



Foxtail_14769. Photograph courtesy of Henry Domke, MD.
www.henrydomke.com

Interventional radiology techniques play an important role in the management of many patients with hepatocellular carcinoma.

Interventional Radiological Treatment of Hepatocellular Carcinoma

Cliff R. Davis, MD

Background: Locoregional treatments of hepatocellular carcinoma (HCC) have evolved over the past 20 years. Interventional radiologists have developed an important role in the palliative and curative treatment of the disease. This review summarizes commonly used interventional radiological treatment protocols to assist practitioners in understanding the techniques used to treat HCC.

Methods: Various searches were performed to evaluate recent publications regarding systemic treatments of HCC as well as transplant/surgery, chemoembolization, yttrium-90 radioembolization, percutaneous radiofrequency ablation (RFA), cryoablation, and percutaneous ethanol injection (PEI).

Results: No standard for chemoembolization was found. Two studies evaluating survival with chemoembolization vs medical therapy found benefits with the former. PEI offers favorable outcomes in small HCC but has increased recurrence and decreased long-term survival compared with RFA. Local recurrence, response rates, and mortality from RFA rival surgical resection in HCC < 3 cm. Cryoablation appears to be effective, and yttrium-90 radioembolization is an additional tool.

Conclusions: Chemoembolization improves survival and offers improved tumor response compared to systemic treatment. More studies are needed to standardize chemoembolization preparations and techniques. RFA provides better results than PEI but has not been compared with cryoablation. Radioembolization appears to be as effective as chemoembolization, but the preprocedure evaluation and costs may limit its use.

Introduction

The incidence of hepatocellular carcinoma (HCC) is sharply on the rise in the United States and worldwide. It is currently the third most common fatal malignancy in the world, and in the United States, the incidence of HCC is increasing faster than any other malignancy.^{1,2}

Cirrhosis due to chronic hepatitis C or B is blamed for the marked increase in the number of cases. Most patients were unknowingly infected with the viruses in the 1970s or 1980s and are developing symptoms now.

An understanding of the nature of HCC and its imaging characteristics is important in the assessment of treatment options. Tumors frequently occur in patients with underlying cirrhosis, commonly with chronic hepatitis C or B. It is now widely accepted that a dysplastic nodule commonly found in cirrhotic livers slowly degenerates to low-grade HCC.^{3,4} Low-grade (well-differentiated) HCC tends to develop round, well-defined, encapsulated masses. Over time, focal areas within a low-grade HCC tend to degenerate to poorly differentiated grades. Poorly differentiated disease tends to infiltrate the liver and invade the venous or

From Tampa General Hospital, Radiology Association of Tampa/Department of Interventional Radiology, Tampa, Florida.

Submitted June 15, 2009; accepted February 23, 2010.

Address correspondence to Cliff R. Davis, MD, Tampa General Hospital, Radiology Association of Tampa/Department of Interventional Radiology, Room J-342, 1 TGH Circle, Tampa, FL 33606. E-mail: cliffrdavis@yahoo.com

No significant relationship exists between the author and the companies/organizations whose products or services may be referenced in this article.

arterial network, which causes the tumor to spread more aggressively. Three-phase computed tomography (CT) or dynamic magnetic resonance imaging (MRI) findings have been shown to correlate well to histologic tumor grade. As dysplastic nodules degenerate to malignancy, they decrease portal venous enhancement⁵⁻⁷; as HCC progresses in histological stage, tumors tend to have increased arterial enhancement. A low-grade HCC tends to have mild arterial enhancement and is iso-intense or slightly hypointense on portal venous phases of contrasted imaging. High-grade HCC tends to have bright, brisk arterial enhancement (Fig 1A) with markedly decreased portal phase enhancement. Tumor grade and size greatly affect prognosis, with or without surgical treatment. Vascular invasion and multifocal disease within the liver also predict significantly poorer long-term survival regardless of treatment type.^{8,9}

The use of interventional radiology techniques to treat HCC has developed primarily due to the limitations of other treatment methods. Until the recent approval of sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals Inc, Wayne, NJ) by the US Food and Drug Administration (FDA), no systemic chemotherapeutics showed significant increases in survival in patients with HCC.^{10,11} Without dose modulation or stereotactic techniques, external beam radiation has had a limited role in the treatment of HCC due to radiation toxicity to adjacent normal liver.¹² Surgical resection can significantly improve outcomes, offering 5-year survival rates of 25% to 75% depending on tumor grade and size. However, such surgery requires wide resection margins, and underlying cirrhosis limits the volume of liver that can be resected without causing liver failure.^{8,13,14} Liver transplantation and resection portend the best long-term overall survival rates in early HCC, approximately 75% at 5 years. However, survival rates drop significantly, to 40% to 50%, if there is malignant vascular invasion in the explant.^{9,15,16} Comparatively, symptomatic treatment of HCC has an estimated 1-year survival rate of approximately 22% and a 5-year survival rate of only 5%.¹

Several scoring methods have been developed to assess the prognosis of patients with cirrhosis and/or HCC. In patients with end-stage liver disease without HCC, mortality is often estimated with the Child-Pugh score and the modified Model for End-stage Liver Disease (MELD) score. Initially designed to predict mortality for placement of transhepatic portosystemic shunts and for liver transplantation, the MELD and Child-Pugh scores are often used to weigh treatment options and predict mortality in patients with end-stage liver disease.¹⁷⁻²⁰ The modified MELD score is a numerical grade obtained by placing a patient's INR (the prothrombin time measured as international normalized ratio), creatinine, and total bilirubin into an equation. While there is no maximum MELD number, a score greater than 45 is rarely compatible with survival longer

than 1 month. In Florida, liver transplant allocation is determined by the patient's modified MELD score, so those with a higher MELD score are listed higher on the list.²¹ When assessing patients for locoregional treatment, the MELD score can assist in determining the possibility that a patient will need and/or receive a transplant in the near future.

Although several staging and scoring systems have been developed to determine the prognosis of patients with HCC, none has emerged as the most accurate in all populations.^{22,23} The most widely used staging systems include the Okuda, the Cancer Liver Italian Program (CLIP), and the Barcelona Clinic Liver Program (BCLC). A comparison of these systems is beyond the depth of this paper, but most staging systems use TNM staging combined with findings of portal vein invasion on imaging with α -fetoprotein (AFP) levels and Child-Pugh status.^{23,24} Prognosis in patients with HCC varies greatly due to these factors. For instance, patients with a CLIP stage of 0 have a median survival of 53 months, and those classified as CLIP stage IV have a median survival of 3.4 months.²⁴

As discussed in the transplant section of this issue, most transplant programs adhere to the Milan criteria for classifying patients as transplant and nontransplant candidates.²¹ Milan criteria for transplant consideration include a single tumor ≤ 5 cm, or up to 3 tumors ≤ 3 cm each. The presence of distant metastatic disease also eliminates a patient from being a transplant candidate.²¹ Extending criteria are present at some single institutions (eg, the University of California at San Francisco, the University of Pittsburgh, Mayo Clinic).²⁵

Most patients seen in the Interventional Radiology department at our hospital are referred from the Hepatology or Transplant Surgery department. If a diagnosis of HCC is suspected based on imaging findings, the case is reviewed at a biweekly multidisciplinary conference to determine the best treatment plan for each patient. The conference is attended by staff from the Transplant Surgery, Hepatology, Radiation Oncology, and Interventional Radiology departments. The patient is first categorized as a transplant or nontransplant candidate. If a transplant candidate is expected to have a lengthy wait on the transplant waiting list, we may offer more aggressive treatments in hopes of preventing progression and/or metastatic disease. If the transplant candidate has a high MELD score and is expected to receive a transplant in the near future, we may be less aggressive to avoid the possibility of a treatment complication altering the patient's transplant status. Tumor stage, number, location, size, and histological grade (if a biopsy was performed), as well as underlying liver disease, portal vein invasion, and renal function, are measured to tailor treatments to each patient.

The rapid evolution of interventional radiology techniques and protocols, as described below, often

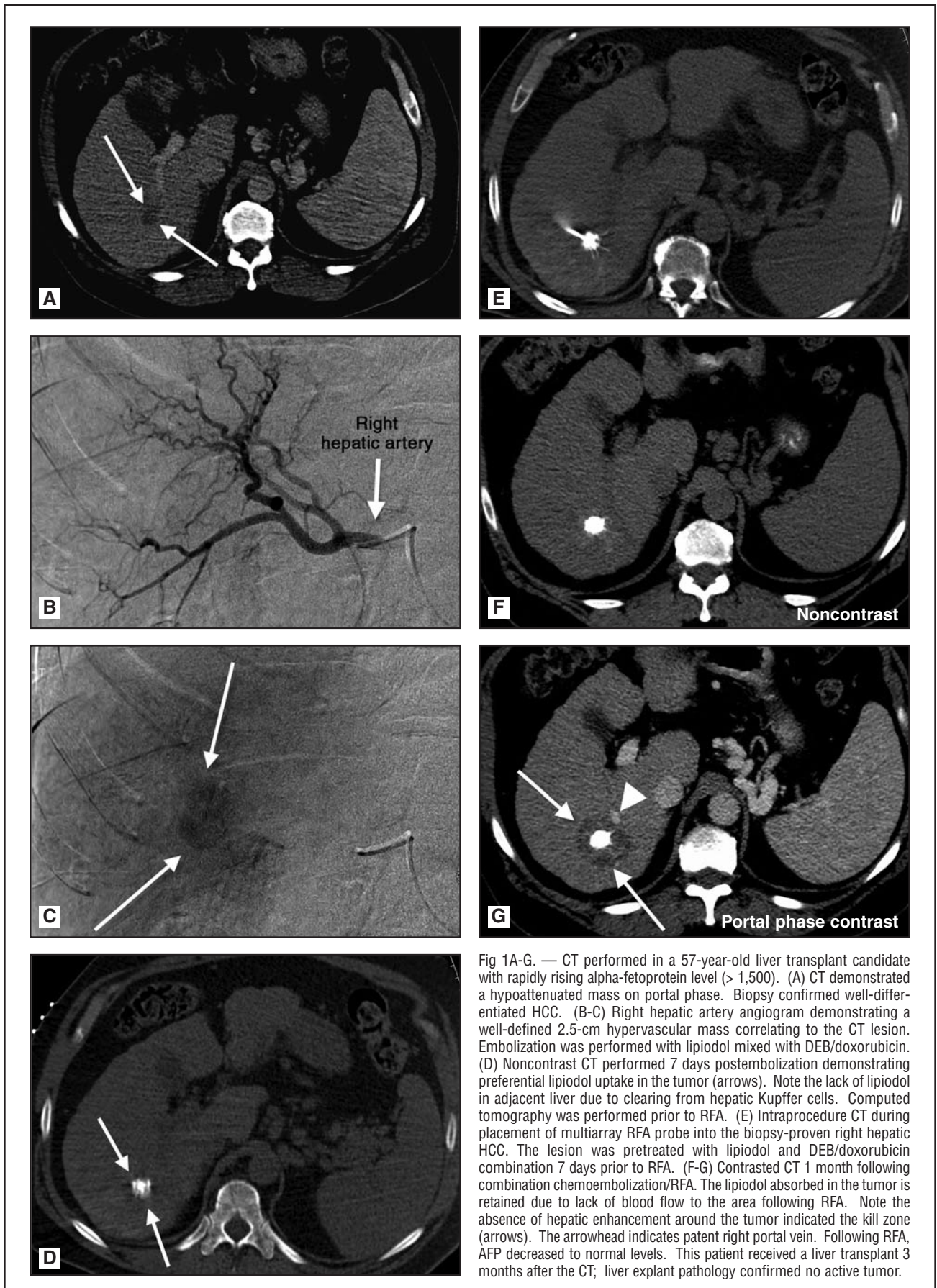


Fig 1A-G. — CT performed in a 57-year-old liver transplant candidate with rapidly rising alpha-fetoprotein level ($> 1,500$). (A) CT demonstrated a hypoattenuated mass on portal phase. Biopsy confirmed well-differentiated HCC. (B-C) Right hepatic artery angiogram demonstrating a well-defined 2.5-cm hypervascular mass correlating to the CT lesion. (D) Noncontrast CT performed 7 days postembolization demonstrating preferential lipiodol uptake in the tumor (arrows). Note the lack of lipiodol in adjacent liver due to clearing from hepatic Kupffer cells. Computed tomography was performed prior to RFA. (E) Intraprocedure CT during placement of multiarray RFA probe into the biopsy-proven right hepatic HCC. The lesion was pretreated with lipiodol and DEB/doxorubicin combination 7 days prior to RFA. (F-G) Contrast CT 1 month following combination chemoembolization/RFA. The lipiodol absorbed in the tumor is retained due to lack of blood flow to the area following RFA. Note the absence of hepatic enhancement around the tumor indicated the kill zone (arrows). The arrowhead indicates patent right portal vein. Following RFA, AFP decreased to normal levels. This patient received a liver transplant 3 months after the CT; liver explant pathology confirmed no active tumor.

causes confusion and complicates the development of standard protocols for studies needed to evaluate the outcomes of the various techniques. This review is intended to provide practitioners with a better understanding of treatment types, protocols, and terminology associated with the treatment of HCC by interventional radiology.

Treatment Types

Primary interventional radiology treatments for HCC of the liver fall into three general categories: (1) (chemo)embolization, (2) radioembolization, and (3) percutaneous treatment. Each has distinct benefits and differing roles in the treatment of HCC, in both surgical and nonsurgical patients.

(Chemo)embolization

Embolization is a term used to describe vascular occlusion from an endovascular technique, such as placing a coil or other substrate in the vessel that is injected through a catheter under fluoroscopy. The effectiveness of embolization in the treatment of HCC is primarily due to the differences in the blood flow requirements of the liver and tumor. HCC is a hypervascular tumor, relying heavily on the arterial blood supply for nutrients and oxygen. It utilizes 5 to 7 times the amount of arterial flow per volume of tissue compared with the surrounding liver tissue (Fig 1B-C). The surrounding hepatocytes rely on the portal vein for 75% of their blood flow. Following embolization of the artery, the reduction in the arterial blood supply to the tumor causes hypoxia and cell death to the tumor but typically spares adjacent liver cells, as the portal vein remains patent.²⁴

Chemoembolization combines embolization with the intra-arterial administration of drugs directly to the tumor. Several techniques have evolved that use a combination of cytotoxic drugs and physical embolic material. Lipiodol, which is iodinated poppy seed oil, was likely the first “chemoembolic” agent used to treat tumors. For reasons that remain unknown, lipiodol adheres to the tumor cell wall and is actively transported into these cells, causing lysis.²⁶ The Kupffer cells in the adjacent liver parenchyma are able to phagocytize the oil and remove it over a period of days. HCC does not contain Kupffer cells and therefore cannot remove the lipiodol.²⁷ It will remain in the extracellular tumor for months to years and can be visualized on CT and MRI to identify the tumor and monitor response (Fig 1D).

Lipiodol is an excellent agent for intra-arterial hepatic embolization for several reasons. First, as an embolic agent, it is viscous and water insoluble, causing temporary occlusion of the capillaries downstream when injected into the artery.²⁸ Because HCC is hypervascular, it tends to selectively uptake lipiodol when infused into a feeding artery.²⁹ Compared to hepatocytes, lipiodol is more lethal to tumor cells due to its

transport through the cell wall, as described above. As lipiodol is radiopaque, it makes fluoroscopic visualization obvious during catheter injections, which can limit nontarget embolization of adjacent arteries.

When a suspension of chemotherapeutics and lipiodol is injected intra-arterially, the lipiodol acts as a carrier and an embolic agent. The lipiodol and the chemotherapeutic agent are insoluble and separate minutes after embolization.²⁸ During arterial injection, the lipiodol/chemotherapeutic solution is delivered preferentially to the tumor due to blood flow characteristics described earlier.^{28,29} This results in higher concentrations of the agents in the tumor. The local concentration of the chemotherapeutics after chemoembolization is many times higher compared with systemic intravenous therapy.²⁹

In the 1970s and 1980s, numerous studies investigated the benefits of systemic chemotherapy on HCC. Most protocols contained doxorubicin as a result of early reports of survival benefits with single-agent doxorubicin therapy.³⁰⁻³² Two reports suggested that a combination of systemic cisplatin and doxorubicin offered significant tumor responses; however, survival benefits were limited due to side effects and liver toxicity.^{33,34} Interventional radiologists began mixing lipiodol with the same chemotherapeutic agents used in the systemic trials to improve local concentrations and decrease side effects. The first interventional radiology study of chemoembolization with lipiodol mixed with mitomycin C, cisplatin, and doxorubicin demonstrated a tumor response rate of 85% with no progression of disease in 38 of 38 patients over 1 year.³⁵ With these promising results, the combination or addition of these chemotherapeutics to lipiodol became more popular.

An initial misconception regarding the technique of mixing chemotherapy with lipiodol was later clarified. It was initially believed that the chemotherapy agents are released slowly from the lipiodol. In actuality, these agents are quickly washed through the liver into the systemic circulation. Peak levels are reached within 5 minutes of embolization and are then quickly eliminated.³⁶ This process can cause systemic effects from all these agents, including hair loss, possible cardiac toxicity, nausea, and diarrhea. As none of these agents has been shown to significantly improve survival when given intravenously, we must conclude that the increased response with chemoembolization occurs during the short time that the tumor cells are hypoxic and the chemotherapeutics are at high concentrations in the tumor.^{9,29}

In an attempt to improve the delivery of chemotherapeutic agents to tumors, a new embolic material has been developed: drug-eluting beads (DEBs). LC Bead microspheres (Biocompatibles International, UK) and HepaSpheres (BioSphere Medical Inc, Rockland, MD) are the only two such products currently available in the

United States. Both products ionically bind to negatively charged chemotherapeutics, and are most commonly attached to doxorubicin (Fig 2). These beads range from 100 to 1,200 μm and have been proven in vitro and in vivo to slowly elute the doxorubicin up to 7 days after embolization.³⁶ Total dose of doxorubicin (75 mg to 150 mg) bound in DEB treatment is similar to doses used in the lipiodol/doxorubicin protocols. However, peak systemic levels of doxorubicin after DEB embolization are approximately 5% of those after doxorubicin/lipiodol embolization, and levels remain stable over 7 to 10 days.³⁶

Relative contraindications to chemoembolization include portal vein tumor invasion, chronic renal insufficiency (estimated glomerular filtration rate [eGFR] < 40 mL/min/1.73 m²), elevated bilirubin (> 3 mg/dL), and total liver involvement of tumor greater than 50%.³⁷ These contraindications can occasionally be circumvented with the use of CO₂ in lieu of iodinated contrast. Subsubselective embolization, intended to embolize as little surrounding liver as possible, can often be utilized for patients with higher degrees of liver disease. Embolization with portal vein invasion can be safe in lipiodol chemoembolization but has not been determined with DEB chemoembolization.³⁸

Following chemoembolization, a postembolization syndrome (PES) can occur that includes pain over the treatment area, nausea, fatigue, and possible vomiting. PES is not considered a complication as it is caused by the reduced blood flow to the treatment area. There is often transient elevation in the white blood cell count and liver enzymes for 48 to 72 hours associated with the PES. Complications include liver abscesses (< 1%),

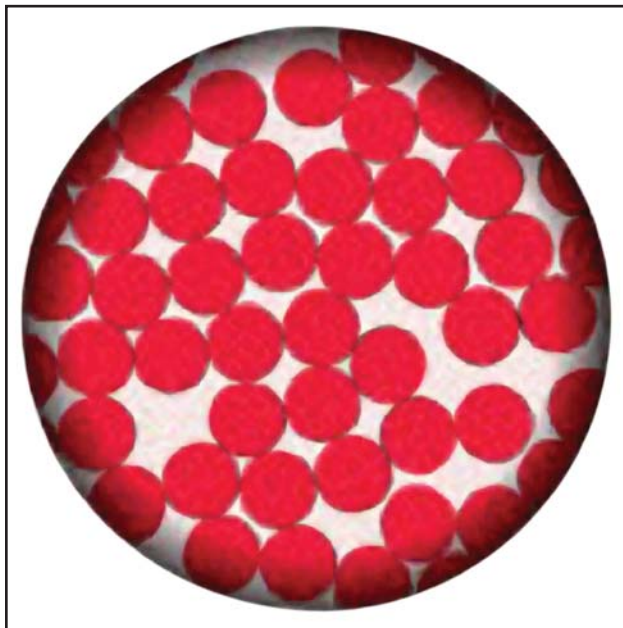


Fig 2. — Photomicrograph of drug-eluting beads (DEBs) 300 to 500 μm . The beads turn a brilliant red after binding to doxorubicin as this photomicrograph demonstrates.

gallbladder necrosis (< 1%), liver failure (1%), nontarget embolization (< 1%), and transient bilirubin toxicity.^{37,39-41} Postembolization abscess is more common in patients with previous biliary-enteric anastomoses and occurs in at least 5% of cases. This is thought to be due to increased bacterial flora in the intrahepatic biliary system that thrives in the necrotic tumor bed following embolization.⁴²

Two major randomized controlled trials (RCTs) have demonstrated improved survival with chemoembolization vs conservative/medical treatment. The first, performed by Llovet et al⁴³ in 2002, compared chemoembolization (gelatin sponge and doxorubicin), bland embolization, and conservative treatment. The study was stopped early when survival benefits were demonstrated after several inspections. Two-year survival probabilities were 63% for the chemoembolization group and 27% for the control group. The second RCT, performed by Lo et al⁴⁴ in 2002, evaluated chemoembolization and response to cisplatin/lipiodol embolization vs symptomatic treatment. The 3-year survival rate was 26% in the chemoembolization group vs 3% in the symptomatic treatment group. Several meta-analyses have been performed to include smaller RCTs and cohort studies, which also concluded that chemoembolization improves survival.^{45,46} A recently published RCT comparing systemic doxorubicin vs chemoembolization in unresectable HCC demonstrated that only patients with well-compensated liver function had survival benefits with chemoembolization.⁴⁷ Median survival following chemoembolization was improved only in the chemoembolization group in Child-Pugh A patients with albumin > 3.3 g/dL (36 vs 60 weeks).

A recent RCT comparison of DEB/doxorubicin and doxorubicin/lipiodol embolization demonstrated decreased systemic side effects and decreased rates of liver failure with the DEB treatment.⁴⁸ These findings suggest that the lower systemic doxorubicin levels after DEB treatment correlates with systemic effects. This report also noted an improved objective tumor response with DEB/doxorubicin compared with doxorubicin/lipiodol embolization. A second recent RCT demonstrated improved tumor response, longer time to progression, and fewer recurrences with DEB/doxorubicin compared with embolization alone with similar-sized particles (bland embolization).⁴⁹ Long-term survival results with the DEB/doxorubicin combination were not compared to other methods as longer follow-up was necessary.

Yttrium-90 Radioembolization

Radioembolization refers to the target infusion of radioactive substances via the artery feeding the tumors. Although numerous small studies have evaluated radioembolization with different radioactive agents, in recent years yttrium-90 (⁹⁰Y) has emerged as

the primary choice. In the United States, two ^{90}Y preparations are available: TheraSphere[®] (Yttrium-90 Glass Microspheres, Theragenics Corp, Buford, GA) and SIR-Spheres[®] (Yttrium-90 Microspheres, Sirtex Medical Ltd, Lane Cove NSW, Australia). The FDA has approved TheraSphere for HCC and SIR-Spheres for metastatic disease to the liver. The treatments are performed in the same manner and the preparations are similar, differing in the size and number of particles to which the ^{90}Y is attached. The particles infused in radioembolization are not intended to cause total arterial occlusion, thus sparing arterial flow to the adjacent liver and decreasing postembolization symptoms.⁵⁰ The ^{90}Y is a pure beta radiation emitter, making it optimal for intra-arterial injection. Beta radiation particles are high-energy but cannot penetrate greater than 11 mm in human tissue. The half-life of ^{90}Y is 64 hours; therefore, 94% of the radiation emitted occurs within the first 11 days after treatment.⁵¹ As described above, HCC typically receives 5 to 7 times the arterial flow compared with adjacent liver. Injecting the radiation particles in the hepatic artery results in a disproportionate distribution to the tumor, and high doses of radiation are delivered directly to the tumor over the following 10 days.⁵⁰

Although the technique for injection of ^{90}Y microspheres is similar to chemoembolization with regard to materials and location of injection, the evaluation and preprocedure workup is more involved.⁵⁰ Nontarget embolization with ^{90}Y has increased morbidity when compared to chemoembolization. If ^{90}Y is infused into small, unnamed duodenal/pancreatic branches not previously embolized, nonhealing radiation ulcers may develop in the affected bowel; this occurs in approximately 4% to 5% of treatments.⁵² To avoid this complication, lengthy mapping angiograms of the celiac and superior mesenteric arteries are required, and coil



Fig 3. — Tumor shunting in HCC. During an arterial injection of contrast in the distal right hepatic artery, the feeding arteries to the tumor are visualized (arrow). There was shunting to the hepatic venous system (arrowhead shows larger vessel). Embolization with small particles would flow through the tumor into the systemic circulation through the shunt.

embolization is performed on all branch vessels adjacent to the hepatic arteries.

An additional step necessary in pretreatment evaluation for ^{90}Y is the estimation of tumor shunting. HCC commonly has small arteriovenous shunts that would allow radioactive particles from ^{90}Y infusion to flow from the hepatic artery into the hepatic venous system and then to the lungs (Fig 3).⁵⁰ Immediately following the celiac/superior mesenteric artery branch vessel coil embolization procedure, approximately 170 MBq of technetium-99m macroaggregated albumin (^{99}Tc -MAA) is injected in the planned treatment artery (right or left hepatic artery). The MAA has similar particle size to the ^{90}Y beads and will predict distribution, but the ^{99}Tc has no adverse effect at that dose due to the different particle energy (gamma) it emits. Patients are then immediately transferred to the nuclear medicine department for planar body nuclear medicine scan. The amount of radiation being emitted outside the liver is then determined, which correlates to the tumor shunt fraction. If the dose outside the liver is 20% or greater, it suggests

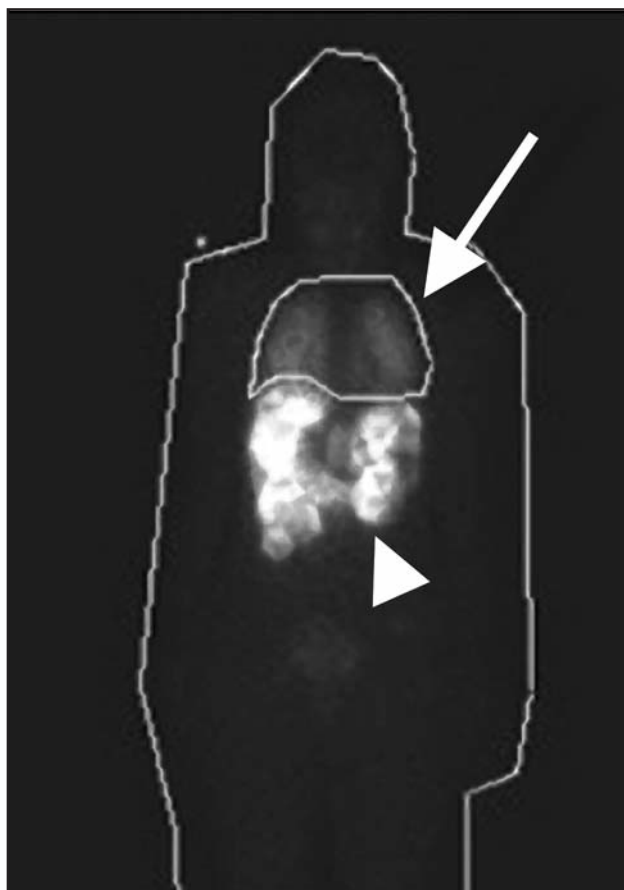


Fig 4. — Preradioembolization ^{99}Tc -MAA scan. After coil embolization of all nonhepatic branches of the common hepatic artery, ^{99}Tc -MAA was injected intra-arterially into the proper hepatic artery to evaluate for tumor shunting to the lungs. The heterogenous uptake in the liver (arrowhead) is due to extensive hypervascular hepatic tumors. There was > 20% activity in the lungs (arrow) in this examination due to arteriovenous tumor shunting. Due to the degree of shunting, the patient was no longer considered a candidate for ^{90}Y treatment.

significant tumor shunting and ^{90}Y treatment is contraindicated.⁵⁰ The shunt most commonly allows the dose to be carried to the lungs as it is the next capillary network after the hepatic veins (Fig 4). A shunt of greater than 20% with typical injected ^{90}Y doses could cause radiation lung exposure greater than 30 Gy, which can cause radiation pneumonitis.⁵² In addition, any suggestion of radiation activity in the bowel after the hepatic artery $^{99}\text{Tc-MAA}$ injection is a contraindication to treatment since a ^{90}Y injection at the same location would put the patient at risk for radiation ulcers.

Compared to chemoembolization, ^{90}Y radioembolization does offer benefits in some patients. Patients with bilobar disease or extensive multifocal HCC can often be treated with one treatment (Fig 5A-D). Main portal vein thrombosis is considered a relative contraindication for chemoembolization but can be safely treated with ^{90}Y radioembolization, given partial retention of arterial flow in the treatment area.⁵³

No RCTs have yet evaluated survival with ^{90}Y treatment compared to medical treatment of HCC. One recent prospective study, which included 291 patients, showed response rates of 42% to 52%, with survival averages in Child-Pugh A patients of 17 months.⁵⁴

An ongoing issue involves whether ^{90}Y embolization is better than chemoembolization at treating oligocentric HCC. No RCTs have compared the two treatments, although a recent retrospective analysis demonstrated no difference in tumor response or survival between chemoembolization and ^{90}Y radioembolization in HCC treatment.⁵⁵ Side effects from ^{90}Y radioembolization include fatigue (57%), pain (23%), and nausea/vomiting (20%). Approximately 20% of patients have grade 3-4 bilirubin toxicity, and > 75% have significant drops in systemic lymphocytes counts.^{52,54,55} Major complication risks for ^{90}Y radioembolization include bowel/gastric ulcers (4%), biliary/gallbladder injury requiring surgery (< 1.5%), and radiation pneumonitis (< 1%).^{52,54}

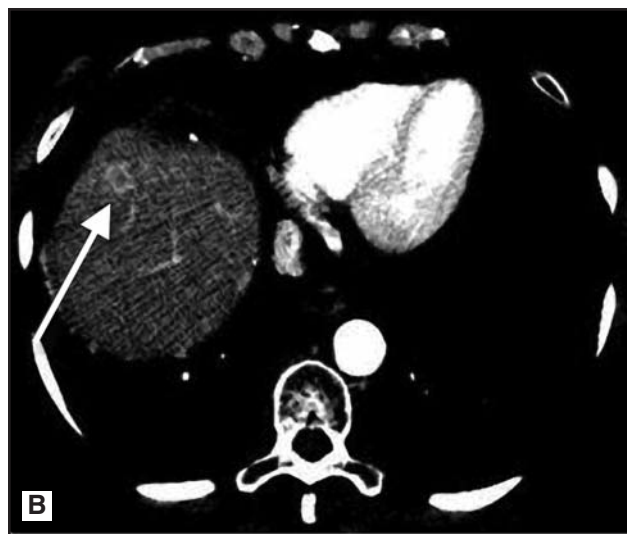


Fig 5A-B. — Arterial phase CT in a nontransplant candidate with nonoperable multifocal HCC. Arrows show arterial enhancing lesions.

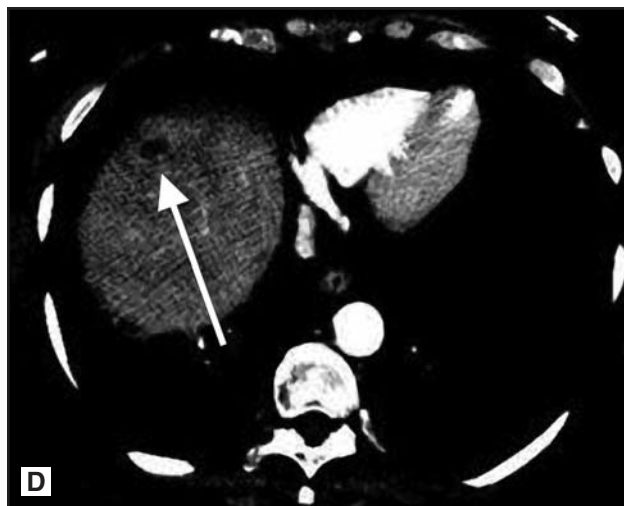
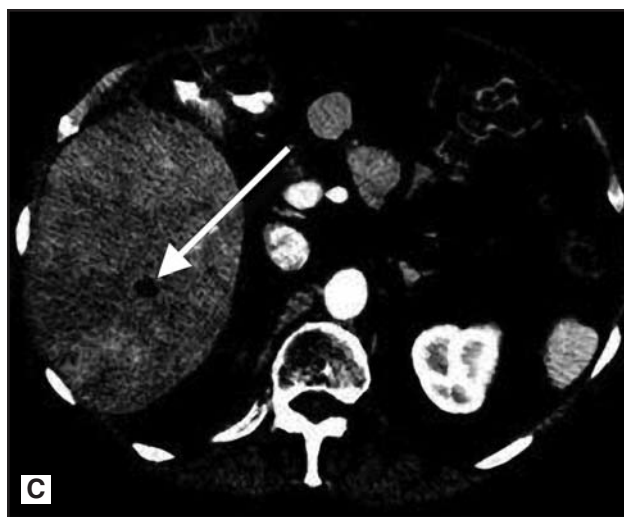


Fig 5C-D. — Lesions in Fig 5 at 6 weeks following ^{90}Y radioembolization. Arrows show two areas of necrosis in the location of the previous tumors. Note the heterogeneous enhancement of the surrounding liver, often seen following ^{90}Y treatment.

Percutaneous Thermal Ablation

Percutaneous thermal ablation is accomplished primarily by freezing (cryoablation) or heating (radiofrequency ablation, RFA) of the tumors. The use of percutaneous ethanol injection (PEI), which was once considered the primary treatment for HCC, has decreased due to recent reports demonstrating better outcomes with thermal ablation. All of these procedures are performed with image guidance, commonly CT in the United States.

Percutaneous Ethanol Injection

In the early 1990s, PEI was considered the primary percutaneous treatment for HCC. The materials used for PEI are inexpensive, and the procedures are straightforward. PEI is simply a fine-needle injection of the tumor under image guidance with 95% ethyl alcohol. The theory as to its efficacy lies in the fact that the tumors tend to be soft and the surrounding liver is cirrhotic and hard, which restricts the alcohol from diffusing out into the liver. In addition, there is often a capsule around small, well-differentiated HCC tumors.³ The volume of ethanol to be injected is determined by calculating the volume of the tumor. PEI is limited in that it often requires more than four treatments to treat each mass, even with tumors < 3 cm.⁵⁶

Three large, well-designed RCTs have compared RFA with PEI in the treatment of HCC.⁵⁶⁻⁶⁰ All demonstrated increased local recurrence, decreased survival, and increased number of treatments with PEI compared with RFA. The largest RCT, performed in 2005 by Shiina et al,⁵⁸ included 232 patients, each with fewer than three tumors < 3 cm, who were randomized to RFA or PEI. The 4-year survival rate was 75% in the RFA group and 57% in the PEI group. No difference in complications was seen; however, procedure time and cumulative hospital stay were both increased in the PEI group. Although few complications are associated with each ethanol injection session (< 1%), patients often require four to eight injections, and the risks are then additive — causing the total number of complications to rival or surpass RFA despite the smaller needles involved.⁶⁰ Risks include liver necrosis, hemorrhage, portal vein thrombosis, gallbladder injury, and bowel necrosis. If RFA is not available, PEI is an acceptable treatment choice and offers a 2-year recurrence-free survival rate of approximately 62%. Although the materials used in PEI are inexpensive, additional considerations include increased physician time and resources required when ultrasound or CT is utilized for image guidance. Also, each lesion will likely require multiple treatments.⁶⁰

Cryoablation

Cryoablation technology relies on physical properties of argon gas that, when decompressed, reaches temperatures far below freezing. In vitro and in vivo studies over the past 50 years have determined that cell

death is certain at temperatures of -20°C and that rapid freezing with slow thaw cycles cause immediate cell death at higher temperatures.⁶¹ The actual temperature at which a tumor cell will lyse, either acutely or within 24 hours of cryoablation, is a matter of debate. The required temperature may also be specific to tumor and organ cell types.^{62,63} Recent studies of temperature zones around a cryoablation probe in the liver demonstrated small zones that reached -20°C .⁶⁴ Thaw-freeze cycles increase the kill zone with higher temperatures, but to what extent in each organ is unknown. Since cryoablation probes are needle-shaped (14G), large kill zones are not possible with a single probe. Therefore, large masses may require 3 or 4 probes. Each additional probe increases procedure time and the risk of organ injury and bleeding.⁶⁵

The benefits of cryoablation, when compared with RFA, include markedly reduced procedure pain and the ability to visualize an “ice ball” formation on CT or ultrasound during treatment (Fig 6A-D). The freezing technique of cryoablation causes less pain and often allows cryoablation to be performed under conscious sedation, making it a viable option for patients who are poor anesthesia candidates.⁶⁶ The ability to visualize the ice ball allows more precise evaluation of the treatment zone in real time. This allows the operator to reposition or add an additional probe if a portion of the tumor is not included in the treatment zone. A further benefit of cryoablation includes a reduced “heat sink” effect, a term used to describe the local variation in ablation temperature due to vessels flowing through the ablation zone.^{64,65} Heat sink can allow tumors that are adjacent to large vessels to remain outside the kill temperature. Cryoablation is often able to overcome this obstacle more effectively than RFA can. Lastly, cryoablation maintains cellular integrity of connective tissue in vessel walls, or adjacent viscera linings, such as gallbladder, bowel, and kidney.⁶⁷

There is a paucity of research on long-term survival of cryoablation and HCC. Several studies have evaluated cryosurgery for the treatment of liver malignancies, but data are limited regarding percutaneous cryoablation.⁶⁸ Cryosurgery is simply cryoablation performed with a surgical laparotomy or laparoscopic field, often performed with intraoperative ultrasound guidance. It is difficult to discern if cryosurgery and cryoablation effects are comparable, considering the increased risks of open surgery and the lack of image guidance by an interventional radiologist. No RCTs have been conducted on the survival benefits of cryoablation vs RFA, although many investigators believe cryoablation is as effective as RFA in treating HCC.⁶⁸ Several studies have described increased complications associated with open cryosurgery, often related to postprocedure hemorrhage.^{69,70} The risks of hemorrhage appear to be related to a lack of cauterization at the boundaries of the ablation and the ability of the ice ball to crack into

the organ being treated.⁷⁰ Death has occurred in several reports in the first 24 hours after cryosurgery, and the mortality rate approached 1.5% in a meta-analysis, mostly attributable to hepatic hemorrhage or a phenomenon termed “cryoshock.” Cryoshock, a rare syndrome of multiorgan failure, coagulopathy, and disseminated intravascular coagulation (DIC), is specific to cryotherapy in the liver.⁷¹ Cryoshock appears to be related to large-volume ablations as most cases have been reported in patients with large treatment zones and extensive disease.⁷²

Radiofrequency Ablation

Radiofrequency ablation technology began over 80 years ago with the introduction of the Bovie electro-surgical device (Bovie Medical Corp, Clearwater, FL), named for the inventor, William T. Bovie. In RFA, current

is applied from grounding pads placed on the patient’s extremities to a needle probe placed by the operator. As the current approaches the probe, it causes ionic excitation in the cells, developing heat. The kill zone is dependent on the maximum temperature obtained and the length of time the cells are exposed to that temperature. A temperature of 50°C causes immediate cell death and is the target temperature, but lesser temperatures will also cause lysis if applied for longer periods of time.^{73,74} The diameter of the kill zone around the probe is related to the electrical resistance of the tissue being ablated, which varies little in humans.⁷⁵ The kill zone in liver tissue is approximately 1.7 cm from a single probe. To address this limited coverage, complex stellate-like probes have been developed that, when deployed, are shaped like the tines of an umbrella, thus allowing a markedly increased kill zone. Several manufacturers have developed probes that provide 5-cm kill zones when properly used (Fig 1E-G and Fig 7).

The kill zone diameter and the effects of RFA have been extensively studied in the liver as opposed to



Fig 6A. — Noncontrast CT following lipiodol chemoembolization of a 4-cm left hepatic HCC. Embolization was performed to mark the lesion for planned cryoablation. Cryoablation was utilized instead of RFA, given the subcapsular tumor location and proximity to the abdominal wall. The patient was also a poor candidate for general anesthesia. Lipiodol (arrows) stains the tumor and delineates tumor margins.

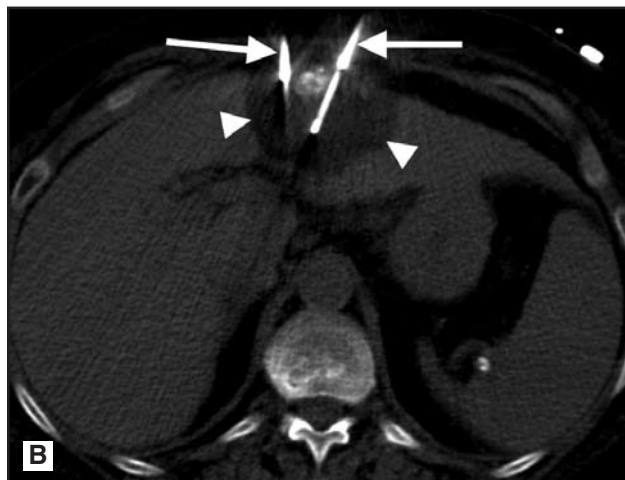


Fig 6B. — CT during cryoablation of a left hepatic tumor performed under conscious sedation. Note the lipiodol marking the mass. Several cryoprobes were necessary given the large tumor size (arrows). The ice ball is well delineated on noncontrast CT (arrowheads).



Fig 6C-D. — Arterial and portal venous phase CT at 1 year following cryoablation of a large left hepatic HCC. Significant involution of mass has occurred (arrows). The left portal vein adjacent to the mass is patent.

cryoablation. There are, however, some drawbacks and limitations of RFA. As the treatment zone is not reliably visualized during the procedure as it is in cryoablation, initial proper placement of the probe is imperative. Treatment of subcapsular liver tumors with RFA can cause severe pain to the patient, often necessitating general anesthesia. Nontarget ablation of the bowel or gallbladder can cause necrosis and perforation if inadvertently treated. Heat sink is a major limitation of RFA as large vessels (> 3 mm) that pass through the ablation zone can prevent adjacent tissue from reaching cytotoxic levels, thereby leaving positive margins in place.⁷⁶⁻⁷⁸

Recent studies of complete response rates from RFA in masses < 3.5 cm have approached 70%, confirmed by subsequent surgical resection or explantation of the treated liver.⁷⁹⁻⁸² An RCT of RFA compared to partial hepatectomy in HCC < 5 cm demonstrated equal survival rates and recurrence-free periods from 1 to 4 years.⁸² These findings currently make RFA the procedure of choice for local ablation in small HCCs when surgery or transplantation is not an option.

Complications from RFA are reported to be approximately 7%.⁸³ The most common complication is hemorrhage, but major hemorrhage requiring transfusion occurs in < 1% of cases. Additional risks from RFA include injury to the liver, abscess (1%), pneumothorax (< 1%), and biliary injury (< 1%). These risks compare favorably to surgical resection, which has reported complication risks of 9% to 22%.⁸⁴ Postprocedure pain from ablation is comparable to embolization. Lesions > 5 cm have poor long-term complete response rates with RFA, but these patients have also shown poor results with any type of local or systemic treatment, given the higher risks of vascular invasion.¹¹ Initial reports of high tumor-seeding rates from RFA in the 1990s raised fears of spreading disease outside the liver in transplant candidates.⁸⁵ However, several recent studies comprising thousands of patients have demonstrated seeding rates of approximately 1%.^{60,79-82}

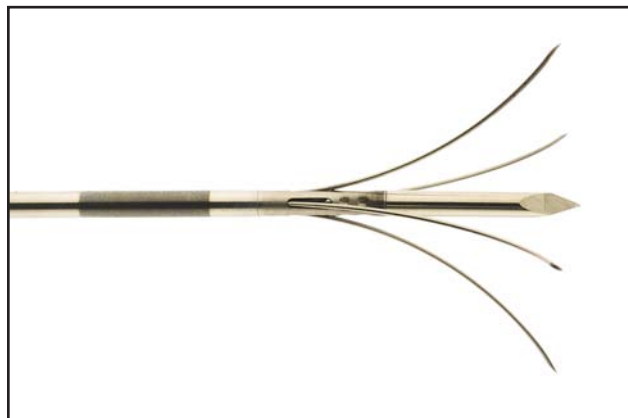


Fig 7. — Example of a multiarray RFA probe (RITA Talon, RITA Medical Systems, Inc, Mountain View, CA). With the tines retracted, the probe is 14 gauge; when fully deployed, this device is capable of 4-cm diameter burns. Photograph compliments of Angiodynamics/RITA.

This may be due to an improved technique of “burning the tract,” which involves applying a low level current to the RFA probes as they are removed to kill any “hitch-hiking” tumor cells along the probe tract.⁸⁶

Combination Therapies

Combination regional treatment has become a recent area of research and treatment advances, especially regarding combination embolization and RFA. The efficacy of this combination is thought to be due to the increased tumor sensitization to heat kill following chemoembolization. Doxorubicin, even at low levels, has been shown to sensitize cells to heat kill by as much as 5°C.⁸⁷ Combining these procedures can increase the ablative zone in RFA up to 6 to 7 cm, which should decrease recurrence rates.^{88,89} In recent studies, local control and long-term survival were increased with combination RFA and chemoembolization compared with either single procedure in tumors < 3 cm.⁸⁸⁻⁹³ Combination ablation therapies, which can be performed in a single session, may also improve survival. A recent prospective randomized trial evaluated the combination of PEI/RFA and demonstrated improved tumor responses and survival rates in large HCCs compared with RFA alone.⁹⁴

Conclusions

The use of chemoembolization has become commonplace in the treatment of HCC. However, studies of survival benefits are limited due to the poor prognosis of those with concomitant cirrhosis and the lack of large multicenter trials. The extensive array of embolization agents makes the compilation and analysis of data more difficult as different institutions use various agents and protocols to treat HCC. Without RCTs that compare treatment protocols, it is impossible to determine the most effective embolic material and chemotherapeutic agent for treating HCC. Early reports suggest the DEB/doxorubicin embolization offers improved tumor response and decreased side effects. However, the studies need to be extended to evaluate survival outcomes. As continued comparative studies are published, interventional radiologists will need to tailor treatment protocols to a more universal approach for different patient groups.

Percutaneous thermal ablation has proven to be as effective as resection in tumors < 5 cm and offers favorable results for tumors < 7 cm for patients without other treatment options. Cryoablation appears to offer similar tumor responses to RFA, but the issue of increased complications needs attention with a comparative study. The use of cryosurgery has decreased due to reports of surgical complications, but whether this correlates to percutaneous cryoablation complications is less clear. At institutions without thermal ablation technology, PEI remains an inexpensive way to treat tumors < 3 cm but offers less benefit than RFA.

Yttrium-90 offers excellent tumor response in hospitals with the resources for treatment, although RCTs on long-term survival compared to conservative therapy are needed to confirm that the tumor response correlates to survival benefits. Two small recent studies have suggested ⁹⁰Y and chemoembolization are equally effective in treating oligocentric HCC. Yttrium-90 also offers treatment options to patients with more extensive tumor burden and portal vein thrombosis.

Combination therapies with thermal ablation, PEI, and chemoembolization will hopefully further increase survival rates in patients with HCC. Recent reports have shown improvements in survival from combinations of many of these techniques. Improved tumor response appears to be helpful in prolonging the lives of patients who are not considered transplant candidates.

The incidence of HCC has rapidly increased both worldwide and in the United States. Currently, traditional surgery can treat only a small percentage of patients. Liver transplantation remains the most successful approach to treating HCC with underlying cirrhosis, but only approximately 25% of patients with HCC are candidates; additionally, many patients reside in states with limited transplant programs. Survival rates will likely continue to improve with increased screening, refined locoregional treatments, and newly developed systemic chemotherapeutics. It is hoped that the treatment of hepatitis C and B will also continue to improve and that measures to decrease infection rates will prove effective in reversing the current trends.

A multidisciplinary approach to HCC is imperative, especially at institutions that offer transplantation. Tailored treatment for each patient is required to prevent progression of disease in liver transplant candidates and to prolong survival in nontransplant candidates. The role of an "interventional oncologist" is developing in large tertiary centers, and continued specialization is likely as knowledge increases and specialized HCC centers develop across the country.

References

1. El-Serag HB, Mason AC, Key C. Trends in survival of patients with hepatocellular carcinoma between 1977 and 1996 in the United States. *Hepatology*. 2001;33(1):62-65.
2. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol*. 2009;27(9):1485-1491.
3. Kondo F. Histological features of early hepatocellular carcinomas and their developmental process: for daily practical clinical application: hepatocellular carcinoma. *Hepatol Int*. 2009;3(1):283-293.
4. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology*. 2007;132(7):2557-2576.
5. Hayashi M, Matsui O, Ueda K, et al. Correlation between the blood supply and grade of malignancy of hepatocellular nodules associated with liver cirrhosis: evaluation by CT during intraarterial injection of contrast medium. *AJR Am J Roentgenol*. 1999;172(4):969-976.
6. Takayasu K, Muramatsu Y, Furukawa H, et al. Early hepatocellular carcinoma: appearance at CT during arterial portography and CT arteriography with pathologic correlation. *Radiology*. 1995;194(1):101-105.
7. Hayashi M, Matsui O, Ueda K, et al. Progression to hypervascular hepatocellular carcinoma: correlation with intranodular blood supply evaluated with CT during intraarterial injection of contrast material. *Radiology*. 2002;225(1):143-149.

8. Pawlik TM, Delman KA, Vauthey JN, et al. Tumor size predicts vascular invasion and histologic grade: implications for selection of surgical treatment for hepatocellular carcinoma. *Liver Transpl*. 2005;11(9):1086-1092.
9. Jonas S, Bechstein WO, Steinmüller T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology*. 2001;33(5):1080-1086.
10. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378-390.
11. Burroughs A, Hochhauser D, Meyer T. Systemic treatment and liver transplantation for hepatocellular carcinoma: two ends of the therapeutic spectrum. *Lancet Oncol*. 2004;5(7):409-418.
12. Fuss M, Salter BJ, Herman TS, et al. External beam radiation therapy for hepatocellular carcinoma: potential of intensity-modulated and image-guided radiation therapy. *Gastroenterology*. 2004;127(5 Suppl 1):S206-S217.
13. Otto G, Heuschen U, Hofmann WJ, et al. Survival and recurrence after liver transplantation versus liver resection for hepatocellular carcinoma: a retrospective analysis. *Ann Surg*. 1998;227(3):424-432.
14. Poon RT, Fan ST, Lo CM, et al. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg*. 2002;235(3):373-382.
15. Figueras J, Jaurrieta E, Valls C, et al. Survival after liver transplantation in cirrhotic patients with and without hepatocellular carcinoma: a comparative study. *Hepatology*. 1997;25(6):1485-1489.
16. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology*. 1999;30(6):1434-1440.
17. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33(2):464-470.
18. Wiesner RH, McDiarmid SV, Kamath PS, et al. MELD and PELD: application of survival models to liver allocation. *Liver Transpl*. 2001;7(7):567-580.
19. Kremers WK, van Ijperen M, Kim WR, et al. MELD score as a predictor of pretransplant and posttransplant survival in OPTN/UNOS status 1 patients. *Hepatology*. 2004;39(3):764-769.
20. Brown DB, Fundakowski CE, Lisker-Melman M, et al. Comparison of MELD and Child-Pugh scores to predict survival after chemoembolization for hepatocellular carcinoma. *J Vasc Interv Radiol*. 2004;15(11):1209-1218.
21. Schwartz M. Liver transplantation for hepatocellular carcinoma. *Gastroenterology*. 2004;127(suppl 1):268-276.
22. Cillo U, Bassanello M, Vitale A, et al. The critical issue of hepatocellular carcinoma prognostic classification: which is the best tool available? *J Hepatol*. 2004;40(1):124-131.
23. Georgiades CS, Liapi E, Frangakis C, et al. Prognostic accuracy of 12 liver staging systems in patients with unresectable hepatocellular carcinoma treated with transarterial chemoembolization. *J Vasc Interv Radiol*. 2006;17(10):1619-1624.
24. Marrero JA, Fontana RJ, Barrat A, et al. Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. *Hepatology*. 2005;41(4):707-716.
25. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. *Liver Transpl*. 2002;8(9):765-774.
26. Chou FI, Fang KC, Chung C, et al. Lipiodol uptake and retention by human hepatoma cells. *Nucl Med Biol*. 1995;22(3):379-386.
27. Kan Z, McCuskey PA, Wright KC, et al. Role of Kupffer cells in iodized oil embolization. *Invest Radiol*. 1994;29(11):990-993.
28. Konno T. Targeting cancer chemotherapeutic agents by use of lipiodol contrast medium. *Cancer*. 1990;66(9):1897-1903.
29. Sasaki Y, Imaoka S, Kasugai H, et al. A new approach to chemoembolization therapy for hepatoma using ethiodized oil, cisplatin, and gelatin sponge. *Cancer*. 1987;60(6):1194-1203.
30. Olweny CL, Toya T, Katongole-Mbidde E, et al. Treatment of hepatocellular carcinoma with adriamycin. Preliminary communication. *Cancer*. 1975;36(4):1250-1257.
31. Olweny CL, Katongole-Mbidde E, Bahendeka S, et al. Further experience in treating patients with hepatocellular carcinoma in Uganda. *Cancer*. 1980;46(12):2717-2722.
32. Lai CL, Wu PC, Chan GC, et al. Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. *Cancer*. 1988;62(3):479-483.
33. Leung TW, Tang AM, Zee B, et al. Factors predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, doxorubicin and 5-fluorouracil chemotherapy. *Cancer*. 2002;94(2):421-427.
34. Leung TW, Patt YZ, Lau WY, et al. Complete pathological remission is possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. *Clin Cancer Res*. 1999;5(7):1676-1681.
35. Solomon B, Soulen MC, Baum RA, et al. Chemoembolization of hepatocellular carcinoma with cisplatin, doxorubicin, mitomycin-C, ethiodol, and polyvinyl alcohol: prospective evaluation of response and survival in a U.S. population. *J Vasc Interv Radiol*. 1999;10(6):793-798.

36. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol*. 2007;46(3):474-481.
37. Brown DB, Cardella JF, Sacks D, et al. Quality improvement guidelines for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy. *J Vasc Interv Radiol*. 2009;20(7 suppl):S219-S226, S226.e1-10.
38. Georgiades CS, Hong K, D'Angelo M, et al. Safety and efficacy of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma and portal vein thrombosis. *J Vasc Interv Radiol*. 2005;16(12):1653-1659.
39. Sakamoto I, Aso N, Nagaoki K, et al. Complications associated with transcatheter arterial embolization for hepatic tumors. *Radiographics*. 1998;18(3):605-619.
40. Takayasu K, Arai S, Ikai I, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology*. 2006;131(2):461-469.
41. Brown DB, Geschwind JF, Soulen MC, et al. Society of Interventional Radiology position statement on chemoembolization of hepatic malignancies. *J Vasc Interv Radiol*. 2009;20(7 Suppl):S317-S323.
42. Kim W, Clark TW, Baum RA, et al. Risk factors for liver abscess formation after hepatic chemoembolization. *J Vasc Interv Radiol*. 2001;12(8):965-968.
43. Llovet JM, Real MI, Montañá X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. 2002;359(9319):1734-1739.
44. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology*. 2002;35(5):1164-1171.
45. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology*. 2003;37(2):429-442.
46. Cammà C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology*. 2002;224(1):47-54.
47. Mabel M, Esmaeel M, El-Khodary T, et al. A randomized controlled trial of transcatheter arterial chemoembolization with lipiodol, doxorubicin and cisplatin versus intravenous doxorubicin for patients with unresectable hepatocellular carcinoma. *Eur J Cancer Care (Engl)*. 2009;18(5):492-499.
48. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol*. 2010;33(1):41-52.
49. Malagari K, Pomoni M, Kelekis A, et al. Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with BeadBlock for hepatocellular carcinoma. *Cardiovasc Intervent Radiol*. 2009 Nov 24. Epub ahead of print.
50. Salem R, Lewandowski RJ, Atassi B, et al. Treatment of unresectable hepatocellular carcinoma with use of 90Y microspheres (TheraSphere): safety, tumor response, and survival. *J Vasc Interv Radiol*. 2005;16(12):1627-1639.
51. SIR-Spheres® (Yttrium-90 Microspheres) [package insert]. Lane Cove NSW, Australia: Sirtex Medical Limited; 2006.
52. Riaz A, Lewandowski R, Kulik L. Complications following radioembolization with yttrium-90 microspheres: a comprehensive literature review. *J Vasc Interv Radiol*. 2009;20(9):1121-1130.
53. Salem R, Lewandowski R, Roberts C, et al. Use of Yttrium-90 glass microspheres (TheraSphere) for the treatment of unresectable hepatocellular carcinoma in patients with portal vein thrombosis. *J Vasc Interv Radiol*. 2004;15(4):335-345.
54. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology*. 2010;138(1):52-64.
55. Kooby DA, Egnatashvili V, Srinivasan S, et al. Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. *J Vasc Interv Radiol*. 2010;21(2):224-230.
56. Ishii H, Okada S, Nose H, et al. Local recurrence of hepatocellular carcinoma after percutaneous ethanol injection. *Cancer*. 1996;77(9):1792-1796.
57. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology*. 2003;228(1):235-240.
58. Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology*. 2005;129(1):122-130.
59. Lin SM, Lin CJ, Lin CC, et al. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut*. 2005;54(8):1151-1156.
60. Orlando A, Leandro G, Olivo M, et al. Radiofrequency thermal ablation vs. percutaneous ethanol injection for small hepatocellular carcinoma in cirrhosis: meta-analysis of randomized controlled trials. *Am J Gastroenterol*. 2009;104(2):514-524.
61. Permpongkosol S, Nicol TL, Link RE, et al. Differences in ablation size in porcine kidney, liver, and lung after cryoablation using the same ablation protocol. *AJR Am J Roentgenol*. 2007;188(4):1028-1032.
62. Gage AA, Baust J. Mechanisms of tissue injury in cryosurgery. *Cryobiology*. 1998;37(3):171-186.
63. Chua KJ, Chou SK, Ho JC. An analytical study on the thermal effects of cryosurgery on selective cell destruction. *J Biomech*. 2007;40(1):100-116.
64. Permpongkosol S, Nicol TL, Khurana H, et al. Thermal maps around two adjacent cryoprobes creating overlapping ablations in porcine liver, lung, and kidney. *J Vasc Interv Radiol*. 2007;18(2):283-287.
65. Bilchik AJ, Wood TF, Allegra D, et al. Cryosurgical ablation and radiofrequency ablation for unresectable hepatic malignant neoplasms: a proposed algorithm. *Arch Surg*. 2000;135(6):657-662; discussion 662-664.
66. Allaf ME, Varkarakis IM, Bhayani SB, et al. Pain control requirements for percutaneous ablation of renal tumors: cryoablation versus radiofrequency ablation — initial observations. *Radiology*. 2005;237(1):366-370.
67. Sung GT, Gill IS, Hsu TH, et al. Effect of intentional cryo-injury to the renal collecting system. *J Urol*. 2003;170(2 Pt 1):619-622.
68. Awad T, Thorlund K, Gluud C. Cryotherapy for hepatocellular carcinoma. *Cochrane Database Syst Rev*. 2009;(4):CD007611.
69. Adam R, Hagopian EJ, Linhares M, et al. A comparison of percutaneous cryosurgery and percutaneous radiofrequency for unresectable hepatic malignancies. *Arch Surg*. 2002;137(12):1332-1339; discussion 1340.
70. Pearson AS, Izzo F, Fleming RY, et al. Intraoperative radiofrequency ablation or cryoablation for hepatic malignancies. *Am J Surg*. 1999;178(6):592-599.
71. Seifert JK, Morris DL. World survey on the complications of hepatic and prostate cryotherapy. *World J Surg*. 1999;23(2):109-113; discussion 113-114.
72. Kerker S, Carlin AM, Sohn RL, et al. Long-term follow up and prognostic factors for cryotherapy of malignant liver tumors. *Surgery*. 2004;136(4):770-779.
73. McGahan JP, Browning PD, Brock JM, et al. Hepatic ablation using radiofrequency electrocautery. *Invest Radiol*. 1990;25(3):267-270.
74. Lounsbury W, Goldschmidt V, Linke Ca, et al. The early histologic changes following electrocoagulation. *J Urol*. 1961;86:321-329.
75. Organ LW. Electrophysiologic principles of radiofrequency lesion making. *Appl Neurophysiol*. 1976-1977;39(2):69-76.
76. Lu DS, Raman SS, Limanond P, et al. Influence of large peritumoral vessels on outcome of radiofrequency ablation of liver tumors. *J Vasc Interv Radiol*. 2003;14(10):1267-1274.
77. Chang I, Mikityansky I, Wray-Cahen D, et al. Effects of perfusion on radiofrequency ablation in swine kidneys. *Radiology*. 2004;231(2):500-505.
78. Pompili M, Mirante VG, Rondinara G, et al. Percutaneous ablation procedures in cirrhotic patients with hepatocellular carcinoma submitted to liver transplantation: assessment of efficacy at explant analysis and of safety for tumor recurrence. *Liver Transpl*. 2005;11(9):1117-1126.
79. Mazzaferro V, Battiston C, Perrone S, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. *Ann Surg*. 2004;240(5):900-909.
80. Lu DS, Yu NC, Raman SS, et al. Radiofrequency ablation of hepatocellular carcinoma: treatment success as defined by histologic examination of the explanted liver. *Radiology*. 2005;234(3):954-960.
81. McGhana JP, Dodd GD 3rd. Radiofrequency ablation of the liver: current status. *AJR Am J Roentgenol*. 2001;176(1):3-16.
82. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg*. 2006;243(3):321-328.
83. Gervais DA, Goldberg SN, Brown DB, et al. Society of Interventional Radiology position statement on percutaneous radiofrequency ablation for the treatment of liver tumors. *J Vasc Interv Radiol*. 2009;20(7 Suppl):S342-S347.
84. Koffron AJ, Aufferberg G, Kung R, et al. Evaluation of 300 minimally invasive liver resections at a single institution: less is more. *Ann Surg*. 2007;246(3):385-392; discussion 392-394.
85. Llovet JM, Vilana R, Brú C, et al. Increased risk of tumor seeding after percutaneous radiofrequency ablation for single hepatocellular carcinoma. *Hepatology*. 2001;33(5):1124-1129.
86. Jaskolka JD, Asch MR, Kachura JR, et al. Needle tract seeding after radiofrequency ablation of hepatic tumors. *J Vasc Interv Radiol*. 2005;16(4):485-491.
87. Ahmed M, Liu Z, Lukyanov AN, et al. Combination radiofrequency ablation with intratumoral liposomal doxorubicin: effect on drug accumulation and coagulation in multiple tissues and tumor types in animals. *Radiology*. 2005;235(2):469-477.
88. Lencioni R, Crocetti L, Petruzzi P, et al. Doxorubicin-eluting bead-enhanced radiofrequency ablation of hepatocellular carcinoma: a pilot clinical study. *J Hepatol*. 2008;49(2):217-222.
89. Yamakado K, Nakatsuka A, Ohmori S, et al. Radiofrequency ablation combined with chemoembolization in hepatocellular carcinoma: treatment response based on tumor size and morphology. *J Vasc Interv Radiol*. 2002;13(12):1225-1232.
90. Liao GS, Yu CY, Shih ML, et al. Radiofrequency ablation after transarterial embolization as therapy for patients with unresectable hepatocellular carcinoma. *Eur J Surg Oncol*. 2008;34(1):61-66.

91. Akamatsu M, Yoshida H, Obi S, et al. Evaluation of transcatheter arterial embolization prior to percutaneous tumor ablation in patients with hepatocellular carcinoma: a randomized controlled trial. *Liver Int.* 2004;24(6):625-629.
92. Yang W, Chen MH, Wang MQ, et al. Combination therapy of radiofrequency ablation and transarterial chemoembolization in recurrent hepatocellular carcinoma after hepatectomy compared with single treatment. *Hepatol Res.* 2009;39(3):231-240.
93. Veltri A, Moretto P, Doriguzzi A, et al. Radiofrequency thermal ablation (RFA) after transarterial chemoembolization (TACE) as a combined therapy for unresectable non-early hepatocellular carcinoma (HCC). *Eur Radiol.* 2006;16(3):661-669.
94. Zhang YJ, Liang HH, Chen MS, et al. Hepatocellular carcinoma treated with radiofrequency ablation with or without ethanol injection: a prospective randomized trial. *Radiology.* 2007;244(2):599-607.