HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

Overview of Ablative Therapy for Hepatocellular Carcinoma

Steven C. Rose, MD
Professor of Clinical Radiology
Section Chief, Interventional Oncology
UC San Diego Medical Center
San Diego, California

G&H What is the role of radiofrequency ablation and microwave ablation in the treatment of hepatocellular carcinoma?

SR Both radiofrequency ablation and microwave ablation are thermal ablative technologies that generate heat to cause destruction of tissue. Both technologies use energy from points along the electromagnetic wave spectrum to generate frictional heat: radiofrequency is an alternating electrical current of approximately 460,000 hertz (Hz) that causes rapid precession of ionic dipolar molecules, whereas microwave is a nonelectrical energy source of either 9.15 million Hz or 2.54 billion Hz that causes rotation of water molecules. Molecular frictional heat is then passively conducted outward to achieve the volume of tissue coagulation necrosis, generally in the order of 4 cm in diameter.

Radiofrequency ablation and subsequently microwave ablation have been the dominant percutaneous ablative technologies for the treatment of hepatocellular carcinoma (HCC) from approximately 1995 until perhaps 5 years ago. HCC can also be treated with cryoablation, although most practitioners use heat with radiofrequency ablation or microwave ablation. Research has shown that these percutaneous image-guided thermal ablative technologies are as effective as surgical resection with respect to improvement in overall survival for tumors that are 2 cm and smaller, and perhaps up to 3 cm (although efficacy falls off beyond 3 cm). The practicality and effectiveness of these treatments is also dependent on the number of tumors. One tumor is ideal, but 2 or 3 tumors may be suitable for some practitioners in select situations. If there are more than 3 tumors, most practitioners elect to use a different treatment.

Tumor location is also critical and can limit the use of these technologies. The practitioner must have safe access to advance the device from the skin, through the liver, and into the targeted tumor. For example, if the tumor is near the dome of the liver, the device needs to traverse the pleura and, potentially, the lungs. If the tumor is near the heart, diaphragm, central bile duct, bowel, or stomach, there is a risk of collateral damage to these critical structures when heat is conducted outward. Thus, there are limitations to thermal ablation.

G&H What advances have taken place recently involving ablative therapy for HCC?

SR Recently, especially during the last 5 years, radiation therapy, including transcatheter radioembolization, has been used to intentionally kill a limited volume of the liver that includes the tumor. One form of radiation therapy, known as yttrium-90 radiation segmentectomy, is delivered as radioisotope-loaded microspheres administered through a microcatheter into the artery that supplies the segment in which the tumor resides. Radioembolization has been used for approximately 15 years in general practice, but until recently, most of the doses were palliative. In cases of palliative dosimetry, the practitioner prescribes sufficient radiation such that the targeted segment of the liver absorbs approximately 100 to 120 Gray (Gy). The basis for palliative dosimetry is preferential delivery of radioactive microspheres to hypervascular tumors that are supplied by hepatic arteries (as opposed to nontumorous liver that is predominantly supplied by the portal vein). Alternatively, ablative dosimetry targets a relatively small volume of the liver but with the prescribed dose of yttrium-90 substantially increased so as to completely destroy the segment of the liver that contains the tumor. The threshold for achieving ablative dosimetry is at least 200 Gy, although, frequently, administered doses may reach 300 to 500 Gy. The key to safe and effective ablative dosimetry is to avoid radiation injury to the rest of the liver. Early data indicate that radiation segmentectomy is minimally toxic; greatly increases complete tumor necrosis, time to progression, and survival; and has outcomes that approach those of surgical resection.

Another important recent advance has been the improvement of external beam therapy to deliver ablative doses of radiation. One form of this therapy uses photons, specifically gamma rays, which are pure energy forms. These gamma rays are targeted so as to focus on a small volume of the liver, but are introduced from different directions such that surrounding tissues do not receive toxic levels of radiation. The other form of external beam radiotherapy, proton beam therapy, uses high energy particles that are projected into the liver. These particles penetrate a predictable distance and give off most of their destructive energy in the last few centimeters into the targeted tumor.

Although radiofrequency ablation and microwave ablation remain important, these advances in transcatheter and focused external beam radiation therapy have improved the ability to ablate HCC in areas where it was previously precarious to do so using thermal ablation. In addition, the tumor size limitations of thermal ablation can potentially be extended by several centimeters. In short, more tools are available in the tool box to offer curative treatment. Practitioners now have more ablative choices to pick from, which will likely increase the number of patients who can potentially receive curative treatment. It is now known that patients with HCC have diseased livers that are prone to developing new cancers in other locations, so "cure" may not be completely accurate, but their long-term survival is clearly much better than with a palliative technique such as chemoembolization or palliative radioembolization.

G&H Are there any other intriguing recent developments in ablative technology for HCC?

SR An interesting field of study has been the area of abscopal (ie, off-target) effects. When practitioners perform locoregional therapy, especially thermal ablation, many humoral factors are released, cytokines in particular. These cytokines can stimulate an immunogenic response that may help kill cancer outside the zone of ablation. They may also stimulate oncogenic factors that can stimulate the growth of tumors. A number of researchers are developing techniques that manipulate these abscopal effects and immune responses in an attempt to increase the effectiveness and safety of thermal ablation and other ablative technologies.

G&H Can these ablative therapies be used in combination with other modalities or treatments?

SR A number of investigators have demonstrated an improved ability to successfully treat tumors with diameters of 3 to 5 cm by combining thermal ablation with transcatheter chemoembolization. The particles in the chemoembolization suspension reduce the throughput of blood, which in turn decreases heat loss (known as the heat sink effect). Because the heat generated by the microwave or radiofrequency device is more effectively retained, the increased ability of heat to be conducted outward allows the ablation zone to expand further. Lipiodol is an iodinated poppy seed oil that is commonly emulsified and delivered as a component of chemoembolization. It is highly radiodense. HCCs tend to accumulate lipiodol selectively and retain it indefinitely because tumors do not have lymphatic systems. Introducing lipiodol into the tumor radically improves the ability to visualize it on a computed tomography (CT) scan, thus enhancing the ability to accurately target tumors for subsequent ablation.

G&H How safe are these therapies? Are there any significant risks?

SR With respect to thermal ablation, if the tumor is in a safe area that is easy to target, the rate of serious complications is likely 3% to 5%, with the most common complications being bleeding (primarily from the liver), infection, and nontarget thermal injury. If the tumor is in a difficult-to-target area, the risk increases and the type of complication depends on the location. For example, if the tumor is near the dome of the liver, and the practitioner has to traverse the lungs to access it, there is an approximately 25% chance of developing a pneumothorax. If the tumor is near the central bile duct, the risk of catastrophic biliary injury increases. When the tumor is adjacent to the bowel, the practitioner occasionally may need to displace the bowel by introducing liquids, air, or balloons to reduce the risk of conducted heat causing a thermal injury.

As for radioembolization, serious risks (category 3 or greater) are likely in the same range of 3% to 5%, although the specific injuries are different. Bleeding complications usually occur at the femoral artery vascular access site. Arteries that the catheters traverse may be injured, rarely requiring stent placement. The risk of radiation-induced hepatic deterioration depends on the volume of liver irradiated and the degree of hepatic dysfunction at baseline. The possibility of developing radiation-induced ulcers in the gastrointestinal tract is approximately 1%.

I cannot address the specific safety issues regarding stereotactic body radiotherapy. Nevertheless, case selection is important. In properly selected patients, the risks are likely in the same order as with transcatheter radioembolization. If the tumor is in a difficult area (eg, next to the chest wall, heart, or bowel), there is a significant risk of causing radiation injury to those structures. The ability to reliably suspend respiration is also important in order to minimize the tumor and liver motion during radiation treatment. To help target the tumor, radiopaque fiducial markers may need to be placed in close proximity.

G&H How does a practitioner choose which of these treatments to use in a patient with HCC?

SR Probably the best platform for making the correct decision is a multidisciplinary liver tumor board. At our institution, this tumor board includes the managing hepatologists, medical oncologists, surgical oncologists, transplant surgeons, radiation oncologists, interventional radiologists, and diagnostic radiologists. Having all of these specialties convene to concurrently provide their expert insights is critical for the development of an optimal plan tailored to the patient's unique situation.

G&H What are some of the factors that go into this decision?

SR Multiple variables need to be considered for selecting the best image-guided locoregional therapy to treat a given patient's HCC. For thermal ablation, the main factors that should be considered are the size and the location of the tumor. If a 2-cm tumor can be approached without having to traverse a critical structure, and it is possible to expand the volume of tissue necrosis for a centimeter beyond the tumor in all directions and not run the risk of damaging other critical structures, then thermal ablation is a good, and often the best, choice. Other factors include the number of tumors and the overall health of the liver.

For radioembolization safety, adequate liver reserve is key. If the radiation doses are tightly focused (segmental or subsegmental), patients with moderately elevated Model for End-Stage Liver Disease scores can still be treated. One critical aspect of transcatheter techniques is ensuring that the treated arteries supply the entirety of the tumor. Another important aspect of transcatheter techniques is ensuring that the embolic microspheres, especially the much smaller yttrium-90 microspheres (25-35 mcm), remain within the targeted portion of the liver and tumor, and do not pass through arteriovenous shunts. Such shunts can allow particles to pass into either the portal venous system or the draining hepatic veins. Shunted microemboli can cause injury to either nontumorous liver or the lungs. To test for pathologic arteriovenous shunting, surrogate particles (macroaggregated albumin)—which are approximately the same size as the therapeutic microspheres but are loaded with a nontherapeutic gamma-emitting radioisotope (technetium-99m)—are injected into the hepatic artery with subsequent imaging of the liver and lungs. The degree of shunting can then be objectively quantified. Patients with excessive lung shunting (typically >30 Gy) can be excluded, or strategies to reduce lung shunting can be utilized.

G&H Could you explain in further detail how the location of the tumor impacts which treatment is chosen?

SR Presume a patient has 1 tumor whose size (eg, 2 cm) is compatible with any of the technologies that have been mentioned. If the tumor is subcapsular in location, it can be challenging to safely advance an ablative device through nontumorous liver and then into the tumor. Puncturing the tumor directly dramatically increases the risk of bleeding and of seeding the track or the peritoneum with viable tumor cells. Tumor dissemination is a catastrophe for patients who are potential liver transplant candidates, as they are then excluded from transplantation, a procedure that can realistically provide a survival benefit of 20 years or more. For this reason, many transplant surgeons view percutaneous thermal ablation as a relative contraindication in patients who are potential transplant candidates. The practitioner must also consider critical nontarget structures that are nearby: the chest wall, abdominal wall, adrenal glands, colon, small bowel, stomach, and heart. Therefore, most practitioners prefer thermal ablation for tumors that are not abutting the liver capsule. Central tumors near the hilum of the liver present a different set of issues. Large-caliber blood vessels (>3 mm in diameter) with rapidly flowing blood can strip away the heat generated by the radiofrequency or microwave device (the aforementioned heat sink effect). This phenomenon protects the integrity of the blood vessels but also leaves a cuff of viable tumor nearby. In addition, the bile ducts, which are sensitive to thermal injury, course alongside the vessels. The central bile duct should be avoided.

For the transcatheter techniques, the location of the tumor is less of an issue because the hepatic arteries, with a few exceptions, remain within the liver parenchyma. For this reason, embolic particles remain localized to a specific portion of the liver. Yttrium-90 radioembolization involves emission of beta particles. Because this form of radiation involves the mass of electrons, it gives off its destructive energy close to the site of the embedded microsphere (with a median penetration of 2.5 mm). Notable exceptions are the hepatoenteric arteries that exit the liver and travel to extrahepatic structures such as the stomach, duodenum, or abdominal wall. Cone beam CT represents a major advance for the detection of these arteries. Once detected, a number of strategies are available to avoid nontarget embolization. Examples include coil embolization to occlude the hepatoenteric artery, advancement of the delivery microcatheter distally past the origin of the vessel, or use of temporary antireflux devices.

Tumors also recruit ingrowth of arteries from adjacent liver or extrahepatic structures by releasing humoral growth factors. A tumor may therefore derive its blood supply from multiple sources, both from within and outside of the liver. A key to successful transcatheter therapies is to identify and deliver the therapeutic agent in one or more arteries that supply the entirety of the tumor. Alternatively, one could occlude the other competing arterial sources so as to redirect the tumor blood supply to a hepatic arterial source that can be treated.

G&H With the development of these new procedures, are radiofrequency ablation and microwave ablation still the best option for some cases of HCC?

SR Yes, radiofrequency ablation and microwave ablation are definitely the appropriate options for a sizable number of patients. Because the aforementioned newer technologies can treat tumors in locations that are challenging for radiofrequency ablation or microwave ablation, potentially curative ablation can now be applied to a greater portion of HCC patients. In addition, chemoembolization combined with lipiodol can be used to improve CT targeting for thermal ablation and may extend the suitability of thermal ablation to include tumors as large as 5 cm.

G&H How can a practitioner choose between microwave ablation and radiofrequency ablation?

SR The data published thus far (albeit from the late 1990s to the early 2000s) that compare thermal ablation outcomes to those of surgical resection are mostly based on radiofrequency ablation. Although there have been no good prospective, randomized, controlled trials directly comparing radiofrequency ablation to microwave ablation, the trend recently has been toward increased use of microwave ablation due to its more rapid and deeper tissue heating.

Dr Rose has no relevant conflicts of interest to disclose.

Suggested Reading

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