TABLE 111-5 TREATMENT OPTIONS FOR HEPATOCELLULAR CARCINOMA

Surgery
Resection
Liver transplantation
Local Ablative Therapies
Radiofrequency ablation (RFA)
Microwave ablation (MWA)
Cryosurgery
Percutaneous ethanol injection (PEI)
Regional Therapies: Hepatic Artery Transcatheter Treatments
Transarterial chemotherapy
Transarterial embolization
Transarterial chemoembolization
Transarterial drug-eluting beads
Transarterial radiotherapies:
^{90}Yttrium microspheres
^{131}Iodine– Ethiodol
Proton beam radiation
Conformal External-Beam Radiation and Intensity-Modulated Radiation Therapy
Systemic therapies
Molecularly targeted therapies (sorafenib, etc.)
Chemotherapy
Immunotherapy
Hormonal therapy + growth control
Supportive Therapies

setting is to use liver-sparing treatments and to focus on treatment of both the tumor and the cirrhosis.

Surgical Excision The risk of major hepatectomy is high (5–10% mortality rate) due to the underlying liver disease and the potential for liver failure, but acceptable in selected cases and highly dependent on surgical experience. The risk is lower in high-volume centers. Preoperative portal vein occlusion can sometimes be performed to cause atrophy of the HCC-involved lobe and compensatory hypertrophy of the noninvolved liver, permitting safer resection. Intraoperative ultrasound is useful for planning the surgical approach. The ultrasound can image the proximity of major vascular structures that may be encountered during the dissection. In cirrhotic patients, any major liver surgery can result in liver failure. The Child-Pugh classification of liver failure is still a reliable prognosticator for tolerance of hepatic surgery, and only Child A patients should be considered for surgical resection. Child B and C patients with stages I and II HCC should be referred for OLTX if appropriate, as well as patients with ascites or a recent history of variceal bleeding. Although open surgical excision is the most reliable, the patient may be better served with a laparoscopic approach to resection, using RFA, MWA, or percutaneous ethanol injection (PEI). No adequate comparisons of these different techniques have been undertaken, and the choice of treatment is usually based on physician skill. However, RFA has been shown to be superior to PEI in necrosis induction for tumors <3 cm in diameter and is thought to be equivalent to open resection and, thus, is the treatment of first choice for these small tumors. As tumors get larger than 3 cm, especially ≥5 cm, the effectiveness of RFA-induced necrosis diminishes. The combination of transcatheter arterial chemoembolization (TACE) with RFA has shown superior results to TACE alone in a prospective, randomized trial. Although vascular invasion is a preeminent negative prognostic factor, microvascular invasion in small tumors appears not to be a negative factor.

Local Ablation Strategies RFA uses heat to ablate tumors. The maximum size of the probe arrays allows for a 7-cm zone of necrosis, which would be adequate for a 3- to 4-cm tumor. The heat reliably kills cells within the zone of necrosis. Treatment of tumors close to the main portal pedicles can lead to bile duct injury and obstruction. This limits the location of tumors that are anatomically suited for this technique. RFA can be performed percutaneously with CT or ultrasound guidance, or at the time of laparoscopy with ultrasound guidance.

Local Injection Therapy Numerous agents have been used for local injection into tumors, most commonly ethanol (PEI). The relatively soft HCC within the hard background cirrhotic liver allows for injection of large volumes of ethanol into the tumor without diffusion into the hepatic parenchyma or leakage out of the liver. PEI causes direct destruction of cancer cells, but it is not selective for cancer and will destroy normal cells in the vicinity. However, it usually requires multiple injections (average three), in contrast to one for RFA. The maximum size of tumor reliably treated is 3 cm, even with multiple injections.

CURRENT DIRECTIONS Resection and RFA each obtain similar results. However, a distinction has been made between the causes and prevention strategies needed to prevent early versus late tumor recurrences after resection. Early recurrence has been linked to tumor invasion factors, especially microvascular tumor invasion with elevated transaminases, whereas late recurrence has been associated with cirrhosis and virus hepatitis factors and, thus, the development of new tumors. See the section on virus-directed adjuvant therapy below.

Liver Transplantation (OLTX) A viable option for stages I and II tumors in the setting of cirrhosis is OLTX, with survival approaching that for noncancer cases. OLTX for patients with a single lesion ≤5 cm or three or fewer nodules, each ≤3 cm (Milan criteria), resulted in excellent tumor-free survival (≥70% at 5 years). For advanced HCC, OLTX has been abandoned due to high tumor recurrence rates. Priority scoring for OLTX previously led to HCC patients waiting too long for their OLTX, resulting in some tumors becoming too advanced during the patient's wait for a donated liver. A variety of therapies were used as a "bridge" to OLTX, including RFA, TACE, and hepatic arterial ^{90}Y-radioembolization. These pretransplant treatments allow patients to remain on the waiting list longer, giving them greater opportunities to be transplanted, because they can stabilize the tumor and prevent it from

TABLE 111-6 SOME RANDOMIZED CLINICAL TRIALS INVOLVING TRANSHEPATIC ARTERY CHEMOEMBOLIZATION (TACE) FOR HEPATOCELLULAR CARCINOMA

Author	Year	Agents 1	Agents 2	Survival Effect
Kawaii	1992	Doxorubicin + Embo	Embo	No
Chang	1994	Cisplatin + Embo	Embo	No
Hatanaka	1995	Cisplatin, doxorubicin, + Embo	Same + Lipiodol	No
Uchino	1993	Cisplatin, doxorubicin, + oral FU	Same + Tamoxifen	No
Lin	1988	Embo	Embo + IV FU	No
Yoshikawa	1994	Epirubicin + Ethiodol	Epirubicin	No
Pelletier	1990	Doxorubicin + Gelfoam	None	No
Trinchet	1995	Cisplatin + Gelfoam	None	No
Bruix	1998	Coils + Gelfoam	None	No
Pelletier	1998	Cisplatin + Ethiodol	None	No
Trinchet	1995	Cisplatin + Gelfoam	None	No
Lo	2002	Cisplatin + Ethiodol	None	Yes
Llovet	2002	Doxorubicin + Ethiodol	None	Yes

Abbreviations: Embo, embolization; FU, 5-fluorouracil.