Percutaneous Ablation of Hepatic Tumors

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ABSTRACT

The liver is a common site of both primary and secondary malignancy resulting in significant morbidity and mortality. Careful patient evaluation and triage allows for optimal utilization of all oncologic therapies, including radiation, systemic chemotherapy, surgery, transarterial therapies, and ablation. Although the role of interventional oncologists in the management of hepatic malignancies continues to evolve, the use of percutaneous ablation therapies has proven to be an effective and minimally invasive modality for treatment. Percutaneous ablation therapies have diversified from direct ethanol injection to multiple modalities including radiofrequency ablation (RFA), cryoablation, acetic acid injection, laser ablation, microwave ablation, high-intensity focused ultrasound, and irreversible electroporation. RFA is the most commonly utilized modality for hepatic interventions and has proven efficacy in both hepatocellular carcinoma and colorectal carcinoma metastases. Although tumor size remains a challenge, combination therapies and new device innovations continue to allow for improved ablation zones and more durable results.

KEYWORDS: Percutaneous, hepatocellular carcinoma, hepatic metastases, ablation

Objectives: Upon completion of this article, the reader should be able to state the utility of image-guided tumor ablation for local control of early-stage primary and secondary liver neoplasms, as well as patient evaluation and selection, technical aspects of the ablation procedure, and patient follow-up.

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The role of the interventional radiologist in the percutaneous treatment of patients with hepatic malignancies has been evolving for over 20 years. Early work focused on the use of absolute ethanol administered under ultrasound guidance.¹ Since then, numerous percutaneous ablation modalities have been developed, and are the continued focus of research. One explanation for this extensive research is simple; primary and secondary hepatic malignancies are quite common and a significant source of mortality. Primary liver cancer is the fifth

most common cancer worldwide and the third most common cause of cancer mortality. In the United States, hepatocellular carcinoma (HCC) is the fastest growing cause of cancer-related death among men and has demonstrated a trend of increasing rates at younger ages.² According to the World Health Organization, ~16,000 Americans died of HCC in 2005 (the most recent year for which data are tabulated).³ Secondary involvement of the liver, for example from colorectal carcinoma, is even more common. Projected totals for

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2009 indicate 146,970 new cases of colorectal cancer; approximately half of patients with colorectal carcinoma will develop hepatic metastases over the course of their illness.⁴ The percutaneous treatment of liver dominant colorectal metastases has proven to be a viable option for those patients unable to undergo surgical resection.⁵ This review focuses on image-guided tumor ablation for local control of early stage HCC and small liver metastases in surgically unresectable patients.

PATIENT EVALUATION

The combined expertise of an interdisciplinary oncology team including hepatology, radiation therapy, medical oncology, oncologic surgery, transplant surgery, pathology, radiology, and interventional oncology is critical in the formulation of treatment plans for cancer patients.⁶ Given the wide range of participants involved, multidisciplinary meetings are useful to triage challenging and complex patients, as well as for establishing two-way referral patterns. As an integral part of the team, interventional oncologists must be able and willing to conduct a thorough assessment of the cancer patient. A typical clinical evaluation should include the history of present illness (HPI), review of systems, past medical and surgical history, assessment of performance status, family and social history, allergies, medications, physical exam, laboratory review, imaging review, and discussion of prognosis and treatment options.⁶

Although many of the above components of the initial evaluation are the elementary steps of a standard history and physical, a few deserve additional discussion. When obtaining the HPI, attention should be paid to prior radiation therapy and chemotherapy as well as the overall chronology of the disease and its progression. Performance status is an overall evaluation of practical functional level and ability of patients to care for themselves, serves as a correlate for overall patient wellbeing, and is one of the most potent prognostic indicators for overall survival.⁶ The Eastern Cooperative Oncology Group Scale of Performance Status is a 6-point scale ranging from 0 to 5 with 0 representing normal activities without limitations and 5 indicating death.⁷ Quality of life evaluation is somewhat similar to performance status, but more directly focuses on the patient's ability to perform activities of daily living (eating, bathing, dressing) and instrumental activities of daily living (driving, shopping, paying bills).⁸

The laboratory review should start with a complete blood count, creatinine, and prothrombin time, and/or international normalized ratio. Additional tests such as a liver function panel, and relevant tumor markers such as α -fetoprotein, carcinoembryonic antigen, chromogranin A, and CA 19-9 should be obtained as needed for the specific malignancy in question.⁶

Personal review of cross-sectional imaging is critical to the evaluation process; simply reviewing the radiology report is not sufficient. Baseline imaging should optimally be performed within the month prior to therapy to allow for more accurate comparisons of tumor response. Careful evaluation of tumor number, size, morphology, adjacent structures, and extrahepatic spread will aid in the determination of treatment modality and feasibility.⁶

Patient prognosis is guided by staging. The Child-Turcotte-Pugh (CTP) score is used for the assessment of liver disease. The CTP score is not a staging system of malignancy, but rather a measure of hepatic reserve. The CTP score is derived from a point system based on serum levels of albumin, total bilirubin, and prothrombin time, as well as the presence of ascites and encephalopathy. As the CTP score increases, life expectancy decreases and surgical risk increases. HCC staging systems include the Okuda staging system, the Cancer of the Liver Italian Program classification (CLIP), the Barcelona Clinic Liver Cancer Staging classification (BCLC), the United Network for Organ Sharing (UNOS TNM), the Chinese University Prognostic Index, the Liver Cancer Study Group of Japan, and the American Joint Committee on Cancer / International Union Against Cancer. No single staging system has been proven superior compared with the alternative. However, the BCLC and CLIP staging systems for HCC appear to be the more preferred systems for interventional oncologists. Transplant centers use the UNOS staging.⁹

After a thorough evaluation, all therapeutic options should be considered when formulating a treatment plan. Surgery remains the gold standard for eligible patients with colorectal metastases, and orthotopic liver transplant is a curative option for some HCC patients. Surgical resection of HCC is often not an option due to inadequate functional liver reserve (FLR) due to cirrhosis.¹⁰ Interventional oncologists play a key role in treating those patients not eligible for or unwilling to undergo surgery. Depending upon tumor size and number, ablation may be the sole treatment of choice, or offered in combination with other regional and systemic therapies. Tumor location will affect the feasibility and safety of percutaneous ablation versus a surgical approach. Such patients are a rich source of two-way referrals with surgical oncology.

PATIENT SELECTION FOR PERCUTANEOUS ABLATION

Image-guided percutaneous ablation is an established therapeutic choice for nonsurgical patients with early stage HCC (BCLC class A) and is an option for metastases under 3 cm.^{5,11} Percutaneous ablation provides the least invasive approach and quickest recovery

available when compared with laparoscopic or open surgical techniques and to transcatheter therapies.

Tumors <3 cm in diameter can be completely thermally ablated in a single treatment session in more than 80% of cases. Local failure rates increase rapidly as tumor diameter increases above 3 cm. Tumors >3 cm should be considered for combination treatment with transcatheter therapies. There are no absolute guidelines for number of tumors that can be ablated. Understanding of the natural history of the cancer being treated is helpful. Patients presenting with more than four tumors in the liver likely harbor additional lesions that are occult on imaging, but will become apparent on follow-up scans, offsetting the benefit of ablation. A period of observation during systemic or regional therapy will allow the natural history to declare itself, and if oligonodular disease is confirmed, ablation can then be performed.

Contraindications to percutaneous ablation include uncorrectable coagulopathy, liver failure, uncorrectable proximity to critical structures, and extrahepatic metastases (except in the case of small, slow-growing lung metastases or minimal adenopathy).¹¹ Mortality rates in the treatment of HCC range from 0.1 to 0.5%. Major complication rates are in the range of 2.2 to 3.1%. The most common causes of death are sepsis, hepatic failure, colon perforation, and portal vein thrombosis. There have been several deaths due to cardiac or pericardial injury. Tumors in precarious locations should be referred for laparoscopic or open ablation. The most common complications are intraperitoneal bleeding, hepatic abscess, bile duct injury, hepatic decompensation, and grounding pad burns. Tract ablation or embolization may help to prevent bleeding. Patients with prior biliary stents or surgery are at increased risk for liver abscess, and should receive prophylactic antibiotics.¹² Ablation zones should be kept 1 cm away from the liver hilum to avoid major bile duct injuries. The grounding pads should be checked periodically during the procedure, especially during prolonged ablations at high wattage, to monitor for skin burns. Tumor seeding occurs in 0.2 to 0.6% of cases and is of particular concern in patients who are candidates for liver transplantation.¹³

SELECTION OF ABLATION MODALITY

Ablation modalities include chemical (ethanol and acetic acid) and thermal ablation techniques (radiofrequency, microwave, laser, and cryoablation). In the developed world, radiofrequency ablation (RFA) is the percutaneous ablative modality in most common use. Percutaneous cryoablation and microwave devices have come on the market in the United States more recently, and laser devices are available in Europe. Thermal ablation applicators come in expandable arrays of various geometries and as straight needles. Overall, ablation outcomes

among the various vendors are similar. The interventional oncologist should have a comfortable working familiarity with one of each type (expandable and straight) to treat hepatic tumors.

Chemical ablation is still in common use in countries with less access to expensive technology, and is a very effective therapy for small HCC nodules. RFA has eclipsed chemical ablation in the developed world primarily for reasons of efficiency because complete ablation can usually be achieved in a single session with thermal ablation versus multiple sessions of ethanol injection. Chemical ablation remains a useful tool for patients who are poor candidates for thermal ablation, such as those with tumors adjacent to heat sinks or nontarget structures, medically fragile patients who cannot tolerate deep sedation required for thermal ablation, or patients who develop cardiac complications when exposed to radiofrequency current. Chemical ablation works poorly in metastatic disease. Unlike in HCC patients where the cirrhotic liver provides a fibrotic barrier to contain the ethanol within a vascular tumor, most metastases are of firmer consistency and higher interstitial pressure than the normal hepatic parenchyma, so injected liquids follow the path of least resistance and track out into the surrounding liver.

Cryoablation is less commonly used in the liver than RFA. Cryoablation requires placement of multiple applicators, has a longer ablation protocol, is more expensive, and does not allow tract ablation, raising concern for an increased risk of bleeding. However, it is relatively painless, allowing treatment of fragile patients who cannot tolerate anesthesia. The ice ball is easily visible on computed tomography (CT), permitting safe ablation adjacent to critical structures, unlike heating techniques for which the thermal injury volume cannot be monitored in real time.

SELECTION OF IMAGING GUIDANCE MODALITY

Liver ablation can be performed under ultrasound (Fig. 1), CT, or even magnetic resonance imaging (MRI) guidance in institutions with MRI-compatible equipment. Ultrasound is the most efficient modality for tumors that can be targeted adequately, but the echogenic cloud of steam generated during thermal ablation obscures the target and makes repositioning of the probe for overlapping burns difficult. Ultrasound contrast agents available in Europe and Asia are very helpful for targeting and monitoring the ablation. CT provides better depiction of both the target and the probe, but working in the gantry takes more time and is less suited to complex access angles. It can be difficult to fit ablation probes within the gantry, particularly when treating shallow tumors. CT and ultrasound can be used concurrently to combine the advantages of each technology.

Figure 1 A 65-year-old woman with liver cirrhosis. Arterial phase contrast-enhanced computed tomography scan (A) and ultrasound (B) reveal 3-cm-diameter segment 7 hepatocellular carcinoma (arrow). Intraprocedural ultrasound image (C) taken during percutaneous radiofrequency ablation (RFA) shows multitined RF electrode (arrowhead) positioned within lesion. Postablation ultrasound image (D) demonstrates typical hyperechoic appearance of ablated lesion (arrow), due to microbubbles generated during ablation.

Alternatively, image fusion software can be used to superimpose the superior depiction of diagnostic CT or MRI datasets on real-time ultrasound scans to allow ultrasound-guided probe placement into sonically occult tumors.¹⁴ When available, MRI guidance offers the added advantage of real-time thermal monitoring of the ablation zone.

PERCUTANEOUS ABLATION PROCEDURE

Percutaneous ablation is usually performed in an outpatient under intravenous moderate sedation or monitored anesthesia care. Both chemical and cryoablation are relatively well tolerated and can be performed under local anesthesia with light sedation. Ablation with heat is very painful and requires deep sedation, with the patient breathing spontaneously but unresponsive to voice. An oxygen mask is often required to maintain adequate oxygen saturation, with attention to proper neck and jaw position to maintain an unobstructed airway. Monitoring of electrocardiogram, pulse, blood pressure, and pulse oximetry is maintained throughout the procedure.

After careful review of the diagnostic images, preliminary scanning is performed to choose an appropriate site for probe entry based on trajectory to the target, probe length, nontarget structures that must be avoided, and physical constraints of the CT or MRI

gantry these guidance modalities are used. When thermal ablation is planned close to bowel, body wall, or diaphragm, infusion of 500 to 1000 mL 5% dextrose to create artificial ascites should be performed to protect against nontarget thermal injury and decrease intra- and postprocedure pain.¹⁵ The type and number of probes and number of ablations are planned to achieve a total ablation zone 5 to 10 mm larger than the tumor. This additional circumferential margin of ablation treats microscopic satellite lesions and mitigates local recurrence. Tumor diameters equal to or larger than the size of a single ablation zone require multiple overlapping burns.¹⁶ Geometric modeling assuming spherical target and ablation zones predicts that eight perfectly overlapped ablations would be needed to cover a tumor 1 cm larger than the probe, a practical impossibility that accounts for the high local failure rate as tumor diameter increases above 3 cm.

Another technical consideration is perfusion-mediated cooling by adjacent veins (the “heat-sink” effect). Veins as small as 3 mm have sufficient flow to provide convective cooling that limits the size of the ablation zone. Placement of a balloon occlusion catheter into the hepatic vein or inferior vena cava during the ablation may help to mitigate this effect.¹⁷

Thermal ablation is monitored by automated systems within the generator that provide feedback on

time, temperature, and/or impedance, with treatment protocols specified by each manufacturer. At the conclusion of the procedure, most thermal systems allow for ablation of the needle track to decrease the risk of bleeding and tumor seeding. Triple-phase enhanced CT or MRI may be performed at the conclusion of the procedure to evaluate for completeness of the ablation, recognizing that the intense inflammatory reaction to thermal ablation results in substantial perilesional enhancement and abnormal perfusion patterns in the surrounding liver. The ablation zone should be non-enhancing. Peripheral, irregular nodular areas of enhancement near the ablation area are concerning for residual tumor.

Unlike radiofrequency and microwave systems, cryoprobes are straight hollow needles producing spherical or elliptical ice balls. These need to be placed in an array within the tumor 2 cm apart and 1.5 cm from the tumor margins, such that the conglomerate ice ball encompasses the entire tumor plus a 1 cm margin. A good rule of thumb is one probe for each centimeter of tumor diameter.

Chemical ablation should be performed under ultrasound guidance to allow for real-time monitoring of the injection. Specialized needles for chemical ablation have closed diamond-tips with sideholes, or a radial array with multiple sideholes on the tines to disperse the ethanol (QuadraFuse, Rex Medical, Conshohocken, PA). The planned volume of ethanol is calculated using the formula for the volume of a sphere, adding 0.5 cm to the tumor radius. During injection, dispersion of the highly echogenic ethanol is monitored by ultrasound. Any leakage of ethanol into surrounding veins or back along the needle track is cause to reposition the needle. Depending upon the evenness of dispersion of the liquid, injection at multiple locations may be necessary. Once the target has become obscured by the echogenic ethanol, treatment is stopped. Repeat injection at another session is often required before complete ablation is achieved.

Postprocedure care should focus on pain and nausea relief and monitoring for complications. Stable patients can be discharged after 4 hours observation. Postablation pain and fever can usually be managed with ibuprofen, but some patients may require narcotic analgesic medications, especially for thermal injuries near the liver capsule.

Follow-up clinical, laboratory, and imaging assessment should be performed one month after treatment to monitor for complications and confirm the completeness of the ablation. A thin peripheral rim of arterial phase enhancement is typically still seen, and can persist for months. If this baseline scan indicates a complete ablation, serial imaging should be performed at 3-month intervals (Fig. 2). Microscopic residual tumor may take a year to become apparent on imaging,

Figure 2 Eight-month postablation computed tomography scan for tumor shown in Fig. 1 shows complete response to radiofrequency ablation, evidenced by a lack of contrast enhancement of necrotic tumor (arrow).

with rare cases of local recurrence not detected until 18 months later. It is important to counsel patients hoping for a “cure” that complete ablation cannot be assured until the 1-year follow-up imaging. For patients with ^{18}F -fluorodeoxyglucose avid tumors, positron emission tomography (PET) is also useful for follow-up and may detect residual disease earlier than CT or MRI.¹⁸

RESULTS OF PERCUTANEOUS ABLATION

Percutaneous ethanol injection is very effective for small HCC (<3 cm diameter), with complete ablation achieved in 80 to 100% of tumors, and survival of 90 to 98% at one year and 40 to 60% at 5 years.¹¹ Importantly, although comparison studies to surgical resection and thermal ablation have shown somewhat inferior local control with ethanol, disease-free and overall survival are equivalent.^{19,20}

The effectiveness of percutaneous thermal ablation is influenced by tumor location adjacent to heat sinks and, most importantly, tumor size. Thermal ablation of HCC <3 cm diameter achieves complete response in over 90%, whereas 50 to 70% of tumors 3 to 5 cm in diameter are completely ablated. Results for ablation of HCC larger than 5 cm are poor.¹¹ Thermal ablation of HCC smaller than 5 cm has demonstrated equal survival benefit compared with surgical resection, with 5-year overall survival of 50 to 60% in CTP class A patients.²¹ Disease-free survival is primarily driven by the rate of appearance of new HCC foci in the cirrhotic liver.

Thermal ablation of liver metastases follows similar guidelines as far as tumor size and local control rates. Better results have been reported using MRI-guided laser ablation, with local control rates of greater than 95% for liver metastases up to 4 cm.²² Long-term outcomes are driven by the natural history of the primary

cancer, with appearance of new intra- and extrahepatic metastases being the rule. Percutaneous RFA of colorectal metastases results in 1-, 3-, and 5-year survival rates ranging from 91 to 93%, 28 to 69%, and 25 to 46%, respectively.²³

CONCLUSION

Image-guided tumor ablation is an effective therapy for local control of early stage HCC and small liver metastases in surgically unresectable patients when percutaneous treatment is feasible and safe. Survival in early HCC is similar to that achieved by operative resection. Advances in imaging guidance and targeting, ablation technology, and integration with other regional and systemic therapies will increase opportunities for multimodality control of larger or multifocal disease.

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