Hepatocellular Carcinoma ranks fifth in frequency in cancer in the world and is the most common liver cancer [1]. The peak age of incidence is during the sixth and eighth decades. There is a 4:1 male predominance. The incidence of HCC in the United States has increased during the past two decades, from 1.4 per million in 1976–1980 to 2.4 per million in 1991–1995 [2]. It is estimated that by 2010, HCC will have exceeded lung cancer as the foremost cause of cancer mortality [1]. This article will review the epidemiology, clinical presentation, staging, pathology, laboratory findings, radiology and treatment of HCC.

Epidemiology
Worldwide, HCC is the third most common cause of cancer-related death; the most common cause of HCC is hepatitis B infection. Most of the cases [3] are found in Asia. There has been an increase in HCC in the USA, which can be attributed to the increased rate of hepatitis C virus infection and the improved clinical management of patients with cirrhosis. The main risk factors for the development of HCC include hepatitis B virus infection, alcoholic liver disease, tyrosinemia and hemochromatosis. Additional risk factors include excessive androgens, α₁-antitrypsin deficiency, and exposure to aflatoxins, thorotrast, oral contraceptives, and vinyl chloride [2,4].

Clinical presentation
The development of HCC is usually silent in nature and may go undiagnosed. On physical examination an enlarged liver with a hard palpable surface may be detected. In advanced cirrhosis, the liver may appear to be small and shrunken. Paraneoplastic manifestations include hypercalcemia, hypoglycemia, feminization, polycythemia, and watery diarrhea. Common symptoms include abdominal pain, fatigue and weight loss. In advanced disease, there is loss of hepatic synthetic function that may lead to hepatic encephalopathy. Portal hypertension is sometimes accompanied by ascites and variceal bleeding. Tumor invasion into the main portal vein can also result in splenomegaly and ascites. In the setting of inflammation or tumoral complications such as hemorrhage and necrosis, right upper quadrant pain may be present. An enlarging mass compressing the adjacent extrahepatic biliary structure can lead to painless obstructive jaundice or cholangitis.

Staging
Evaluation and treatment of patients with HCC is dependent on accurate staging. Several classification systems exist: CLIP (Cancer of the Liver Italian Program), BCLC (Barcelona Clinic Liver Cancer), and JIS (Japan Integrated Staging). Tables 1 and 2 present the latest tumor staging by the American Joint Commission of Cancer.

Pathology
The development of HCC from premalignant lesions occurs in stages. The regenerative nodules may evolve into dysplastic nodules (low and high grade). These may subsequently develop...
into early HCC, and if left untreated may become advanced carcinomas. The gross pathology of HCC is a direct reflection of the imaging findings. HCC may appear as a single mass or as multifocal nodules of variable sizes, and sometimes can be diffusely infiltrative. Macroscopically, small HCC of at least 2 cm in diameter are divided into two types: distinctly nodular and indistinctly nodular [6]. In the gross specimen, the tumor is usually paler than normal liver parenchyma. The vascular supply in early HCC is distinct from that in advanced HCC. The early tumor will have a blood supply from the portal vein as well as from the hepatic artery [6]. As the tumor evolves the blood supply is mostly arterial with minimal portal supply. Microscopically, tumors range from well-differentiated to highly anaplastic. The most common histologic pattern is the trabecular pattern. The scirrhous type is the least common pattern [6].

**Laboratory findings**

Alpha-fetoprotein, although not a specific or sensitive marker for HCC, is elevated in approximately half the cases of HCC [7]. AFP is produced in large amounts by the fetal liver, but its expression declines sharply at birth. Elevated AFP is reported in yolk sac tumors, cirrhosis, massive liver necrosis, chronic hepatitis, pregnancy, fetal distress, and fetal neural tube defects [7]. AFP can be used as an unfavorable prognostic marker in patients with HCC [7]. Other tumor markers with less sensitivity include des-gamma-carboxyprothrombin, α-L and isoenzymes of γ-glutamyl transferase [7]. Gamma-catenin proteins may be present among the AFP-negative liver tumors [6].

**Radiology**

**Computed tomography**

CT is the most commonly used imaging modality to diagnose HCC in the United States. On unenhanced CT, HCC appears hypodense, except in diffuse hepatic steatosis where it may appear denser relative to the lower attenuation of the liver parenchyma. In some instances, increased attenuation within the HCC may be due to hemorrhage or calcifications, whereas fatty metamorphosis of HCC will appear as areas of low attenuation.

CT evaluation of the liver in a patient with a clinical suspicion of HCC is performed at two dynamic stages of contrast enhancement: late arterial at approximately 33 seconds following the administration of intravenous contrast, and a portal venous sequence is utilized before and after administration of the SPIO. Their effect is due to susceptibility changes. A T2* sequence is utilized before and after administration of the SPIO.

The imaging protocol for the MRI evaluation of HCC includes a thin-section imaging and permits three-dimensional reconstruction. Newer generation scanners offer the advantages of fast scanning with thin-section imaging and permits three-dimensional reconstruction for preoperative vascular mapping.

**Magnetic resonance imaging**

The imaging protocol for the MRI evaluation of HCC includes a combination of T1-weighted images, T2-weighted images with fat suppression, and dynamic contrast-enhanced 3D gradient-echo sequences of the liver. The T1 technique is a breath-hold gradient echo sequence with an in-phase time to echo of 4.1 msec at a 1.5 T field-strength magnet. HCC may demonstrate a high signal on T1-weighted images due to fat, protein or copper content. Typically it is hypointense-isointense to the liver. The T2-weighted sequence is a fast-suppressed fast-spin echo obtained at TE ranges (60–80 msec). Similar to CT, a dynamic contrast-enhanced sequence is essential for lesion detection [11].

For liver imaging, contrast agents can be divided into liver-specific and liver-non-specific contrast agents. The liver-specific agents include reticuloendothelial-specific contrast agents (super-paramagnetic iron oxide) such as ferumoxides and ferucarbotran [11]. These agents are iron-containing molecules that are taken up by the reticuloendothelial system, namely Kupfer cells in the liver. Their effect is due to susceptibility changes. A T2* sequence is utilized before and after administration of the SPIO. This sequence is a gradient echo sequence with TE/TR = 16/100 msec and a 30 degree flip angle. The longer TE enhances the

AFP = alpha-fetoprotein
TE = time to echo
SPIO = super-paramagnetic iron oxide

TR = repetition time
susceptibility effects of the SPIO. Small cysts, hemangiomas and metastases will not demonstrate uptake and will appear with a high signal relative to the liver [12]. Most well-differentiated HCC will demonstrate uptake of contrast due to their Kupfer cell content. Feridex® (Ferumoxides Berlex Laboratories, Montville, NJ), an SPIO, is used in our institution.

The non-liver-specific contrast agents are gadolinium-chelates, such as Gd-DTPA (Magnevist Schering AG, Germany). Three phases of contrast enhancement are used in MRI (20 sec, 50 sec, 90 sec). Sometimes the first phase of enhancement may be the only phase in which a tumor can be seen. The fibrous capsule shows low signal intensity on both the T1-weighted and T2-weighted images. This capsule will enhance on delayed contrast-enhanced images. MRI can detect the invasion of tumor into the adjacent veins (hepatic and portal vein) or the biliary system.

Double-contrast MR imaging, i.e., the use of gadolinium in conjunction with SPIO is considered significantly more accurate than only SPIO-enhanced MR imaging in identifying hepatocellular carcinoma [11]. Magnetic resonance imaging of the liver can identify the number and size of lesions. Post-Gd images can evaluate the degree of vascular and biliary involvement. MRI also plays an important role in tumor surveillance: the detection of enhancement on the earlier phases of contrast administration and washout in the delayed-phase administration are confirmatory of recurrent or residual tumor. In image guide intervention MRI may also be useful.

Summary

Hepatocellular carcinoma will continue to be one of the most common malignancies worldwide. Improved survival occurs following resection or liver transplantation. The appropriate preoperative stratification and staging of these patients is essential. CT and MRI will undoubtedly continue to play a major role in the detection and diagnosis of HCC. These imaging techniques should be optimized for the evaluation of suspected HCC. The radiology report from the CT or MRI examination should include a comprehensive review of key diagnostic information for appropriate staging. This includes lesion size and number. Also to be noted are segmental and vascular involvement, regional and distant adenopathy as well as metastases, and finally, the presence of ascites, varices and cirrhosis.

References


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Capsule

Human multidrug resistance 1 (MDR1) gene

The 20 common amino acids in proteins are represented in the genome by a triplet code of four DNA bases giving a total of 64 (43) different codons, with the majority of amino acids being encoded by more than one codon. Different synonymous codons affect RNA structure and stability and also affect protein translation rates. In bacteria, they are also known to affect protein folding. Can they have a similar effect in eukaryotes? Kimchi-Sarfaty et al. studied the human multidrug resistance 1 (MDR1) gene and show that a relatively common single nucleotide polymorphism – which changes ATC for ATT (both isoleucine), in combination with two other polymorphisms – causes a change in the conformation of the protein and also underlies its altered drug and inhibitor interactions.

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