Liver-Directed Therapies for Hepatocellular Carcinoma

Cletus A. Arciero, MD, and Elin R. Sigurdson, MD, PhD, Philadelphia, Pennsylvania

Abstract

Hepatocellular carcinoma (HCC) is a major cause of cancer-related death worldwide. This disease can be treated through several surgical and nonsurgical approaches. Although the only curative options for patients with HCC are surgical (resection or transplantation), most patients unfortunately present with advanced neoplastic disease or experience the effects of chronic liver disease, making surgical resection implausible. Several additional options are available for treating this population. Ablative therapies such as percutaneous ethanol injection, cryotherapy, radiofrequency ablation, laser ablation, and microwave hyperthermic ablation can be used with varying degrees of success. Transarterial chemoembolization can be used in patients with advanced disease or advanced chronic liver disease that cannot be treated with resection or ablation. This article explores the various liver-directed therapies, including surgical resection, and defines morbidity, mortality, and survival for each. (JNCCN 2006;4:768–774)

Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer worldwide, and the fourth leading cause of cancer-related deaths. Chronic liver disease secondary to hepatitis B and C and the development of HCC are strongly correlated. Patients with cirrhosis caused by hepatitis are estimated to have a 1% to 2% per year risk for developing HCC, usually 30 to 50 years after initial infection with hepatitis B or C. Although 80% of cases are currently occurring in developing countries, the incidence is continually increasing in developed countries. The incidence in the United States is currently less than 5 per 100,000 population with an estimated 18,000 cases in 2005.

HCC is an aggressive disease, especially in the setting of chronic liver disease and cirrhosis. The median survival from diagnosis is often only 6 to 20 months. Patients often present with advanced disease, and those who do not often suffer from chronic liver disease that limits their treatment options. With the exception of liver transplantation, this article examines liver-directed therapies for HCC and their effects on outcomes.

Resection

Surgical resection is the only chance for cure in patients with HCC. Five-year survival rates for patients undergoing successful surgical resection can reach 40% to 50%. Unfortunately, most patients with HCC never undergo surgical resection because of advanced disease at diagnosis or coexisting chronic liver disease. Most commonly, potential surgical candidates must present with a solitary lesion and have disease confined to the liver, no evidence of vascular invasion, good underlying hepatic function, and no evidence of portal hypertension. Resectability rates using these criteria range from 10% to 15% in high-incidence regions to 15% to 30% in low-incidence regions. However, some centers will also consider patients for resection who have multiple lesions, vascular invasion not involving the main portal pedicles, or portal hypertension but otherwise preserved synthetic function.

The major questions arise when determining perioperative hepatic function, which often profoundly affects intraoperative mortality. Patients who are noncirrhotic have a less than 5% mortality rate, whereas the mortality rate for patients with cirrhosis is 10%. Traditionally, patients with cirrhosis with small, peripheral lesions and Child-Pugh classification A would be eligible for resection. However, Child-Pugh classification may not be sufficient to determine the suitability of a candidate for resection.
Liver-Directed Therapies for Hepatocellular Carcinoma

Studies have shown up to 38% of patients with Child-Pugh class A will develop postresection liver failure.\textsuperscript{12} Therefore, other studies must be performed to estimate the risk for postoperative liver failure, such as the hepatic venous pressure gradient, indocyanine green clearance, lidocaine metabolite clearance, computed tomographic (CT) volumetry, aminopyrine clearance, and galactose elimination. Indocyanine green clearance is routinely used in many high volume centers as a key part of the preoperative evaluation of patients with HCC.\textsuperscript{13} Applying these techniques can limit the resection of 5% to 15% of patients who would be cleared for surgery through traditional classifications schemes and allow for resection in patients otherwise considered to have inadequate hepatic reserve.\textsuperscript{12,14,15}

Another preoperative consideration for patients deemed borderline surgical candidates is portal vein embolization (PVE). The purpose is to allow hypertrophy of the anticipated remnant to decrease postoperative morbidity and mortality associated with hepatic dysfunction. As an adjunct to resection, PVE may actually allow for increased resectability in patients who otherwise could not tolerate an extended resection. The intervening period between PVE and surgical resection allows for the appearance of advanced disease that would obviate the benefit of surgical resection.\textsuperscript{16,17}

The surgical approach to resection of a hepatoma varies among centers, based on surgeon preferences and patient characteristics. Various surgical devices are available to aid in the hepatic dissection, and include vascular stapling devices, ultrasonic dissecting instruments, and various cautery devices. The extent of the resection depends largely on the tumor, the amount of normal liver removed, and the health of the remaining liver. In patients without cirrhosis and otherwise healthy livers, anatomic surgical resection of up to two thirds of the hepatic parenchyma can be performed without significant morbidity or mortality. But, patients with cirrhosis can often only tolerate a limited (less than one fourth total parenchyma) nonanatomic resection of their disease.

Perioperative morbidity and mortality, and overall survival of surgical resection for HCC depend on underlying liver disease. In the perioperative period, mortality rates range from less than 1% to 24%.\textsuperscript{3,8,10,11,18,19} Most of the perioperative mortality is caused by postoperative liver failure, with less than 10% of perioperative mortalities related to intraoperative blood loss. Perioperative mortality in a patient with cirrhosis is 14% to 24% compared with 0.8% to 7% in patients who are noncirrhotic.\textsuperscript{8,10,11,18–21} Other factors that portend an increased mortality include intraoperative blood loss more than 1.5 L and postoperative infectious complications.

Patient survival after complete surgical resection of a hepatoma is based on several factors. In general, 5-year survival rates vary widely, with rates of 27% to 49% in Western countries and only 11% in endemic countries.\textsuperscript{10,11,19,21,22} In patients with cirrhosis, the 4-year survival is 35% compared with up to 78% that has been reported in patients who are noncirrhotic.\textsuperscript{22} Other factors that portend a poor prognosis in patients who have undergone resection include vascular invasion (no 5-year survivors), lesions larger than 5 cm (5-year survival, 37%), and preoperative tumor rupture (median survival, 26 months).\textsuperscript{23–26} Vascular invasion outcome, as it pertains to recurrence and survival, has varied in the literature. Increased recurrence and decreased rates have been noted in patients with macrovascular invasion, but not always in those with microvascular invasion.\textsuperscript{27,28} Increased survival rates are noted in Child-Pugh A patients with lesions smaller than 5 cm (> 40%).\textsuperscript{10,11,22} Further increases are noted in select patients with only one lesion, no evidence of vascular invasion, and no evidence of intrahepatic metastases, lesion 5 cm or larger, and negative margin larger than 1 cm (5-year survival, approximately 70%).\textsuperscript{29–32}

Ablative Strategies

Complete surgical resection and transplantation are the only chance for cure in patients with HCC. Preoperative workup and selection can determine which patients will experience low morbidity and mortality with prolonged survival. However, many patients either have advanced tumors or severe liver disease that preclude surgical resection. For those patients, several ablative procedures can be used to prolong survival.

In patients with unresectable hepatomas, several liver-directed therapies can be used. These ablative therapies include percutaneous ethanol injection, cryoablation, radiofrequency ablation, and transarterial chemoembolization. Each technique allows for the ablation of the target lesions in patients, often regardless of underlying liver disease.
Patients with treated lesions smaller than 5 cm often experience 70% to 75% complete ablation rates. But complete ablation rates drop to less than 60% when lesions of 5 to 8 cm are treated. Survival rates vary from 0% to 70% in most studies, largely depending on the size and number of lesions. Single-session treatments can also be administered but require high volumes of ethanol (60–150 mL) administered under general anesthesia. Morbidity and mortality are low, with few reported deaths. Complications include hemorrhage, portal vein thrombosis, hemobilia, and rare cases of needle-tract seeding.

The procedure itself is uncomfortable and must be repeated multiple times. A typical treatment regimen consists of twice-weekly injections, each 1 to 8 mL ethanol, for a total of 4 to 12 sessions, depending on the size and number of lesions. Single-session treatments can also be administered but require high volumes of ethanol (60–150 mL) administered under general anesthesia. Morbidity and mortality are low, with few reported deaths. Complications include hemorrhage, portal vein thrombosis, hemobilia, and rare cases of needle-tract seeding.

The results of PEI often depend on the size of the lesion. Patients with lesions smaller than 5 cm often experience 70% to 75% complete ablation rates. But complete ablation rates drop to less than 60% when lesions of 5 to 8 cm are treated. Survival rates vary from 0% to 70% in most studies, largely depending on the size of the lesion. Patients with treated lesions of 5 cm or smaller have 3- and 5-year survival rates of 79% and 49%, respectively, but those with large lesions (5–10 cm) or multiple lesions have 3-year survival rates of only 42% and 31%, respectively. Child-Pugh class also influences survival, with 3-year survival rates of 72% and 25% for patients with Child-Pugh class A or B, respectively.

Several retrospective analyses have produced comparable results between PEI and resection when applied to patients with small tumors. In a study of 63 patients with lesions smaller than 4 cm, recurrence rates were 45% for PEI and 66% for resection. Survival rates at 1 and 4 years were 81% and 44% for PEI and 86% and 34% for resection, respectively. Huang et al. reported on 76 patients with 1 or 2 hepatomas 3 cm or smaller and Child-Pugh class A or B, noting no significant difference in recurrence or survival between PEI and surgical resection in a follow-up analysis ranging from 12 to 59 months. A recent prospective, randomized trial of 180 patients compared PEI with surgical resection for solitary hepatomas up to 5 cm in diameter. Of these patients, 90 underwent segmentectomy (1–3 segments) and 71 received PEI (19 refused to be randomized), with no statistical difference in either disease-free or overall survival. These few studies show that PEI can produce equivalent results to resection for small hepatomas and may be ideal for patients who are unable to undergo surgery.

Cryoablation

Cryoablation for treating hepatomas uses a probe to freeze a targeted lesion to –35°C. Two freeze–thaw cycles are generated with either argon gas or liquid nitrogen, and the resulting ice crystals cause cellular dysfunction, rupture, and death. It is used for unresectable lesions, usually 4 or fewer lesions at a time. It is often considered for lesions larger than 5 cm when PEI is ineffective. The goal is to achieve treatment margins of 0.5 to 1 cm.

The morbidity of cryoablation ranges from 8% to 41%, and the mortality from 0% to 17%. Complications, which include myoglobinuria, acute renal failure, pleural effusions, hypoesthesia, and hemorrhage caused by ice ball or capsular fracture, can be life-threatening. Coagulopathy can also occur secondary to hepatic injury. Most mortalities associated with the procedure result from cryoshock, which can occur in up to 1% of patients, usually within the first 48 hours after surgery. This phenomenon results in multiorgan failure with systemic inflammatory response and eventually death in many cases.

The results of cryoablation are mostly based on nonrandomized, retrospective studies that examine multimodality therapies rather than cryoablation alone. Complete ablation can be documented in up to 85% of lesions treated. Five-year survival rates for cryoablation range from 32% to 55%, with lower survival rates noted when lesions of 5 cm or larger are ablated. Recurrence rates for cryoablation approach 14%. In direct comparison to radiofrequency ablation (RFA), cryoablation has a higher recurrence rate (14% vs. 2%) and higher morbidity (41% vs. 3%). Cryoablation is most often performed laparoscopically or through
laparotomy, although the technology has also been applied percutaneously. Cryoablation is not used often to ablate hepatomas because of its high morbidity and the availability of other low-morbidity ablative approaches.

Radiofrequency Ablation

Radiofrequency ablation (RFA) is an ablative technique that can be used percutaneously, laparoscopically, and through open approaches. RFA uses a high-frequency alternating current from an electrode tip transferring energy into the surrounding tissues, resulting in tissue temperatures greater than 60°C and tumor necrosis. RFA is an ultrasound-guided technique that can ablate lesions up to 3 cm with a single probe, and larger lesions through multiple, stepwise applications of a single probe to achieve the desired 1-cm negative margin. As with PEI, the application of RFA is designed for patients who cannot undergo resection and have no evidence of extrahepatic disease.

The morbidity of the procedure is low, with most reports showing rates of 2.2% to 11%. Complications include pleural effusions, abscesses, acute renal failure, intra-abdominal hemorrhage, pneumothorax, and hypoxemia. The more troubling complications arise from placing a probe too close to the diaphragm or an intra-abdominal organ, resulting in ablation of the surrounding viscera with the accompanying complications of perforation, diaphragmatic injury, or pulmonary damage. These injuries can be avoided by using an open approach to provide adequate exposure and protection of the diaphragm and surrounding viscera. Advanced laparoscopic techniques can also avoid these complications. The percutaneous approach does not afford this protection, but for centrally located lesions this approach negates the risk associated with general anesthetics. Overall, RFA is well tolerated, with mortality rates of 0.3% to 0.8%.

RFA causes complete tumor necrosis in 80% to 90% of lesions smaller than 3 cm. However, the effectiveness of RFA decreases as lesions get larger, with 50% to 70% complete ablation for lesions 3.5 to 5 cm and only approximately 48% for lesions larger than 5 cm. Studies examining the long-term effectiveness of RFA have shown local control rates of approximately 96%, translating into 3- and 5-year survival rates of 60% to 78% and 33% to 54%, respectively. Larger lesions were noted to result in lower survival rates.

As with most ablative therapies, no randomized trials compare RFA to surgical resection for treating HCC. However, several studies have compared RFA with PEI. Shiina et al. examined 232 patients with 3 or fewer hepatomas of 3 cm or smaller and Child-Pugh A or B. The patients treated with RFA underwent a median 2.1 treatments, whereas patients treated with PEI underwent 6.4 treatments with equivalent morbidity and mortality. A median follow-up of 3.1 years showed a 44% decrease in local recurrences (70% vs. 85%) and 88% decrease in local disease progression (1.7% vs. 11%) combined with an increased survival (74% vs. 57%) for patients undergoing RFA versus PEI.

Researchers from Taiwan noted similar results in 157 patients with 186 lesions of 4 cm or smaller who were randomized to undergo treatment with PEI (either low- or high-dose) or RFA. The RFA group had less tumor progression (18% vs. 33%–45%) and a longer disease-free survival (37 months vs. 1720 months) than either PEI group. Overall 3-year survival was also significantly improved for the RFA group (74%) versus the PEI groups (50%–55%). This study confirmed that RFA is an independent prognostic indicator for local recurrence and cancer-free survival.

A more recent study by Lin et al. examined RFA for hepatoma versus PEI or percutaneous acetic acid injection (PAI). Examining 187 patients with hepatomas of 3 cm or smaller, they again noted a significant advantage for patients undergoing treatment with RFA. Three-year local recurrences rates (14% vs. 31%–34%) and overall survival (74% vs. 51%–53%) were markedly better for the RFA group compared with the PEI/PAI group.

Researchers have shown interest in the combined ablative approach of RFA used with PEI, especially for lesions larger than 5 cm. In a small study of 40 patients with large hepatomas, Sakr et al. used overlapping RFA applications followed by repeated PEI. They noted a higher rate of tumor necrosis than with RFA alone, which may indicate that this combined technique will be used more often.

RFA is an effective ablative technology with low morbidity and very low mortality. Randomized trials have shown RFA to be very effective in treating hepatocellular carcinoma. Larger numbers and longer follow-ups are needed before a definitive statement can be made.

Other Ablative Techniques

Several other ablative technologies have been used to treat HCC in patients deemed unresectable either because of tumor characteristics or patient factors. Two such techniques include laser ablation and...
microwave hyperthermia. Laser ablation techniques, including interstitial laser coagulation and laser thermal ablation, use laser energy to cause tissue destruction. Several reports have exhibited complete ablation rates of 82% to 97%. This ablation success translated into 5-year survival rates of 52%.36–38

Microwave hyperthermia has been used to treat hepatomas. Dong et al.39 examined 234 patients with 339 lesions and noted a 92% complete ablation rate and 5-year survival of 56.7%. Liang et al.40 reported similar findings in a report of 288 patients, with a 5-year survival rate of 52%. Survival rates were noted to be improved for lesions smaller than 4 cm. A recent retrospective comparison of microwave hyperthermic ablation and RFA noted statically similar disease-free and overall survival rates.41

Both strategies are effective at ablating small hepatomas. These successes appear equivalent to other ablative therapies. However, few studies examine these technologies with an adequate duration of follow-up.

Transarterial Chemoembolization

Transarterial chemoembolization (TACE) is a technique applied to large, unresectable hepatomas before surgical resection, ablation, or transplantation is attempted. The technique relies on catheterization of the hepatic artery, followed by selection of the tumor’s feeding vessel and administration of a combination of a chemotherapeutic agent and lipiodol. This is then followed by embolization with gelatin sponge particles or polyvinyl alcohol particles to prevent any further arterial blood flow to the lesion. A combination of ischemia and cytotoxic agents destroys the target lesion.

This therapy has several contraindications, including portal vein thrombosis, retrograde flow through the portal vein, encephalopathy, extrahepatic disease, severe clotting abnormalities, and biliary obstruction. Relative contraindications include elevated levels of bilirubin, lactate dehydrogenase, or aspartate aminotransferase; tumor burden of more than 50% of the liver; cardiac or renal insufficiency; and evidence of portal hypertension (ascites, recent variceal bleed).42 A postembolization syndrome is the most common complication, marked by transient fevers and abdominal pain.43

TACE is most often applied to patients who are unable to undergo resection or ablative therapies or have experienced recurrences after previous surgical/ablative interventions. Several trials have specifically addressed TACE in treating large, unresectable hepatomas; three of these trials showed no benefit. Two studies examined 169 patients and showed no survival advantage for TACE over best supportive care (BSC) despite a marked tumor response.44,45 In a study by Lo et al.,46 80 of 279 patients met selection criteria for enrollment in a randomized, controlled trial comparing TACE with BSC. The TACE group underwent a median of 4.5 treatments and was noted to have a better 3-year actuarial survival compared with the BSC group (26% vs. 3%; P = .002). Although a higher proportion of liver failure deaths were noted in the treatment group, overall survival was still improved in the TACE group.

Llovet et al.47 performed a randomized controlled trial examining TACE versus BSC. In their study of 112 patients (selected from a pool of 903 patients), those in the TACE arm were treated at 2 months and 6 months, and then at 6-month intervals thereafter. Survival was noted to be increased in the TACE arm, with 1- and 2-year survival rates 82% versus 63% and 63% versus 27% when compared with BSC. The caveat to these studies was patient selection, which was varied in each study and therefore makes direct comparisons difficult. A recent meta-analysis examined TACE and its potential for improved survival when compared with symptomatic treatment. Llovet and Bruix48 noted a significant increase in 2-year survival rates in patients treated with TACE versus BSC.

Conclusions

HCC is an aggressive cancer that is common throughout the world. Surgical resection and transplantation remain the only true cures for this disease. Unfortunately, most patients present either with advanced disease or chronic liver disease that precludes either definitive therapy. Several other liver-directed therapies can provide durable tumor responses and prolonged survival. The ablative techniques described provide similar survival rates with varying rates of morbidity and mortality. TACE provides a treatment option for patients unable to undergo any other intervention, although the benefit is unclear. All of the techniques allow clinicians to tailor therapy based on the stage of disease and health of the patient.

References

Liver-Directed Therapies for Hepatocellular Carcinoma


