

Section 2

Clinical disease evaluation

Diagnosis A: Radiology

Ultrasound abdominal scanning is used widely for screening, as it is inexpensive and available in most countries. More definitive evaluation is then often needed for diagnosis, after a suspicious liver nodule is found on screening ultrasound, and is provided by a computed tomography (CT) or magnetic resonance imaging (MRI) scan. To a large extent the choice in the USA depends on the interest and expertise in a given institution. Recently introduced new MRI imaging agents have made this modality excellent for characterization of small lesions, especially those <1.5 cm diameter. These agents include super-paramagnetic iron oxide particles, which are taken up by Kupffer cells, and Gd-EOB-DTPA (gadolinium), which is taken up by hepatocytes, provides dynamic and liver-specific MRI images and is highly liver-specific. Hepatocellular carcinoma (HCC) diagnosis is frequently established by imaging criteria alone, based on the CT or MRI contrast enhancement pattern, with an intense contrast dye uptake by the suspected liver mass in the arterial phase followed by contrast washout in the venous, delayed phase. Many authorities in the field have recommended diagnosis on the scan alone if it has characteristic HCC appearances, without the need for biopsy, which is unlike the practice in all other cancers. This recommendation is based on the safety, sensitivity, and specificity of scans in HCCs ≥ 1.5 cm diameter, especially with “typical features” as well as the low, but present possibility of side effects from biopsy. Of course, atypical vascular lesions have always required biopsy. However, the increasing use of molecular markers (signatures) in oncology is likely to oblige a return to routine biopsy, as these molecular tools require tissue and are becoming mainstream clinical practice for many tumor types. Routinely on a first clinic evaluation, a chest CT is also performed to rule out the presence of lung metastases.

Summary for patients, families, and caregivers

Diagnosis for HCC begins by scanning a patient with imaging tests. For patients with possible HCC, an ultrasound scan of the abdomen is often used for screening. If the physician finds something suspicious on the ultrasound scan, a computed tomography (CT) or a magnetic resonance imaging (MRI) scan can be used to get a more definitive diagnosis. CT scans are also used to check if the cancer has spread to the lungs. A biopsy may be performed as well if the physician finds unusual lesions on the scans.

Further reading

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Diagnosis B: Blood tests, tumor markers

While alpha-fetoprotein (AFP) is frequently used, inexpensive and is a simple blood test to use, it is elevated in only 50% of patients with HCC. AFP is not too sensitive a marker for screening for small, new HCCs (see page 10), but is extremely useful when following the response of an individual patient to therapy or to see if therapy fails. It is also beneficial when used after surgery, resection, or ablation for tracking the possibility of recurrence.

Recently, more HCC-specific tests have come into general clinical practice, such as a glycosylated form of AFP (itself, a fetal form of albumin) called AFP-L3 as well as des-gamma carboxy prothrombin (DCP). US Food and Drug Administration (FDA)-approved kits for measuring both AFP-L3 and DCP are readily available to physicians. Several studies have shown that elevated DCP is common in the presence of portal vein thrombosis (PVT). The molecule is really interesting, as it is an immature form of the coagulation protein, prothrombin. The enzyme responsible for catalyzing the immature to the mature form of prothrombin has an absolute requirement for vitamin K. This highlights an important role for vitamin K in HCC development.

Newer hepatocellular carcinoma tumor markers, proteomics, circulating tumor cells, and circulating DNA

Several new tumor markers are currently being evaluated, but do not yet have a place in routine clinical care. Tumor and liver molecular profiles or signatures were mentioned in the biology section of this book (see page 11). They have entered routine clinical practice for both prognosis and medical therapy selection for colorectal cancer, bronchogenic carcinoma, and melanoma, and are only at the validation stage for HCC. Unlike several other cancers for which single molecular markers are used, it seems that HCC may require a combination of markers or a molecular “signature”.

The recent identification of HCC stem or progenitor cells and their characteristics, including epithelial cell adhesion molecule, cluster of differentiation 133, and cluster of differentiation 90 among others, offer the possibility of identifying specific HCC phenotypes and of targeting the stem cells for therapy. Keratin 19 has also been proposed as an invasive stem-cell marker.

Circulating tumor cells have recently been found in the blood of patients with different tumor types, including HCC, and are a valuable source for molecular genomics and proteomics analyses, without the need for a tumor biopsy to provide the material for this information. This is similarly true for circulating DNA. Newer markers that are currently being evaluated include miRNAs that are thought to be important in controlling cell behavior as well as newly studied serum proteins, including Glypican 3, angiopoietin 2, and vascular endothelial growth factor.

The importance of the microenvironment in HCC (see pages 14–15) has led to proposals that simple blood test estimates of inflammation are important patient prognosticators.

Summary for patients, families, and caregivers

Blood tests may be used to help detect HCC before or after surgery. Blood tests can also determine if therapy is working. Some blood tests for HCC include: alpha-fetoprotein (AFP) test, AFP-L3 test, and des-gamma carboxy prothrombin test.

Tumor markers are substances that can be found in the body that can indicate if a patient has cancer. For HCC, a combination of markers may be needed for a diagnosis. Researchers are still studying tumor markers to help healthcare teams diagnose HCC.

Further reading

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Diagnosis C: Biopsy – a debate

An HCC diagnosis is frequently made with considerable confidence based on the imaging characteristics alone of an arterial phase enhancing (vascular) mass with venous phase washout on CT or MRI scan. However, the standard of oncology care, especially for entry to clinical trials, usually requires the certainty of diagnosis that only a biopsy can provide. Furthermore, in this new age of proteomics for prognostication and treatment selection, a sample of tissue is usually required. Biopsy is a safe procedure in experienced hands, especially in the absence of ascites and where the tumor nodule is not in contact with an intrahepatic vessel. The benefits are certain diagnosis, especially when the radiological characteristics are not typical for HCC or the AFP levels are low. Risks include a slight risk of bleeding and the possibility of the tumor “seeding” into the biopsy needle track. This author’s experience has shown a tumor seeding rate of 1%, and other reports show a tumor seeding rate of <5%. By not doing a biopsy, there is a risk of not having a correct diagnosis and then proceeding with potentially toxic or invasive therapy unnecessarily. Thus, with borderline cases based on clinical and radiological features, biopsy is needed. This whole argument may become moot if histological features or tissue becomes necessary for proteomics or genomics guidance for treatment choice, or if assay of circulating tumor cells becomes routine.

Summary for patients, families, and caregivers

A biopsy of HCC involves the removal of a small piece of liver tissue by a needle placed into the liver through the skin. It is a safe procedure and can confirm that cancer is present when other diagnostic test results were not conclusive. However, there is a small risk of bleeding and a very small chance that cancer cells may spread where the biopsy sample was taken. As always in medicine, the risk of a side effect has to be balanced by the risk of unneeded treatment due to a wrong diagnosis.

Further reading

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Assessment of tumor extent for treatment planning: staging classifications

Functional hepatic reserve, Child-Pugh classification

As previously discussed, patients are grouped by definition into three categories of liver damage severity (A, B, or C), according to the Child-Pugh (CP) classification cirrhosis score (see Table 3). A patient classified as CP A has essentially normal liver function and can receive almost any therapy without extra risk resulting from their liver disease. They typically have a 100% 12-month survival, without HCC or any treatment. Patients who are classified as CP C have poor liver function and can only receive liver transplant. Without transplant, their survival is typically 40% at 12 months, with or without HCC. Patients with a CP B score are a heterogeneous group. At one end, they approach CP C and need great caution in being given therapies. At the other end, they can have quite good liver function and can tolerate many medical therapies, some ablative therapies, and minor resection. They typically have a 60% 12-month survival, without HCC and without treatment. As shown in Figure 4 (page 13), patients can have varied liver disease severity and tumor characteristics across the classification spectrum.

Integrated tumor and liver function staging

Several classification systems have been proposed that integrate both liver prognostic features and HCC characteristics. At this time, two systems are widely used in Europe and the USA, and one in Japan. In Europe, both the Cancer of the Liver Italian Program (CLIP) score and the Barcelona Clinic Liver Cancer (BCLC) system are commonly used; in Japan, the Japan Integrated Staging (JIS) score has received consensus recognition. Other scoring systems have been proposed from Japan, France, Hong Kong, and elsewhere, but they all share the features of integrating both adverse liver and adverse tumor characteristics. Thus, they all incorporate CP liver function features, as well as tumor size and number and presence of PVT. Their purpose is two-fold, namely prognosis and treatment selection. In summary, adverse prognostic factors are:

- A. Tumor factors: large size, multiple tumor nodules, diffuse tumor, presence of PVT, high blood AFP levels, presence of metastases.
- B. Liver factors: high blood bilirubin, aspartate aminotransferase/alanine transaminase, gamma-glutamyl transpeptidase levels; low blood albumin and low platelet levels (the latter a reflection of severity of cirrhosis) and presence of more than minimal ascites.
- C. However, in addition, good prognosis macroenvironmental factors include being female, age >75 years, and especially the combination of both.
- D. Recently, indices of inflammation have been recognized and accepted as important prognostic markers. The most prominent of these is the C-reactive protein and albumin protein blood test (Glasgow Prognostic Score).

Summary for patients, families, and caregivers

To choose the right treatment for a patient, the healthcare team must know the severity of the patient's liver disease. Healthcare teams use the Child-Pugh score to determine the severity of the patient's liver disease. This score consists of three categories of liver damage: A, B, and C:

- Patients with a **Child-Pugh A** score have almost normal liver function. They can receive almost any type of treatment.
- Patients with a **Child-Pugh B** score are treated depending how close they are to a Child-Pugh A or C score.
- Patients with a **Child-Pugh C** score have very poor liver function. They almost always require a liver transplant.

Additionally, comprehensive classification systems combine an assessment of the Child-Pugh score, liver factors, gender, age, tumor size and how far the tumor has spread throughout the body. The combined assessments can help determine possible treatment approaches and how a patient's disease might develop.

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The new patient assessment

The following section will review the clinical evaluation and examination of a new patient with possible HCC. Tables 6 and 7 summarize the clinical presentation, symptoms, and evaluation discussed further in this section.

Medical history and physical examination

The history is important in evaluating putative predisposing factors, including a history of hepatitis or jaundice, blood transfusion, or use of intravenous drugs. A family history of HCC or hepatitis should be sought and a detailed social history taken to include job descriptions for industrial exposure to possible carcinogenic compounds. Physical examination should include assessing stigmata of underlying liver disease, such as jaundice (seen as yellowness in the sclera or white part of the eyes), ascites (abdominal fluid), peripheral edema (leg swelling), spider nevi, palmar erythema (hand redness), and weight loss. Evaluation of the abdomen for hepatic size, masses or ascites, hepatic nodularity and tenderness, and splenomegaly is needed, as is assessment of overall performance status and psychosocial evaluation (Table 6). Basic physical exam includes pulse and blood pressure, and an assessment of whether the patient is clinically sick. Family support evaluation is important at this stage, especially if liver transplantation is being considered.

Blood tests

Blood tests typically include (Table 7):

1. Complete blood count, including hemoglobin, white cell count and platelet count, and prothrombin time (a test for blood coagulation ability).
2. Liver function tests: total bilirubin, albumin, gamma-glutamyl transpeptidase, alkaline phosphatase (ALKP), and the transaminases aspartate aminotransferase and alanine transaminase (serum glutamic oxaloacetic transaminase and serum glutamic-pyruvic transaminase), and cholesterol and serum iron levels.
3. Renal function tests: urea and creatinine.
4. HCC tumor markers: AFP, AFP-L3, and DCP.
5. Measurement of hepatitis C and B serology. If either is positive, more detailed virological measurements and body immune response measurements will need to be obtained.

Radiology

CT or MRI scan should be performed to obtain baseline, pre-therapy assessment of tumor maximum dimensions, tumor number, and location within the liver as well as proximity to main vessels, which will influence ablation approach. The radiology also permits identification of the presence of portal vein invasion or PVT, a major negative prognostic factor, and may allow discernment of the presence of cirrhosis if cirrhotic nodularity can be seen as well as of ascites.

Summary for patients, families, and caregivers

A person's medical history can provide important clues as to whether they are at risk for HCC. During a new patient assessment, the healthcare team may ask about the patient's social life and family history of cancer and liver diseases. They may also ask about the patient's work environment to see if they have been in contact with harmful chemicals at work. The healthcare team will perform a physical exam to record their basic health, check for swelling of the abdomen, look for yellow skin or eyes, and other characteristics that are signs of possible liver disease. They will also ask for blood tests and imaging tests. If a liver transplant might be needed in the future, the healthcare team may also see if the patient has support from their families.

| Symptom | % of patients |
|---|---------------|
| No symptom | 30 |
| Abdominal pain | 40 |
| Routine physical examination finding, abnormal liver blood tests | 24 |
| Weight loss | 20 |
| Cirrhosis symptoms (ankle swelling, abdominal bloating, increased girth-fluid or liver, pruritus, gastrointestinal bleed) | 20 |
| Appetite loss | 11 |
| Other (evaluation of anemia and various diseases) | 12 |
| Routine CT scan screening of known cirrhosis | 17 |
| Weakness/malaise | 15 |
| Jaundice and itching | 5 |
| Jaundice | 5 |
| Tumor rupture (mainly in Africa) | 1 |

Table 6 Clinical presentation and symptoms. CT, computed tomography scan. Adapted from © McGraw-Hill Global Education Holdings, LLC, 2014; Carr BI. Chapter 92. Tumors of the Liver and Biliary Tree. In: Longo DL, Fauci AS, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine*. 18th edition. New York, NY: The McGraw-Hill Companies, Inc; 2012.

| | |
|---|---|
| 1 | Blood tests: full blood count (splenomegaly), liver function tests, ammonia levels, electrolytes, AFP and DCP (PIVKA-2), Ca ²⁺ and Mg ²⁺ ; hepatitis B, C, and D serology (and quantitative HBV DNA or HCV RNA if either is positive); neurotensin (specific for fibrolamellar HCC) |
| 2 | Triphasic dynamic helical (spiral) CT scan of liver (or MRI scan); chest CT scan; upper and lower gastrointestinal endoscopy (for varices, bleeding, ulcers); and brain scan (only if symptoms suggest) |
| 3 | Core biopsy: of the tumor and separate biopsy of the underlying liver |

Table 7 Clinical evaluation. AFP, alpha fetoprotein; CT, computed tomography scan; DCP, des-gamma carboxy prothrombin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MRI, magnetic resonance imaging scan. Adapted from © McGraw-Hill Global Education Holdings, LLC, 2014; Carr BI. Chapter 92. Tumors of the Liver and Biliary Tree. In: Longo DL, Fauci AS, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine*. 18th edition. New York, NY: The McGraw-Hill Companies, Inc; 2012.

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