



Pathophysiology

Liver Cancer

Hepatocellular carcinoma (HCC), also known as malignant hepatoma, is the most common primary malignancy of the liver. HCC arises from hepatocytes, the parenchymal cells of the liver. Cholangiocarcinoma, a malignant neoplasm of the bile ducts, is the next most common primary liver tumor. Although there are other forms of primary liver cancer, HCC accounts for the overwhelming majority of primary disease [1].

Worldwide, primary HCC is the fifth most common solid organ malignancy resulting in more than 700,000 deaths each year. While all other cancer occurrences have held steady or slowly declined, HCC is the only cancer with an increased prevalence and incidence [2–4]. In 2010, the annual incidence of HCC in the United States was at least 6 per 100,000, with two to four times greater incidence in men than women [5].

The majority of people who develop HCC are asymptomatic from the cancer itself. Many will exhibit nonspecific signs and symptoms of cirrhosis or liver dysfunction including jaundice, ascites, and coagulopathy. Tumor size, stretching of the liver capsule or even tumor rupture, can occasionally result in right upper quadrant pain.

Risk factors for HCC include cirrhosis, viral hepatitis (particularly hepatitis B in Asia and C in the United States), and alcohol and nonalcoholic steatohepatitis (NASH). In the United States, alcoholic cirrhosis is a major cause, although NASH's role is becoming increasingly predominant [6]. Other rare and uncommon risk factors include autoimmune disorders such as autoimmune hepatitis and metabolic diseases such as hemochromatosis, alpha-1-antitrypsin deficiency, glycogen storage diseases, Wilson's disease, and certain porphyria.

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Liver Metastases

Other than lymph nodes, the liver is the most common site for metastatic disease from gastrointestinal (GI) malignancies. The GI tract's venous drainage to the portal vein, which constitutes the major blood supply to the normal liver, is the likely explanation of this metastatic pattern. Colorectal cancer (CRC) is the most common source of liver metastases; however, other gastrointestinal primaries, e.g., the stomach, pancreas, and neuroendocrine, are common. With appropriate selection criteria, liver metastases can also be treated with ablation.

Liver Cysts

In addition to malignant lesions, benign hepatic simple cysts can also be treated with ablation. Hepatic cysts usually refer to nonparasitic cysts of the liver. Their cause is unknown and they may be congenital in origin. The cysts are lined by epithelium, which secretes plasma-like fluid. Asymptomatic cysts require no treatment. However, some cysts can become quite large and cause pressure symptoms such as pain that may warrant treatment. Liver ablation or sclerosis is a minimally invasive option for treating symptomatic cysts.

Clinical Indication

In regard to HCC, patients should have a diagnosis confirmed on imaging prior to planning treatment. Ultrasound can be used to screen for HCC; however, suspicious lesions should be further evaluated and confirmed with cross-sectional imaging. Triple-phase CT or MRI of the liver can usually establish the diagnosis and determine the location, size, number of lesions, and overall extent of disease without need for tissue sampling. There are multiple image-based diagnostic systems for HCC, including the Liver Imaging Reporting and Data System (LI-RADS), United Network for

Organ Sharing and Organ Procurement and Transplantation Network (UNOS-OPTN), and the American Association for the Study of Liver Diseases (AASLD) (refer to Chap. 34 for LI-RADS system staging). The decision of what system to use is based on institutional preference. These systems rely on the fact that HCC has a characteristic appearance on cross-sectional imaging because the tumor predominantly has an arterial supply, while the normal liver is primarily supplied by the portal vein. HCC typically has dynamic arterial enhancement with washout of contrast on delayed phases and a characteristic pseudo-capsule compared to the surrounding liver parenchyma.

Treatment algorithms for HCC are often difficult as the field is rapidly changing with new techniques and indications for different treatment options. A dominant treatment algorithm is the Barcelona Clinic Liver Cancer (BCLC) staging system, which takes into account clinical factors such as patient's performance status, tumor size, and comorbidities (refer to Chap. 34 for more information) [7].

Conventional Therapy

Liver Cancer

Therapeutic options for HCC vary according to disease stage, functional status, and clinical condition but can be divided into two main categories: curative and palliative. Unfortunately, less than 30% of patients are eligible for curative therapies at the time of diagnosis. Curative therapies include surgical resection, ablation, and liver transplantation. Palliative options consist of trans-arterial chemoembolization, radioembolization, targeted therapies, and radiation. Cytotoxic chemotherapy has a limited role in the treatment of HCC due to underlying hepatic dysfunction and HCC's chemoresistance properties [8–10].

Candidates for surgical resection typically have no evidence of vascular invasion and will be able to maintain adequate liver reserve post-resection. There is no strict size cutoff for resectability. Some physicians use a range of 3–5 cm as a cutoff, although it often depends on anatomic constraints and the performing surgeon. For lesions that are resectable, 5-year survival rate range anywhere from 30% to 90% [11, 12]. A comprehensive meta-analysis has shown that surgical resection is superior to radiofrequency ablation or percutaneous ethanol injection for treatment of early-stage HCC, with both higher recurrence-free survival rate and longer survival [13]. Overall, surgical resection is often limited due to tumor extent and/or underlying liver dysfunction. Complications from surgery may include hepatic vascular injury, bile leak, or liver failure. Tumor rupture and peritoneal seeding are serious albeit rare complications. Patients with cirrhosis have a higher perioperative mortality rate compared to non-cirrhotic patients undergoing resection.

Key Point

Milan criteria is used to select patients for transplantation:

- One lesion up to 5 cm or up to 3 lesions each <3 cm
- No extrahepatic involvement
- No vascular involvement

Liver transplantation is the only truly curative therapy for HCC. The Milan criteria for transplant candidates include either a solitary lesion <5 cm or up to three lesions measuring <3 cm, without evidence of vascular or extrahepatic involvement. Patients who undergo liver transplantation are typically managed with immunosuppressive drugs. When appropriately selected, transplant patients can have survival rates almost comparable to surgical resection and comparable to those who undergo transplantation for nonmalignant disease [14, 15]. A major limitation to transplantation is the shortage of organs. In the United States, the allocation for livers is based on the Model for End-Stage Liver Disease (MELD) score, with sicker patients having higher scores. While on the waiting list, some patient's tumor burden may progress; this may exclude them from qualifying for a transplant. Patients can be bridged with other forms of treatment to maintain their eligibility. In addition to the surgical risk, transplant-related risks include transplant rejection, immunosuppression, vascular injury, and tumor recurrence in the transplant.

Key Point

The MELD score takes into account creatinine, bilirubin, and INR.

Once in advanced stage (BCLC-C), sorafenib, an FDA-approved VEGF inhibitor, has shown improved overall survival by approximately 2–3 months in prospective randomized trials with notable toxicities such as hand-foot skin reaction, hypertension, and proteinuria [16–18]. Combining sorafenib with locoregional therapies has not demonstrated significant survival improvement [19]. Rare but serious side effects include cardiac-related events, such as myocardial infarction. Regorafenib, an oral multikinase inhibitor, was shown in the RESORCE trial to significantly improve survival in patients with advanced HCC who failed sorafenib [20]. Nivolumab, a fully human IgG4 monoclonal antibody to the programmed death-1 (PD-1) receptor that functions as a cell-cycle checkpoint inhibitor, was shown in

preliminary reports to have sustained objective response in patients with advanced HCC who had failed sorafenib in the CheckMate-040 trial [21]. Preliminary survival data was encouraging as well. FDA approval is expected for both regorafenib and nivolumab in 2017 [20, 22].

Liver Metastases

Although there are different guidelines, surgical resection remains the best therapeutic option for overall survival of liver metastases. For patients deemed unresectable, therapeutic options include systemic chemotherapy or locoregional therapies including ablation. Guidelines for treatments vary for different cancers, but in general, patients are more likely to meet criteria for surgical or interventional therapy if they have focal disease, smaller lesions, unilobar involvement and are without evidence of vascular involvement or distant metastases.

Liver Cysts

When symptomatic, hepatic cysts can be treated surgically or percutaneously with ablation/sclerosis. Simple aspiration is usually inadequate with nearly 100% recurrence rate as the epithelial lining continues to secrete fluid into the cyst. Surgical treatment involves “unroofing” of the cyst, which removes a portion of the wall that extends to the liver surface. Any further fluid from the cyst should then enter the abdomen where it can be absorbed. While historically this procedure was performed via laparotomy, with advances in technique, it can now be performed laparoscopically [23]. Other than pain and scarring, complication rates are low but can include trocar-site infection, bile leak, and bile ascites when the cyst is in close approximation with a bile duct.

Interventional Therapy

Locoregional liver-directed therapies include trans-arterial chemoembolization (TACE), radioembolization (TARE), and percutaneous thermal or alcohol ablation with the former constituting the majority of ablations (refer to Chaps. 34 and 35 for information on TACE and TARE, respectively). Ablative therapy can be done as a standalone treatment but may also be combined with trans-arterial or systemic treatment. Thermal ablations include radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation. Nonthermal ablation is performed with percutaneous ethanol injection (PEI). Ablative therapies may be offered for HCC and liver metastasis.

Radiofrequency ablation (RFA) consists of a generator creating high-frequency rapidly alternating electrical cur-

rents emitted through a needle inserted into the targeted tissue. The alternating electrical currents agitate ions, resulting in friction and subsequent heating of the tissue. The ablation zone is comprised of the tumor and a safety margin of 0.5–1 cm around the lesion. Additionally, a few millimeters of healthy tissue between the tumor and surrounding vasculature is required to avoid injury. Of note, RFA and other thermal ablations can be influenced by a heat-sink effect where the nearby blood flow mitigates and dampens the therapeutic heating resulting in an inadequate ablation. Ablation can be repeated for multiple lesions and can serve as a bridge to other therapies, such as transplantation. RFA is typically used for patients with small or early HCC’s, usually less than 3 cm. For metastatic lesions, up to three lesions each measuring less than 3 cm is preferred as larger or more numerable lesions have a higher rate of recurrence. The lesion should be accessible and ideally away from vital structures such as large vessels or other organs. The most common complications are related to abdominal bleeding and abdominal infection, with each occurring less than 2% [24, 25]. Studies have shown that having previous biliary intervention places the patient at increased risk of developing hepatic abscesses. Prophylactic antibiotics are still controversial but are recommended in high-risk cases with prior biliary intervention [26]. Fluoroquinolones can be used, but regimens and recommendations may differ. Other complications include injury to the bile ducts (1%) and pneumothorax. Risk of mortality is extremely low (0.15%), making RFA a good alternative to surgical resection in patients who are considered high operative risks. The recurrence rates can be low as 5% in the first 20 months [27, 28].

Key Point

Heat-sink effect = inadequate ablation due to nearby blood vessels mitigating and dampening therapeutic heating.

Microwave ablation (MWA) is very similar to RFA in terms of indications, procedural technique, and complications. However, MWA’s mechanism differs significantly from RFA. MWA propagates microwave energy from an antenna into the surrounding tissues resulting in heat and destruction. While RFA relies on electrical conductivity and is limited to tissues adjacent to the probe, MWA can create larger ablation zones and is less prone to heat-sink effects from adjacent large vessels. MWA can be used with multiple probes simultaneously, treating multiple target areas or larger areas concurrently resulting in shorter procedure times. The risk in MWA is associated with rapid heating, as it can quickly destroy tissue and propagate heat to adjacent nontar-

get tissues. This is why some interventional radiologists prefer RFA over MWA for peripheral lesions. One study suggests MWA may be better for larger lesions (>3.5 cm) [29]. Overall, comparisons of MWA to RFA would suggest that MWA should be the superior thermal ablative option, but data is still being studied, and there is no convincing evidence to show that one is better than the other in terms of long-term clinical benchmarks [30].

Key Point

D5W, not normal saline (NS), is used for RFA hydrodissection because of the risk of propagating electrical currents with NS.

For thermal ablations (MWA and RFA), an additional technique called *hydrodissection* can be used immediately prior to thermal ablations if the lesion is too close to other organs. It is a method in which fluid can be infused to create a plane or barrier to protect adjacent tissues (Fig. 36.1). Because normal saline (0.9% NaCl) is ionic, it can propagate electrical current into adjacent tissues during RFA resulting in unintended injury. While separation can be done with any fluid, including sterile water, 5% dextrose in water (D5W) is recommended. D5W is a good choice because it is iso-osmolar and nonionic, which provides both physical and electrical barriers [31–34]. One of the main problems related to hydrodissection includes fluid migration and diffusion that can limit its protective effects. Another issue is its effect on imaging as the fluid can distort the surrounding tissues and can at times impede differentiation of the fluid from bowel on CT.

Key Point

RFA/MWA absolute contraindications:

- Major vessel involvement
- Bile duct involvement

RFA/MWA relative contraindications:

- Poor hepatic reserve
- Coagulopathy
- Active infection
- Decompensated cirrhosis
- HCC >5 cm
- Metastatic lesions >3 cm

Cryoablation uses low temperatures to destroy tissues. The procedural technique is similar to heat-based ablation modalities. Cryoablation does not have the cauterizing abilities of heat-based ablation modalities but is associated with less pain. Cryoablation is not as commonly used as RFA or MWA for several reasons. Firstly, it was historically associated with higher complications rates and, in some instances, even death. Initial reports of cryoablation were associated with “cryoshock,” a cytokine-mediated systemic syndrome consisting of fever, tachycardia, and tachypnea as well as disseminated intravascular coagulation (DIC). Moreover, cryoablation is associated with severe hemorrhage as the intrahepatic ice ball may lead to parenchymal cracking or shearing extending to major vessels. Although some recent studies reported good outcomes with cryoablation, two meta-analyses have shown that cryoablation is associated with much higher complication rates than RFA or MWA [35].

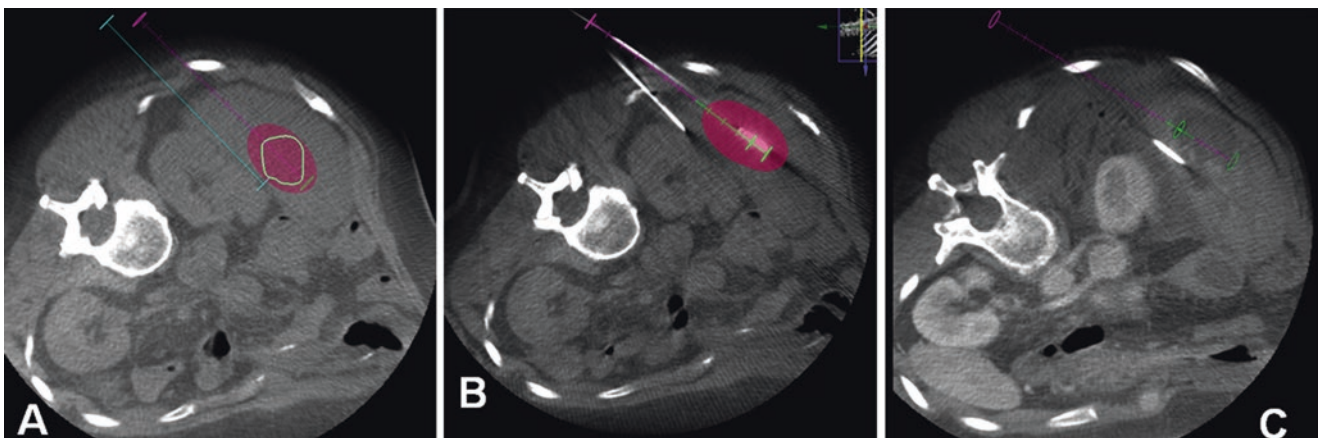


Fig. 36.1 Patient undergoing microwave ablation for a hepatic segment 6 metastatic lesion. (a) Planning CT shows the right kidney is too close in proximity to the planned ablation zone. (b) A treatment needle

was placed to instill 400 mL of D5W to create a safety margin. (c) Post-ablation image shows adequate ablation zone without renal injury following successful hydrodissection

Percutaneous ethanol injection (PEI) has fallen out of use in the treatment of early HCC as multiple studies have demonstrated superiority of RFA ablation compared to PEI [36]. However, PEI still has a role as it is often used for liver sclerosis and treatment of symptomatic hepatic cysts. It can be done in a single or multiple sessions [37]. The procedure itself involves percutaneously accessing the cyst, aspirating the contents, and then injecting alcohol that is retained for a period of time prior to removal. The procedural goal is symptomatic relief even if the actual cystic cavity is not completely destroyed. Unique side effects include hypotension and the signs and symptoms of alcohol intoxication such as nausea, dizziness, and flushing.

Trans-arterial embolization, including both chemoembolization and radioembolization, has been a defining role of interventionists in the treatment of HCC and liver metastasis. These techniques are discussed in Chaps. 34 and 35, respectively.

Prior to the procedure, the patient should have cross-sectional imaging (CT or MRI) to delineate the target lesion, the anatomy, evaluate a safe window, determine ideal ablative modality, as well as assess potential complications and remedies. Patient with increased risk for infections, or hepatic abscess (those with prior sphincterotomy or biliary-enteric anastomosis), should be premedicated with an antibiotic prophylaxis regimen. Immediately prior to procedure, it should also be determined if the patient will need a hydrodissection.

The How to: Radiofrequency and Microwave Ablation

1. Patients can be placed under general anesthesia or conscious sedation. Some patients may have pain and discomfort due to the positioning or the ablation itself. Patients are usually placed supine or left lateral decubitus with the right arm out of the way. Ultrasound is often used for needle positioning, although with RFA the “gas out” (gas emitted by the burning of tissues) limits its value once the ablation has started. RFA requires grounding pads be placed on the patient’s thigh due to the electrical current.
2. Conventional computed tomography (CT), cone beam CT (CBCT), or ultrasound in combination or alone have been used for image guidance during ablations. Imaging is typically obtained at the time of the procedure once the patient is positioned to finalize the approach and determine the ablation

zone desired (Fig. 36.2a). For HCC, contrast-enhanced arterial phase images are often needed to visualize the tumor. The ablation zone consists of the tumor with a 5–10-mm rim of healthy tissue (safety margin). The number of probes, length, and amount of energy delivered will vary depending on the size of the desired ablation zone, manufacturer specifications for the probe, and ablation technology used.

3. If hydrodissection is needed, any device with an initial sharp needle that can be exchanged for a blunt introducer may be used to access the space between the tumor and organ at risk. The blunt introducer can be upsized to a catheter through which the fluid is infused. Repeat imaging is obtained to confirm adequate separation. This catheter can be removed or left in place in case more fluid needs to be infused. (Needles cannot be left in place as they interfere with the ablation.) Some cases may require multiple areas of hydrodissection. Balloon interposition and biliary lavage are additional protective techniques.
4. The thermal ablation probe is advanced under image guidance (see Fig. 36.2b). The probes can be advanced into the lesion or on each side (bracket technique). Computer software is sometimes used to help plan the trajectory. Once positioned, some devices allow the probes to be placed in tissue-lock mode preventing respiratory motion from dislodging the ablation probe from the lesion. Confirmation of adequate probe positioning is essential prior to energy delivery. Needless to say, large vessels and organs, such as adrenal, kidney, and bowel, should be outside the projected ablation zone.
5. With MWA and some RFA devices, ablation is performed by delivering a specified level of energy for a certain amount of time depending on the size of the desired ablation zone. For most RFA machines, however, tissue impedance is used to determine when ablation is complete. Once char is achieved, the impedance goes up and treatment is complete. Repeat imaging with and without contrast should be performed to ensure adequate tumor coverage including a safety margin appropriate for the type of tumor being treated (generally wider for metastatic disease). Note that most probes can coagulate the tract as they are being removed. If a second ablation is required, the probe may be repositioned and the process repeated.
6. Once the ablation is finished, the probes are removed, and imaging is repeated to rule out complications (see Fig. 36.2c).

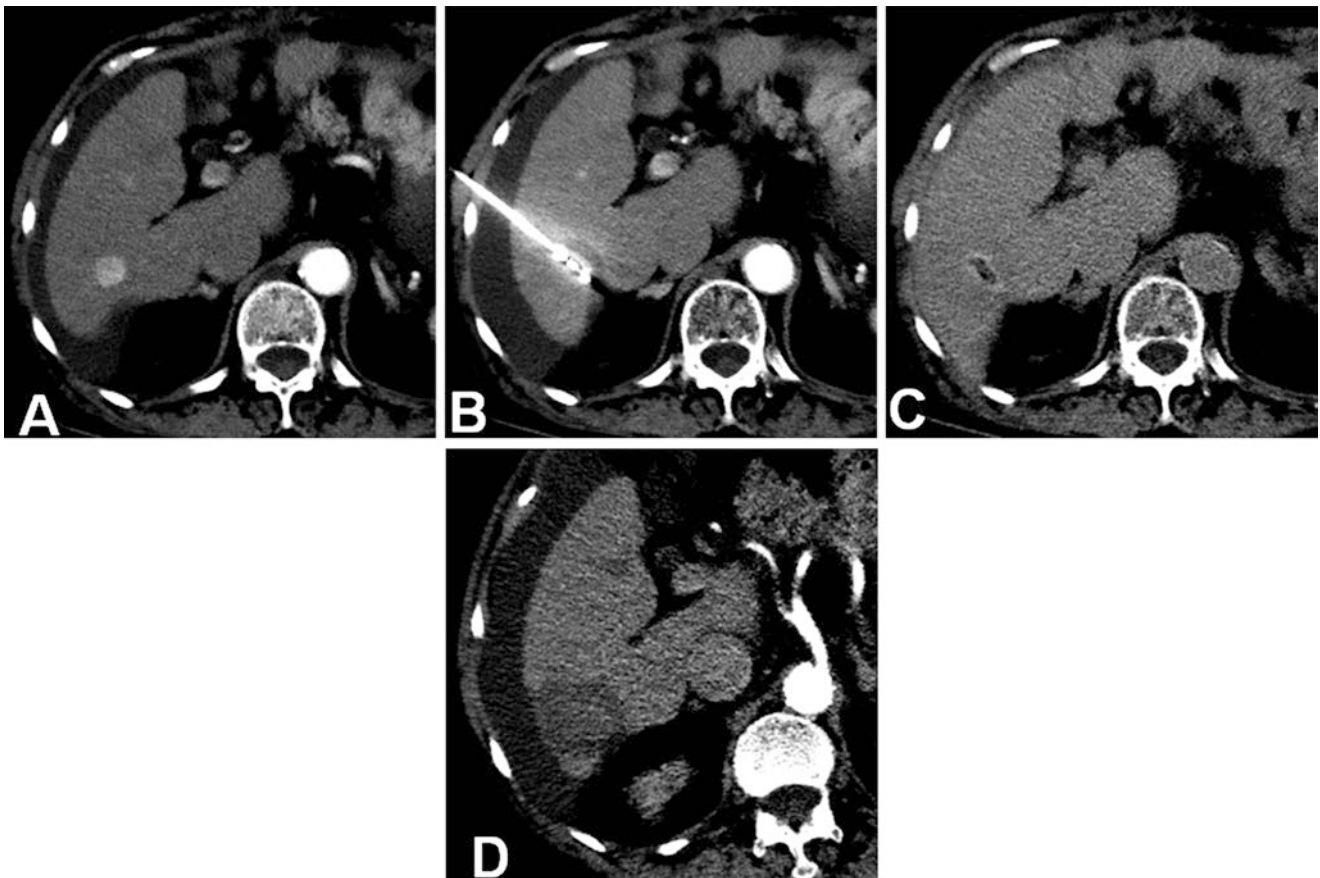


Fig. 36.2 A 79-year-old male with hepatitis B and HCC undergoing microwave ablation therapy for a hepatic segment 6 lesion. (a) Pre-ablation, (b) ablation probe positioning, (c) post-ablation, and (d) 6-month follow-up images are shown demonstrating good treatment response

Key Point

Complications:

- Bleeding
- Tumor seeding
- Hepatic infarction
- Infection (peritonitis, abscess)
- Bile duct injury or bile leak
- Pneumothorax
- Pleural effusion or hemothorax
- Skin burns

For post-procedural care after thermal ablation, it is customary for patients to stay overnight for observation and pain control. Routine post-procedure labs are not needed. Patients are typically discharged the next day with plans to follow up with a clinic visit at 1 month, which should include labs and imaging to assess response (see Fig. 36.2d). If indicated, surveillance imaging and fol-

lowed up clinic visits can be performed every 3 months for the first year, every 6 months for the second year, and as appropriate thereafter.

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