies are needed.[16]
    - This procedure is approved by the National Institute for Health and Care Excellence (NICE).[17]
    - Radiofrequency ablation is considered as a possible first-line treatment for patients with a single small HCC tumour up to 3 cm.[18]
- Microwave ablation - this is approved by NICE. It destroys tumour cells by heat and results in localised areas of necrosis and tissue destruction. Needle electrodes are inserted into the liver, either percutaneously or at laparoscopy or laparotomy, and are attached to a microwave generator.[19]
- Acetic acid, laser or cold ablation may also be used.

Chemoembolisation

- This is the delivery of high concentrations of chemotherapy drugs directly to the tumour via the hepatic artery, using embolising agents such as cellulose.
- It tends to be used in those with preserved liver function with large or multifocal tumours without vascular invasion or extrahepatic spread, and who have no symptoms.[8]
- It seems to be effective in reducing tumour size as well as treating pain or bleeding.

- Careful patient selection is crucial prior to transarterial chemoembolisation, as the procedure may be associated with an increased risk of liver failure.[18]
- Median survival is >2 years and there is work to improve this by using better embolic agents and increasing the local exposure to chemotherapy.[20]

Systemic chemotherapy
Treatment for advanced-stage HCC patients is limited to systemic therapy. Systemic therapy includes standard cytotoxic chemotherapy, targeted chemotherapy such as sorafenib, and immunotherapy.

Sorafenib is recommended by NICE as an option for treating advanced hepatocellular carcinoma only for people with Child-Pugh grade A liver impairment.[21]

Other treatments

- Selective internal radiation therapy is recommended by NICE as a treatment option for primary HCC but uncertainties remain about its comparative effectiveness.[22]
- Image-guided transcatheter treatments are based on selective intravascular delivery of drugs into the arterial vessels supplying the tumour. These treatments are considered for patients with large cancers or multifocal disease that is not amenable to curative treatments. Chemotherapy drugs, embolic particles or radioactive materials can be injected and induce tumour necrosis.[2]

Prognosis

- Due to the absence of specific symptoms in early stages, the lack of early diagnostic markers, and the low percentage (10–20%) of radical resectable HCC on diagnosis, most HCC patients are often diagnosed in an advanced stage with poor prognosis.[5]
- The extent of underlying cirrhosis can also limit the treatment options.
- Median survival from time of diagnosis is about six months.

- Liver failure can occur with death due to cachexia, variceal bleeding and, occasionally, tumour rupture with intraperitoneal bleeding.
- Surgical resection, liver transplantation and ablation by radiofrequency or ethanol injection are now conventional therapies for early-stage disease. With these treatments, survival at five years is between 50% and 70%.[8]
- High AFP concentration is associated with a poor prognosis.[2]

Prevention

- The HBV vaccine will, it is hoped, reduce the incidence of HCC.[4]
- A sensible approach to alcohol consumption would also be beneficial.
- Patients with cirrhosis are at highest risk of developing this malignant disease, and ultrasonography every six months is recommended. Surveillance with ultrasonography allows diagnosis at early stages when the tumour might be curable by resection, liver transplantation, or ablation, and five-year survival higher than 50% can be achieved.[2]

Hepatoblastoma

Hepatoblastoma is the most common malignancy within the rare cohort of paediatric primary liver tumours. It may arise sporadically or in association with germline mutations in specific genetic syndromes.[23]

- One study found that 79% of hepatic malignancies in children were hepatoblastomas (although still uncommon compared with other solid tumours).[24] They usually affect children younger than 3 years. They are extremely rare in adults.
- There are associations with hemihypertrophy, Beckwith-Wiedemann syndrome and familial adenomatous polyposis syndrome. Other associations noted include maternal oral contraceptive exposure, fetal alcohol syndrome and gestational exposure to gonadotrophins.
- Hepatoblastomas are usually unifocal and affect the right lobe of the liver more often than the left lobe.

- They are usually asymptomatic at diagnosis but may present with an abdominal mass and distension, vomiting, anaemia and failure to thrive in a child under the age of 3 years. Disease may be advanced at diagnosis and a minority of patients present with pulmonary metastases.
- AFP levels are raised and can be used to monitor response to treatment.
- Other blood test findings may include a normochromic, normocytic anaemia and a high platelet count.
- Useful imaging techniques include plain abdominal X-ray (may show calcification), ultrasound, CT, MRI, bone scanning and single photon emission computed tomography (SPECT).

Management [25]

- Surgery remains the cornerstone of management and complete resection is crucial for cure. [26]
- With complete surgical resection of the tumour at diagnosis followed by adjuvant chemotherapy, survival rate can be 90-100%.
- Radiotherapy may be required when there is tumour in the resection margins or when there are chemotherapy-resistant pulmonary secondaries.
- Liver transplantation has been used in children with nonresectable tumours.

Prognosis

- A poor prognosis is associated with large tumour size, multifocal disease, extrahepatic disease and metastatic spread. [24]
- Older children and adults also tend to have a worse prognosis. [27]

Cholangiocarcinoma

See the separate Cholangiocarcinoma article.

Other tumours

Other rare primary malignant liver tumours include:

- Fibrosarcoma.
- Angiosarcoma (associated with occupational exposure to vinyl chloride).[9]
- Leiomyosarcoma.
- Lymphoma.

Further reading

- Kumagi T, Hiasa Y, Hirschfield GM; Hepatocellular carcinoma for the non-specialist. BMJ. 2009 Dec 4;339:b5039. doi: 10.1136/bmj.b5039.
- Selective internal radiation therapy for primary hepatocellular carcinoma; NICE Interventional Procedure Guidance, July 2013

References

1. Liver cancer statistics; Cancer Research UK
2. Forner A, Llovet JM, Bruix J; Hepatocellular carcinoma. Lancet. 2012 Mar 31;379(9822):1245-55. Epub 2012 Feb 20.
3. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up; European Society for Medical Oncology (2018).
4. Bosch FX, Ribes J, Diaz M, et al; Primary liver cancer: worldwide incidence and trends. Gastroenterology. 2004 Nov;127(5 Suppl 1):S5-S16.
5. Ren Z, Ma X, Duan Z, et al; Diagnosis, Therapy, and Prognosis for Hepatocellular Carcinoma. Anal Cell Pathol (Amst). 2020 Feb 3;2020:8157406. doi: 10.1155/2020/8157406. eCollection 2020.
6. Kim E, Viatour P; Hepatocellular carcinoma: old friends and new tricks. Exp Mol Med. 2020 Dec;52(12):1898-1907. doi: 10.1038/s12276-020-00527-1. Epub 2020 Dec 2.
7. Calle EE, Rodriguez C, Walker-Thurmond K, et al; Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003 Apr 24;348(17):1625-38.
8. Bruix J, Llovet JM; Major achievements in hepatocellular carcinoma. Lancet. 2009 Feb 21;373(9664):614-6.
9. Chuang SC, La Vecchia C, Boffetta P; Liver cancer: descriptive epidemiology and risk factors other than HBV and HCV infection. Cancer Lett. 2009 Dec 1;286(1):9-14. Epub 2008 Dec 16.
10. Silva MA, Hegab B, Hyde C, et al; Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. Gut. 2008 Nov;57(11):1592-6. Epub 2008 Jul 31.

11. Chidambaranathan-Reghupaty S, Fisher PB, Sarkar D; Hepatocellular carcinoma (HCC): Epidemiology, etiology and molecular classification. Adv Cancer Res. 2021;149:1-61. doi: 10.1016/bs.acr.2020.10.001. Epub 2020 Nov 28.
12. Renne SL, Sarcognato S, Sacchi D, et al; Hepatocellular carcinoma: a clinical and pathological overview. Pathologica. 2021 Jun;113(3):203-217. doi: 10.32074/1591-951X-295.
13. Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver; NICE interventional procedures guidance. April 2021.
14. Ravaioli M, Ercolani G, Neri F, et al; Liver transplantation for hepatic tumors: a systematic review. World J Gastroenterol. 2014 May 14;20(18):5345-52. doi: 10.3748/wjg.v20.i18.5345.
15. McDermott S, Gervais DA; Radiofrequency ablation of liver tumors. Semin Intervent Radiol. 2013 Mar;30(1):49-55. doi: 10.1055/s-0033-1333653.
16. Weis S, Franke A, Mossner J, et al; Radiofrequency (thermal) ablation versus no intervention or other interventions for hepatocellular carcinoma. Cochrane Database Syst Rev. 2013 Dec 19;12:CD003046. doi: 10.1002/14651858.CD003046.pub3.
17. Radiofrequency ablation of hepatocellular carcinoma; NICE Interventional Procedure Guidance, July 2003
18. Salhab M, Canelo R; An overview of evidence-based management of hepatocellular carcinoma: a meta-analysis. J Cancer Res Ther. 2011 Oct-Dec;7(4):463-75.
19. Microwave ablation of hepatocellular carcinoma; NICE Interventional Procedure Guidance, March 2007
20. Bruix J, Sala M, Llovet JM; Chemoembolization for hepatocellular carcinoma. Gastroenterology. 2004 Nov;127(5 Suppl 1):S179-88.
21. Sorafenib for treating advanced hepatocellular carcinoma; NICE Technology Appraisal Guidance [TA474], September 2017.
22. Selective internal radiation therapy for primary hepatocellular carcinoma; NICE Interventional Procedure Guidance, July 2013
23. Morgan Auld F, Sergi CM; Surgical Pathology Diagnostic Pitfalls of Hepatoblastoma. Int J Surg Pathol. 2022 Aug;30(5):480-491. doi: 10.1177/10668969211070178. Epub 2022 Jan 20.
24. Schnater JM, Kohler SE, Lamers WH, et al; Where do we stand with hepatoblastoma? A review. Cancer. 2003 Aug 15;98(4):668-78.
25. Hishiki T; Current therapeutic strategies for childhood hepatic tumors: surgical and interventional treatments for hepatoblastoma. Int J Clin Oncol. 2013 Dec;18(6):962-8. doi: 10.1007/s10147-013-0625-7. Epub 2013 Oct 17.
26. Murawski M, Weeda VB, Czauderna P; Surgical management in hepatoblastoma: points to take. Pediatr Surg Int. 2023 Jan 12;39(1):81. doi: 10.1007/s00383-022-05356-z.

27. Rougemont AL, McLin VA, Toso C, et al; Adult hepatoblastoma: learning from children. J Hepatol. 2012 Jun;56(6):1392-403. doi: 10.1016/j.jhep.2011.10.028. Epub 2012 Feb 10.

Authored by:	Peer Reviewed by: Dr Krishna Vakharia, MRCGP	
Originally Published: 20/11/2023	Next review date: 24/05/2023	Document ID: doc_2253