Abstract  Cirrhosis predisposes to hepatocellular carcinoma (HCC) which develops by sequential steps of de-differentiation of hepatocytes from regenerative nodules via borderline (dysplastic) nodules to frankly malignant HCC. Effective treatment depends on early recognition of HCC, so the key tasks for imaging are firstly recognising the presence of a suspicious lesion, and secondly differentiating between benign, borderline and malignant nodules. Screening of high-risk cirrhotic patients with sonography and measurement of alpha fetoprotein (AFP) is helpful but will not reliably differentiate small HCC from benign or dysplastic nodules. Large HCCs can usually be recognised by their characteristic morphology on imaging, but the appearances of smaller benign and malignant nodules show considerable overlap on unenhanced sonography, CT and MRI. Increasing degrees of histological malignancy are associated with increasing arteriatisation and loss of portal blood supply, so the recognition of HCC requires the use of dynamic imaging with contrast-enhanced CT or T1-weighted MRI with gadolinium enhancement. Sonography with microbubble contrast media now offers another method for detecting arteriised nodules; however, some non-malignant nodules show arterial hypervascularity and a minority of HCCs are hypovascular, so the assessment of perfusion does not conclusively distinguish benign from malignant lesions. Kupffer cell function is another attribute of liver tissue which can be explored using MRI with superparamagnetic iron oxide particles (SPIO). Experience thus far suggests that uptake of SPIO is an effective discriminator between benign and malignant nodules. The combination of SPIO with gadolinium-enhanced MRI offers the opportunity for imaging characterisation of cirrhotic nodules by cellular function as well as by blood supply, and this approach is now proposed as the examination of choice for detecting HCC in cirrhosis.

Keywords  Cirrhosis · Liver · Tumours · Imaging · Hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) in cirrhosis develops by means of a stepwise process of de-differentiation of benign regenerative nodules via dysplastic (borderline) nodules to frank HCC. There is considerable overlap in the imaging appearances of these different types of nodules, but the recognition of HCC is critical because curative treatment depends on early diagnosis. Survival in HCC is directly related to the number, size and extent of lesions at diagnosis. The radiologist needs to be familiar with the evolution of HCC and with the imag-
ing appearances of the different nodular lesions found in cirrhosis.

**Incidence and aetiology**

Hepatocellular carcinoma is the commonest primary malignant tumour of the liver. Worldwide it is thought to result in over one million deaths annually, and the number of cases is continuing to increase. The major risk factor for HCC is cirrhosis. All types of cirrhosis predispose to HCC, but the incidence is particularly high in persistent infection with hepatitis B (HBV) and hepatitis C (HCV), and in alcoholic liver disease. There are major geographic differences in the prevalence of HCC, with up to 50 cases per 100,000 population being found in China, Japan, South East Asia and parts of Africa, whereas the recorded incidence in North America and Europe is <5 per 100,000. Worldwide, the major cause of HCC is HBV infection which is endemic in parts of Africa and in South East Asia where the risk of developing HCC is over 200 times greater in infected patients than in the uninfected population. The incidence of HCC increases with the duration of HBV infection and peaks in the third to fifth decades.

In contrast, the increasing incidence of HCC in the West parallels the marked rise in the number of patients infected by HCV, which has now reached epidemic proportions. Longitudinal studies have shown that the probability of developing HCC once cirrhosis is established is approximately 5–6% per year. Approximately 15–45% of patients with cirrhosis and HCV will develop HCC after 10–15 years of infection with a peak incidence in the fifth and sixth decades.

**Pathology of cirrhotic nodules**

Cirrhosis is a diffuse hepatic parenchymal process which is characterised by fibrosis and nodular regeneration. In the acute stages, liver injury results in cellular necrosis and degeneration, associated with an inflammatory response. After this destructive phase, nodules of regenerative liver parenchyma begin to form, probably driven by growth factors released because of decreased functional liver cell mass [1]. In more advanced disease, different phases of the cirrhotic process occur simultaneously and individual nodules behave independently of each other, so that some will show cellular destruction while others are undergoing regeneration.

Cirrhotic nodules are classified morphologically by their size – in “micronodular” cirrhosis nearly all the nodules are <3 mm, whereas in “macronodular” cirrhosis many nodules are >3 mm. Alcoholic cirrhosis is typically micronodular at first, but nodule size increases with disease progression. Macronodular cirrhosis is most commonly associated with chronic viral hepatitis, but it is occasionally seen with autoimmune and metabolic liver disorders. Hepatocellular carcinoma more commonly arises in macronodular cirrhosis regardless of the underlying aetiology. Both micronodules and macronodules occur in some cases of cirrhosis and may reflect dual aetiologies, particularly viral hepatitis and alcoholic liver disease which frequently co-exist.

The pathogenesis of HCC in cirrhosis is a multistep de-differentiation process which progresses from regenerative nodule (RN) via dysplastic or borderline nodule (DN) to HCC [2]. It is important to recognise that this process produces a continuous spectrum of abnormality, so there is considerable overlap in the imaging and histological characteristics of cirrhotic nodules. Nevertheless, it is important to distinguish benign from pre-malignant or malignant lesions because early liver transplantation provides the only opportunity for cure in patients with both HCC and cirrhosis [3].

**Regenerative nodules**

Regenerative nodules develop as part of the repair process following hepatocyte injury. Histologically, they comprise a local proliferation of hepatocytes surrounded by fibrous septa. Portal tracts are absent at first, but as the nodules enlarge, solitary or multiple portal tracts appear. Their blood supply is similar to that of normal liver – mainly from the portal vein with a small arterial contribution [4]. Haemosiderin deposition, which is fairly common in RNs, produces specific imaging features on MR; whether it increases the risk of developing HCC is controversial [5, 6].

**Dysplastic nodules**

Dysplastic (borderline) nodules are RNs which contain atypical cells without definite histological features of malignancy [1]. They are present in 15–25% of cirrhotic livers at the time of transplantation [7, 8]. The DN, which may be further classified as low grade or high grade depending on the severity of atypia, represent an intermediate step in the pathogenesis of HCC, and malignant transformation within a DN has been seen in as little as 4 months [9]. High-grade DNs may contain a focus of HCC leading to the “nodule within a nodule” appearance on imaging. The DNs are usually larger than RNs, but the two may be impossible to distinguish pathologically [1]. Reticulin staining is helpful because the distribution of reticulin is normal in regenerative nodules and becomes increasingly sparse and irregular in DNs through to HCCs. Compared with RNs, DNs have more unpaired arteries (isolated arteries not accompanied by bile ducts which are indicative of neoplastic angio-