As Drs. Nakakura and Choti point out, the incidence of hepatocellular carcinoma (HCC) is rising in many countries including the United States, mainly as the result of a steady increase in hepatitis C infections. Unfortunately, it now seems that the hepatitis C virus is more carcinogenic than the hepatitis B virus, judging from the frequency with which HCC develops among patients with hepatitis C- vs hepatitis B-induced cirrhosis.[1] Numerous studies have demonstrated changes in various oncogenes and tumor suppressor genes, but no consistent sequence of genetic changes has emerged similar to the adenoma-carcinoma sequence in colon cancer.

Major risk factors for HCC include hepatitis B- and hepatitis C-induced cirrhosis, alcoholic cirrhosis, aflatoxin exposure, and rare metabolic disorders. Most patients presenting with symptoms of abdominal pain and weight loss have advanced disease with very few treatment options. A serum alpha-fetoprotein level above 500 ng/mL is considered diagnostic for HCC, but mildly elevated levels from 20 to 400 ng/mL are seen in cirrhotic patients without tumors. Improvements in imaging have allowed noninvasive tests such as biphasic helical computed tomography (CT) and dynamic magnetic resonance imaging to replace invasive CT angioportography as the preoperative test of choice in both primary and metastatic liver cancer. Because of changes in the cirrhotic liver architecture due to fibrosis, necrosis, and numerous regenerative nodules, along with altered portal hemodynamics, the detection of HCC in the cirrhotic liver may involve several complementary imaging techniques.[2]

**Surgical Resection vs Orthotopic Liver Transplantation**

In the United States, where HCC typically develops in the setting of well-established cirrhosis, fewer than 5% to 10% of patients meet the stringent criteria for resection. The presence of extrahepatic disease, lack of sufficient hepatic reserve, satellite tumors, and main portal vein thrombosis are all contraindications to resection. Even when resection is possible, 70% of patients who have undergone the procedure develop intrahepatic recurrence. The majority of these recurrences are de novo tumors and not recurrences at the surgical margin.[3] In an attempt to lower the high intrahepatic recurrence rate, numerous adjuvant chemotherapy trials have been completed but with no clear benefit. Recent studies of adjuvant retinoids as a chemopreventive strategy and intra-arterial iodine-131-labeled Lipiodol show promising early results but need further follow-up and confirmation. Because so few patients with HCC are candidates for resection and their survival is limited due to intrahepatic recurrence, many physicians favor orthotopic liver transplantation for early HCC. The disappointing survival and tumor recurrence rates reported in early trials of orthotopic liver transplantation were associated with inappropriate patient selection criteria. More recently, orthotopic liver transplantation has been limited to patients with a single tumor less than 5 cm in diameter or with three tumors less than 3 cm each, and the 5-year survival rate has risen to between 60% and 70%.[4,5] Furthermore, the rate of intrahepatic recurrence has decreased to between 4% and 11%.

Thus, for patients with the above characteristics and end-stage cirrhosis, orthotopic liver transplantation appears to be the best option. However, as the waiting times for orthotopic liver
transplantation grow longer, disease progression may disqualify many patients. Given this concern, several institutions have begun pretransplant treatments with chemoembolization, percutaneous ethanol ablation, or percutaneous radiofrequency ablation. Preliminary results using these modalities report increases in the probability of transplantation and in overall survival.[6] However, orthotopic liver transplantation is still limited by a shortage of donated organs.

**Ablation Approaches**

Percutaneous ethanol ablation has been used to treat small HCCs since the early 1980s, with conservative indications specifying HCC tumors less than 3 cm. Larger tumors have also been treated with this method, but the reliability of ethanol being evenly distributed is questionable. Reported overall 5-year survival rates among patients undergoing percutaneous ethanol ablation range from 28% to 51%.[7] However, as with resection, patients treated with this technique develop intrahepatic recurrence and die of HCC progressive disease.[7] No prospective randomized trials have shown that the outcome of percutaneous ethanol ablation is superior to that of other treatment modalities in patients with small HCC.

Hepatic cryosurgery has had limited application in the United States for patients with HCC. The studies from China demonstrate the efficacy of this treatment for small HCC, but no randomized prospective trials have been conducted. Cryosurgery, for the most part, needs to be performed through a laparotomy, thus significantly increasing morbidity and operating expenses. Much of the enthusiasm for tumor ablation is now focused on radiofrequency ablation.

Radiofrequency ablation can be performed using a percutaneous, laparoscopic, or open technique, and the cost is significantly less than for cryosurgery. Compared to percutaneous ethanol ablation, radiofrequency ablation requires fewer treatments and may achieve superior tumor necrosis.[6] Recent studies conducted in both the United States and Europe have demonstrated that radiofrequency ablation is safe, well tolerated, and associated with adequate tumor necrosis for tumors up to 5 cm.[7-9] Further prospective trials are needed, however, and because these patients will still be at risk for the development of new tumors in the liver, future studies should consider multimodality adjuvant treatment.

**Chemotherapy and Chemoembolization**

No systemic chemotherapeutic regimen for HCC has been associated with a survival benefit in a randomized clinical trial.[10] We recently completed a phase II trial using liposomal doxorubicin (Doxil), which demonstrated only a 10% response rate. Further protocols need to be investigated with the understanding that the majority of these patients have a borderline performance status and underlying liver dysfunction. Intra-arterial chemotherapy, although an option for colorectal metastases, has not been beneficial in patients with HCC.[10] Chemoembolization is another popular treatment for HCC, but again, randomized trials are lacking, and it is not clear whether chemoembolization is more effective than embolization alone. Chemoembolization treatments with doxorubicin, mitomycin (Mutamycin), and/or cisplatin (Platinol) have demonstrated no clearly superior regimen.[11] Although there is no significant survival benefit associated with chemoembolization, palliation of pain can be successfully achieved with the technique.

**Conclusions**

The authors should be commended for presenting a thorough review of the difficult and complex problems involved in treating patients with HCC. For patients with resectable HCC and adequate liver reserve, hepatic resection is still the treatment of choice, although tumor recurrence remains a major concern. If the encouraging improved survival and low tumor recurrence data mature and liver organ procurement increases, orthotopic liver transplantation may become the mainstay of treatment for early hepatoma in the setting of end-stage cirrhosis.

With improved technology, radiofrequency ablation will most likely be the ablative method of choice for patients with unresectable disease, since radiofrequency ablation can be performed percutaneously and at one sitting. Most importantly, improvements in the treatment of HCC await novel systemic and regional chemotherapeutic regimens along with potential chemopreventive agents.

—Charles A. Staley, MD

**References:**


Source URL: http://www.cancernetwork.com/oncology-journal/commentary-staley-management-hepatocellular-carcinoma

Links:
[1] http://www.cancernetwork.com/oncology-journal
[4] http://www.cancernetwork.com/authors/charles-staley-md-0