growing in the months until a donor liver becomes available. What remains unclear, however, is whether this translates into prolonged survival after transplant. Further, it is not known whether patients who have had their tumor(s) treated preoperatively follow the recurrence pattern predicted by their tumor status at the time of transplant (i.e., post–local ablative therapy), or if they follow the course set by their tumor parameters present before such treatment. The United Network for Organ Sharing (UNOS) point system for priority scoring of OLTX recipients now includes additional points for patients with HCC. The success of living related donor liver transplantation programs has also led to patients receiving transplantation earlier for HCC and often with greater than minimal tumors.

CURRENT DIRECTIONS Expanded criteria for larger HCCs beyond the Milan criteria (one lesion <5 cm or three lesions, each <3 cm), such as the University of California, San Francisco (UCSF) criteria (single lesion ≤6.5 cm or two lesions ≤4.5 cm with a total diameter ≤8 cm; 1- and 5-year survival rates of 90 and 75%, respectively), are being increasingly accepted by various UNOS areas for OLTX with satisfactory longer-term survival comparable to Milan criteria results. Furthermore, downstaging of HCCs that are too large for the Milan criteria by medical therapy (TACE) is increasingly recognized as acceptable treatment before OLTX with equivalent outcomes to patients who originally were within Milan criteria. Within-criteria patients with AFP levels >1000 ng/mL have exceptionally high post-OLTX recurrence rates. Also, the use of "salvage" OLTX after recurrent HCC after resection has produced conflicting outcomes. Shortages of organs combined with advances in resection safety have led to increasing use of resection for patients with good liver function.

Adjuvant Therapy The role of adjuvant chemotherapy for patients after resection or OLTX remains unclear. Both adjuvant and neoadjuvant approaches have been studied, but no clear advantage in disease-free or overall survival has been found. However, a meta-analysis of several trials revealed a significant improvement in disease-free and overall survival. Although analysis of postoperative adjuvant systemic chemotherapy trials demonstrated no disease-free or overall survival advantage, single studies of TACE and neoadjuvant ^{131}I-Ethiodol showed enhanced survival after resection.

Antiviral therapy, instead of anticancer therapy, has been successful in decreasing postresection tumor recurrences in the postresection adjuvant setting. Nucleoside analogues in HBV-based HCC and peg-interferon plus ribavirin for HCV-based HCC have both been effective in reducing recurrence rates.

CURRENT DIRECTIONS A large adjuvant trial examining resection and transplantation, with or without sorafenib (see below) is in progress. The success of viral therapies in decreasing HCC recurrence after resection is part of a broader focus on the tumor microenvironment (stroma, blood vessels, inflammatory cells, and cytokines) as mediators of HCC progression and as targets for new therapies.

TNM STAGES III AND IV HCC

Fewer surgical options exist for stage III tumors involving major vascular structures. In patients without cirrhosis, a major hepatectomy is feasible, although prognosis is poor. Patients with Child A cirrhosis may be resected, but a lobectomy is associated with significant morbidity and mortality rates, and long-term prognosis is poor. Nevertheless, a small percentage of patients will achieve long-term survival, justifying an attempt at resection when feasible. Because of the advanced nature of these tumors, even successful resection can be followed by rapid recurrence. These patients are not considered candidates for transplantation because of the high tumor recurrence rates, unless their tumors can first be downstaged with neoadjuvant therapy. Decreasing the size of the primary tumor allows for less surgery, and the delay in surgery allows for extrahepatic disease to manifest on imaging studies and avoid unhelpful OLTX. The prognosis is poor for stage IV tumors, and no surgical treatment is recommended.

Systemic Chemotherapy A large number of controlled and uncontrolled clinical studies have been performed with most of the major classes of cancer chemotherapy. No single agent or combination of agents given systemically reproducibly leads to even a 25% response rate or has any effect on survival.

Regional Chemotherapy In contrast to the dismal results of systemic chemotherapy, a variety of agents given via the hepatic artery have activity for HCC confined to the liver (Table 111-6). Two randomized controlled trials have shown a survival advantage for TACE in a selected subset of patients. One used doxorubicin, and the other used cisplatin. Despite the fact that increased hepatic extraction of chemotherapy has been shown for very few drugs, some drugs such as cisplatin, doxorubicin, mitomycin C, and possibly neocarzinostatin, produce substantial objective responses when administered regionally. Few data are available on continuous hepatic arterial infusion for HCC, although pilot studies with cisplatin have shown encouraging responses. Because the reports have not usually stratified responses or survival based on TNM staging, it is difficult to know long-term prognosis in relation to tumor extent. Most of the studies on regional hepatic arterial chemotherapy also use an embolizing agent such as Ethiodol, gelatin sponge particles (Gelfoam), starch (Spherex), or microspheres. Two products are composed of microspheres of defined size ranges—Embospheres (Biospheres) and Contour SE—using particles of 40–120, 100–300, 300–500, and 500–1000 μm in size. The optimal diameter of the particles for TACE has yet to be defined. Consistently higher objective response rates are reported for arterial administration of drugs together with some form of hepatic artery occlusion compared with any form of systemic chemotherapy to date. The widespread use of some form of embolization in addition to chemotherapy has added to its toxicities. These include a frequent but transient fever, abdominal pain, and anorexia (all in >60% of patients). In addition, >20% of patients have increased ascites or transient elevation of transaminases. Cystic artery spasm and cholecystitis are also not uncommon. However, higher responses have also been obtained. The hepatic toxicities associated with embolization may be ameliorated by the use of degradable starch microspheres, with 50–60% response rates. Two randomized studies of TACE versus placebo showed a survival advantage for treatment (Table 111-6). In addition, it is not clear that formal oncologic CT response criteria are adequate for HCC. A loss of vascularity on CT without size change may be an index of loss of viability and thus of response to TACE. A major problem that TACE trials have had in showing a survival advantage is that many HCC patients die of their underlying cirrhosis, not the tumor. Nevertheless, two randomized controlled trials, one using doxorubicin and the other using cisplatin, showed a survival advantage for TACE versus placebo (Table 111-6). However, improving quality of life is a legitimate goal of regional therapy. Drug-eluting beads using doxorubicin (DEB-TACE) have been claimed to produce equivalent survival with less toxicity, but this strategy has not been tested in a randomized trial.

Kinase Inhibitors A survival advantage has been observed for the oral multikinase inhibitor, sorafenib (Nexavar), versus placebo in two randomized trials. It targets both the Raf mitogenic pathway and the vascular endothelial growth factor receptor (VEGFR) endothelial vasculogenesis pathway. However, tumor responses were negligible, and the survival in the treatment arm in Asians was less than the placebo arm in the Western trial **(Table 111-7)**. Sorafenib has considerable toxicity, with 30–40% of patients requiring "drug holidays," dose reductions, or cessation of therapy. The most common toxicities include fatigue, hypertension, diarrhea, mucositis, and skin changes, such as the painful hand-foot syndrome, hair loss, and itching, each in 20–40% of patients. Several "look-alike" new agents that also target angiogenesis have either proved to be inferior or more toxic. These include sunitinib, brivanib, linifanib, everolimus, and bevacizumab **(Table 111-8)**. The idea of angiogenesis alone as a major HCC therapeutic target may need revision.

New Therapies Although prolonged survival has been reported in phase II trials using newer agents, such as bevacizumab plus