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Hepatocellular carcinoma

The most rapidly rising cause of cancer death in Australia

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The mortality rate of primary liver cancer, of which hepatocellular carcinoma is the most common type, has significantly increased over the past few decades, while that of other cancers has been decreasing.

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REMEMBER

- Around the world, hepatocellular carcinoma (HCC), the most common type of primary liver cancer, is the sixth most common cancer and the third most common cause of cancer death. It is the second most common cause of cancer death in men. The majority of cases of HCC in the world occur in the Asia–Pacific region.
- In Australia, the incidence of HCC is rising rapidly, with a 120% increase in incidence between 1991 and 2009. HCC is now the seventh most common cause of cancer death in men in this country, after lung cancer, prostate cancer, bowel cancer, pancreatic cancer, cancer of unknown primary site and melanoma. In Australia, primary liver cancer is the only malignancy to show a significant increase in mortality rate between 1991 and 2010, making it the most rapidly rising cause of cancer death in the country.
- Some 70 to 80% of cases of HCC are associated with chronic liver disease due to hepatitis B or hepatitis C. Cirrhosis of any cause predisposes to HCC, with non-alcoholic fatty liver disease (NAFLD) increasingly being responsible for cases of HCC. Approximately 10% of HCC cases occur in people without cirrhosis, usually in the setting of chronic hepatitis B and possible NAFLD.
- Obesity and type 2 diabetes are independent risk factors for HCC, both in patients with NAFLD and in those with other causes of liver disease (such as chronic viral hepatitis or alcoholic liver disease).
- HCC can be prevented by diagnosing and treating the underlying liver diseases associated with HCC development. Migrants from countries with a high prevalence of viral hepatitis (particularly those from Asia, the Pacific Islands, Africa, Southern Europe and the Middle East), Indigenous Australians and anyone with a risk for bloodborne virus infections should be serologically tested for hepatitis B

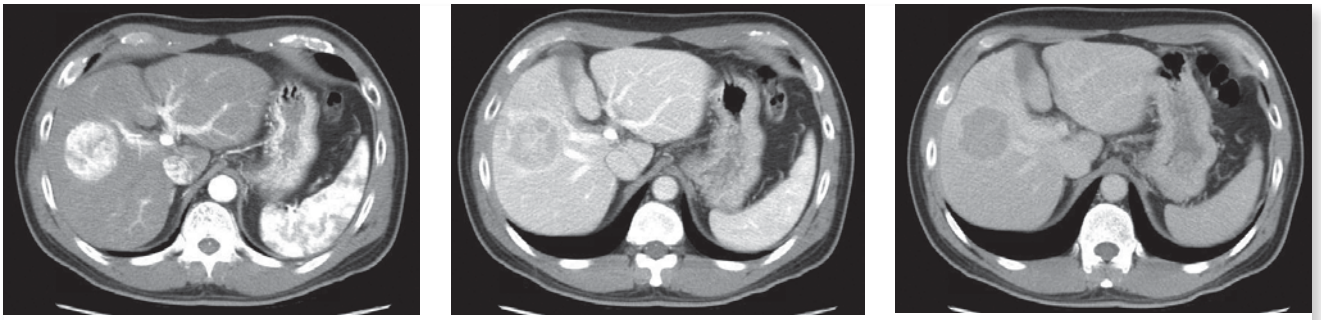

Figure 1. Resectable hepatocellular carcinoma in a patient with chronic hepatitis B treated with entecavir. Characteristic imaging showing enhancement on arterial phase (a, left) and washout on portal and delayed phases (b and c, centre and right respectively).

(HBsAg, anti-HBc, anti-HBs) and hepatitis C (anti-HCV).

- People found to have chronic viral hepatitis should be assessed for antiviral treatment, which can significantly reduce the chance of HCC development. Chronic hepatitis C can be cured in most treated patients using currently available treatments. Antiviral treatment for hepatitis B effectively suppresses viral replication in almost all patients undergoing treatment. Lifestyle interventions tackling excessive alcohol consumption, smoking and obesity may prevent HCC development.
- Early-stage HCC can be diagnosed in those at risk by regular surveillance with six-monthly liver ultrasound scans and serum alpha-fetoprotein (AFP) testing. Early diagnosis significantly increases the chance of undergoing curative treatment.
- International guidelines recommend surveillance for HCC in people with cirrhosis of any cause. It is therefore essential that clinicians identify patients with cirrhosis. Surveillance is also recommended for some people with chronic hepatitis B even in the absence of cirrhosis (i.e. Asian men aged over 40 years, Asian women aged over 50 years, African people aged over 20 years, and those with a family history of HCC). There is no such thing as a 'healthy carrier of hepatitis B'. All HBsAg-positive patients are considered at risk of HCC development.

ASSESSMENT

- All patients at risk for HCC should undergo regular surveillance with six-monthly liver ultrasound scans and serum AFP testing. These are available on Medicare.
- The diagnosis of HCC is usually established with a four-phase contrast CT scan or MRI scan of the abdomen (the latter is not eligible for Medicare rebate). A standard post-contrast CT scan is inadequate for HCC diagnosis. Characteristic imaging features include enhancement (hypervascularity) on arterial phase imaging, with washout (hypovascularity) on portal phase or delayed phase imaging (Figures 1a to c). Liver biopsy is rarely required for confirmation of the diagnosis.
- Prognosis is determined by the stage of the cancer (number and size of lesions and the presence or absence of vascular invasion), as well as the severity of the underlying liver disease (the presence of absence of liver failure).

MANAGEMENT

- Many treatments are available for HCC. Some of these treatments are curative, and others can significantly prolong life expectancy.
- The decision about which treatment is appropriate is determined by the age of the patient, the severity of the underlying liver disease (the presence of liver failure or portal hypertension), the size, number and location of HCC lesions, and the presence of comorbidities.
- Treatment decisions should be made by an experienced multidisciplinary team comprising hepatologists, interventional radiologists and hepatobiliary surgeons as a minimum. A specialist hepatology nurse is indispensable for effective communication with the patient and for co-ordination of their care. Other members of the team may include oncologists, pathologists and social workers.
- Surgical resection is considered in patients without liver failure or portal hypertension. Resection is ideally used for lesions less than 5 cm in maximum dimension but may be limited by tumour location. Surgery in optimal cases is associated with 60 to 70% five-year survival; however, patients must be kept under close surveillance for recurrence or development of new HCC lesions, as 60 to 80% of patients will have another tumour by five years post-resection. Recurrence can be effectively treated if diagnosed early, provided there remains sufficient hepatic reserve.
- Liver transplantation is considered

curative in the treatment of HCC. Patients with a single HCC lesion less than 5 cm in diameter, or up to three lesions all less than 3 cm in diameter, who are unsuitable for surgical resection should be considered for liver transplantation in the absence of a contraindication. Liver transplantation is associated with 80% five-year survival and minimal risk of HCC recurrence when performed in appropriate candidates.

- Patients with disease confined to the liver who are inappropriate for either surgical resection or liver transplantation should be managed with interventional radiology procedures.
- Percutaneous ablation using either radiofrequency or microwave technology is available through major treatment centres, and has survival rates equivalent to surgical resection in small lesions. It usually requires general anaesthesia and overnight admission. Some lesions may be unsuitable for ablation because of location or proximity to adjacent structures.
- Transarterial chemoembolisation (TACE) is the most commonly used procedure in the treatment of HCC. TACE involves the placement of a femoral artery catheter and selective cannulation of the hepatic arterial branch supplying the tumour. A chemotherapy agent is then infused directly into the feeding vessel. TACE usually employs cisplatin or doxorubicin mixed with radio-opaque poppyseed oil (iodised oil) or drug-eluting beads containing doxorubicin. TACE can be used repeatedly if the tumour remains active on follow-up scans or new lesions develop. TACE is usually performed under conscious sedation, with overnight admission. In appropriate individuals, TACE is associated with significantly prolonged survival, although it is rarely curative.
- Patients with advanced HCC with extensive intrahepatic involvement, vascular invasion or metastatic disease are inappropriate for surgical or interventional radiology management. Survival is usually between three and 12 months.
- In patients with advanced HCC and compensated liver disease (Child's A cirrhosis), treatment with sorafenib may reduce the rate of tumour progression and improve survival. Sorafenib is an oral, multikinase inhibitor with antiangiogenic and antiproliferative activity that is TGA-approved and PBS (Authority)-reimbursed for such patients. It is administered as tablets once or twice a day. Sorafenib should be prescribed by experienced clinicians as its use may be associated with significant side effects, including fatigue, skin rash, diarrhoea, hypertension and hand–foot skin reaction (acral erythema). Hand–foot skin reaction, a painful blistering condition affecting hands and feet, can be effectively minimised and managed through patient education and close monitoring. A significant proportion of patients do not benefit from sorafenib; however, no pretreatment predictors of response have been identified.
- There is no effective active treatment for patients with advanced HCC and liver failure. Palliative care management is crucial, and early referral to community or hospital palliative care services can have a major impact on the wellbeing of a patient and their family. Symptomatic management of pain, anorexia and nausea, constipation and fluid retention can all improve the quality of life of the patient.

CONCLUSION

HCC is one of the most common complications of advanced liver disease. Identification and appropriate management of people with chronic viral hepatitis or other liver disease and regular surveillance of those at risk of HCC can increase the chance of effective treatment and significantly improve survival. Late diagnosis is associated with limited treatment options and poor prognosis. MT

FURTHER READING

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COMPTETING INTERESTS: Dr Strasser has received speaker fees from Bayer Health Care.