

Management of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is one of the most common tumors globally, with varying prevalence based on endemic risk factors. In high-risk populations, including those with hepatitis B or C or with cirrhosis, serum α -fetoprotein (AFP) and screening ultrasound have improved detection of resectable HCC. Treatment options, including surgical resection, for patients with HCC must be selected based on the number and size of hepatic tumors, underlying hepatic function, patient condition, and available resources. An approach, which has been summarized shows the corresponding treatment choices under given clinical circumstances. For cirrhotic patients with less than three tumor nodules of a size less than 3 cm or a solitary HCC less than 5 cm, liver transplantation offers long-term survival similar to that observed in patients transplanted for nonmalignant disease. Ablative treatment using either chemical or thermal techniques provides locally effective tumor destruction. Transcatheter arterial chemoembolization (TACE) is commonly used for palliation of unresectable tumors as well as an adjunct to surgical resection, treatment of tumors before transplant, and in conjunction with other ablative therapies in a multimodality approach. Regional approaches to chemotherapy have produced more encouraging results than systemic chemotherapy, although both remain ineffective for long-term tumor control. Several newer treatment modalities are under investigation, including gene therapy, tagged antibodies, isolated perfusion, and novel radiotherapy techniques. (J GASTROINTEST SURG 2006;10:761–780) © 2006 The Society for Surgery of the Alimentary Tract

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BACKGROUND

Hepatocellular carcinoma (HCC) represents one of the most common malignancies globally, accounting for nearly one million new cases per year.¹ In Western populations, the incidence of HCC is low but increasing, with 2.4 cases per 100,000 diagnosed annually between 1991 and 1995.² This low-incidence rate, compared with China, southeast Asia, and southern Africa, is due to environmental factors related to chronic hepatitis B infection, which is the single most important cause of HCC worldwide. In the west, alcohol and hepatitis C are the major risk factors for HCC, with hepatitis B virus infections

playing a secondary role. Untreated HCC has an extremely poor prognosis, with a median survival of 1–8 months³ and a 5-year survival of around 3%.⁴ HCC accounts for a mortality rate of 1.7 per 100,000 persons per year in Western populations.² Though considered incurable in the past, management has undergone major changes over the last two decades. Improved outcomes are in part attributable to earlier detection by using screening methods in high-risk populations, advances in imaging, more accurate patient assessment, improved surgical techniques, and innovation of regional therapies.

Treatment of HCC is multidisciplinary. The involvement of hepatologists, oncologists, radiologists,

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as well as surgeons, is necessary to provide the most up-to-date care and to ensure the best outcomes. Many therapies are available in the armamentarium for HCC, but there has been no consensus on standard of care. With the emergence of new technologies, established therapies become more or less used.

PATIENT ASSESSMENT

Screening

Patients with HCC are identified either because they have symptomatic disease prompting further evaluation or because they have known risk factors that have led to screening studies in an effort to detect HCC at an early stage. Screening for de novo disease in "at risk" patients may include measurement of tumor markers, periodic radiographic imaging, or a combination of the two. Alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II (PIVKA-II, also known as des- γ -carboxy prothrombin or DCP) are the two most well-studied serum markers widely used in patient screening. Although the sensitivity and specificity of serum AFP are only 39%–50% and 76%–86%, respectively,^{5–7} some studies have documented increased numbers of patients with tumor detected at stages amenable to resection.^{8,9} Similarly, the sensitivity of PIVKA-II, a product created by hepatocytes exposed to warfarin-type agents or with nutritional deficiency of vitamin K, has been reported to range from 24%–80%, with specificity of 90%–99% depending upon the detection modality and the cutoff value used for detection.^{10,11} The best use of tumor markers may occur when two or more are used in conjunction for screening, as in the case of PIVKA-II and AFP,¹¹ or the combination of PIVKA-II, AFP, and the hepatoma-specific band of gamma glutamyl transferase¹² where sensitivity reaches 66% and 88%, respectively.

The application of imaging modalities for screening is limited by cost, availability of imaging, and threshold for tumor detection. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography have all been applied to screening, with variable results.^{13–16} Ultrasound is more user dependent but less expensive and more widely available than either of the other two modalities. Over the last decade, AFP and routine use of transabdominal ultrasound have become the most used method for early detection of HCC, although the cost-effectiveness of these approaches is debatable.¹⁷ Some investigators have suggested that regular screening improves survival by detecting smaller lesions (less than 2 cm), with a 5-year survival of more than 62% compared with the 30% 5-year survival in patients with larger lesions. In populations at high

risk for HCC, it has been shown that 30%–50% of patients can be diagnosed with resectable HCC^{18,19}; this represents a doubling over an unscreened population. Others argue the improved outcomes in patients identified with early-stage tumors result only from lead-time bias, and that the real efficacy of screening has yet to be determined.²⁰

Treatment Selection

The treatment approach for patients with HCC has evolved into a complex task that incorporates information regarding tumor extent, the severity of underlying hepatic dysfunction (because 80%–90% of patients with HCC have cirrhosis), the general medical condition of the patient, and available resources. Specific tumor considerations include size, number and distribution of nodules, and local anatomic conditions such as vascular and bile duct relationships. If resection is considered, the position of the lesion is important in determining the amount of liver tissue to be sacrificed as well as the volume of remaining functional parenchyma.

To help select patients for appropriate treatments, current diagnostic imaging aids in detection of extensive intrahepatic disease, vascular involvement, underlying cirrhosis, and extrahepatic metastases. High-resolution triple-phase CT, CT angioportography, and MRI with or without MR angiography all provide sensitive and often complimentary data. However, difficulty still exists in recognizing very small (less than 1 cm) tumors that might be amenable to therapy. Extrahepatic disease, including regional periportal lymph nodes as well as distant metastases, must be excluded. Positron emission tomography with 18-fluorodeoxyglucose has been useful in the evaluation and clinical decision-making at our institution, as it allows for identification of extrahepatic disease and effects patient treatment strategy in up to 30% of encounters.²¹

Laparoscopy with intraoperative ultrasound is useful in patients with HCC and uncertain imaging studies. Montorsi et al.²² used laparoscopy and laparoscopic ultrasound to evaluate 70 patients with radiographic studies suspicious for HCC. Five of the patients (7%) were identified with lesions other than HCC. Previously suspicious tumors were confirmed in 22% of patients.²² Weitz et al.²³ used laparoscopy in 60 potentially resectable patients with HCC before performing laparotomy for hepatectomy. In their series, 14 were spared laparotomy due to upstaging at the time of laparoscopy. Laparoscopy is also useful in staging patients with advanced cirrhosis who are undergoing transplant evaluation. In one report,²⁴ 18 patients with

advanced cirrhosis and indeterminate staging based on radiographic studies underwent laparoscopy with intraoperative ultrasonography. Initial staging was changed in 66% of patients. An added benefit was the ability to apply laparoscopic ablative techniques at the time of laparoscopic staging.

An important factor in the evaluation of patients, especially those with cirrhosis, is the determination of hepatic reserve. Traditionally, the Child-Pugh classification has been used to approximate hepatic reserve. In general, Child A patients can be considered for resections of up to 50% of liver parenchyma, whereas Child B patients tolerate resections up to 25%. Other groups have emphasized preoperative serum bilirubin or transaminase levels in cirrhotic patients as indicators of the feasible extent of hepatic resection.²⁵ Makuuchi and Sano²⁶ advocate the use of total bilirubin in combination with presence or absence of ascites to identify potential operative candidates with the degree of resection dictated by the indocyanine green retention rate. There are recent reports relating the model of end-stage liver disease score to postoperative liver failure and other complications.

Indocyanine green is one of many compounds investigated for the functional assessment of hepatic reserve.^{27–29} As an anionic dye, indocyanine green is cleared rapidly by hepatocytes and excreted in unconjugated bile. The clearance of indocyanine green from the bloodstream predicts the risk of postoperative liver insufficiency. The amount of indocyanine green remaining in the bloodstream of a patient with a normal liver at 15 minutes after its injection should be less than 10%.³⁰ A value of 15%–20% suggests that a two-segment resection will be tolerated, 21%–30% suggests a single segment or wedge resection will be tolerated, and a value greater than 40% indicates that liver failure will probably occur even with a minimal resection.³¹ Opting for a nonanatomic resection in patients with more severe liver dysfunction has the benefit of lower perioperative morbidity and mortality when compared with formal anatomic resections, but likely at the expense of reduced long-term survival.³²

The galactose elimination capacity described by Redaelli et al.³³ is based on the fact that galactose metabolism occurs via the rate-limiting phosphorylation by galactokinase, an enzyme located only in hepatocytes. A galactose elimination capacity of less than 4 mg/min/kg in patients with HCC predicted postoperative complications with a 100% specificity and 52% sensitivity, as well as overall worse survival. Kokudo and colleagues³⁴ have used a combination of the Child-Pugh score with another functional assay, the asialoglycoprotein receptor

quantity, to evaluate cirrhotic patients. This test is based upon technetium 99m-labeled asialoglycoprotein analog combining with a hepatocyte surface glycoprotein and provides a very sensitive surrogate marker of hepatocyte function.

Staging

Staging for HCC has changed over the last two decades as new prognostic factors have been identified through retrospective studies. Current staging systems fall into two broad categories—clinical and pathological. American Joint Committee on Cancer Tumor-Node-Metastasis (AJCC TNM) pathologic staging is the most widely used system, though it depends upon data derived after resection and is not applicable to patients who undergo treatment other than resection.³⁵ Because of the difficulty of applying pathology-based systems to patients before treatment, many clinical staging systems have been developed.

The Okuda system, described in 1985, segregates patients by tumor size, presence of ascites, and biochemical studies including albumin and bilirubin levels.³ An alternative system was devised in 1998 by the Cancer of the Liver Italian Program Investigators, which incorporates Child-Pugh stage, tumor morphology, AFP levels, and presence of portal vein thrombosis. An aggregate score from 0–6 is then calculated.³⁶ This system has been validated in numerous populations and allows for staging of patients without the need for tissue. The Japan Integrated Staging Score from the Cancer Study Group of Japan is another attempt to refine staging for more accurate estimates of survival.³⁷ It combines Child-Pugh staging with a modified version of TNM staging to create a score from 0–5. Both of these systems add a component of functional capacity by using easily measured variables from laboratory or imaging studies.

The most widely used staging system for HCC is the AJCC TNM staging system (see Table 1).³⁸ This system classifies patients based on tumor size, number of tumors, vascular invasion, regional node status, and distant metastases. Although it fits with the tumor/node/metastasis pattern of staging used for many other cancers, the TNM system has been criticized as unnecessarily complex³⁹ and requires tissue for adequate staging.

The diversity of staging systems is often confusing and complicates the ever-expanding literature on treatments of HCC. In a consensus report of the American Hepato-Pancreato-Biliary Association, Henderson et al.⁴⁰ recommended the use of the Cancer of the Liver Italian Program system for clinical staging and the AJCC system when pathological specimens were available. This would ease

Table 1. American Joint Committee on Cancer (AJCC) staging system for hepatocellular carcinoma (HCC)³⁸

T:	Primary
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion or multiple tumors, none > 5 cm
T3	Multiple tumors > 5 cm or tumor involving major branch or portal or hepatic vein
T4	Tumor with direct invasion of adjacent organs other than gallbladder or with perforation or visceral peritoneum
N:	Regional lymph nodes
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Regional lymph node metastasis
M:	Distant metastasis
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Staging:	
Stage I	T1N0M0
Stage II	T2N0M0
Stage IIIA	T3N0M0
Stage IIIB	T4N0M0
Stage IIIC	Any T, N1M0
Stage IV	Any T, any N, M1

communication and reliable comparisons of patient outcomes in the medical literature.

CURRENT TREATMENT OPTIONS

Surgical Resection

A good treatment option for HCC is R0 surgical resection, especially where screening programs identify a significant number of patients with small, asymptomatic lesions. In Western practices, only 15%–30% of patients with HCC are operative candidates due to advanced or multifocal hepatic disease, extrahepatic metastases, or inadequate functional hepatic reserve.^{41,42} Of those explored, only 50%–70% will undergo resection. Technical advances including a broader knowledge of segmental anatomy, vascular occlusion techniques, and intraoperative ultrasound have facilitated tumor resections. Intraoperative ultrasound is now commonly used to define tumor size and relationship to major vascular and biliary structures to achieve an adequate tumor margin. Recently, three-dimensional image analysis techniques have become available that estimate liver volumes, perfusion territory, and detailed intrahepatic anatomy that very closely

resembles the actual pathologic findings found intraoperatively. This can generate an appropriate tactical approach in cases with difficult anatomy and advanced disease to provide adequate margins of resection, either avoidance of large structures or calculation of the volume affected by the watershed, as well as the expected volume of the liver remnant.

Survival data after resection of HCC vary depending on the selection criteria and patient population studied. The results after resection from several recent studies are shown in Table 2. Grazi et al.⁴³ reviewed the outcomes of 408 patients with cirrhosis and HCC who underwent resection between 1983 and 1998. Operative mortality rates decreased from 9% to 1% in 157 patients who underwent HCC resection after 1992; they attribute these results to better operative techniques and postoperative care. These results are reinforced by recent studies of hepatic resections, where mortality rates range from 0%–8%.

Despite a decrease in operative mortality over the last two decades, the overall survival after resection of HCC has changed little. The most significant reasons for poor overall survival after resection are tumor recurrence and poor liver function. Many analyses have identified prognostic factors for disease recurrence and survival. Tumor at the resection margin⁴⁴; presence of cirrhosis⁴⁵; vascular invasion⁴⁶; absence of a tumor capsule, preresection serum AFP level greater than 10,000 ng/ml, poor preoperative performance status, and advanced tumor grade⁴⁷; number of nodules, microvascular portal vein thrombosis and preoperative AST greater than twice normal,⁴⁸ preoperative transcatheter arterial chemoembolization (TACE)⁴⁹; and large volume intraoperative transfusion⁵⁰ have all been identified retrospectively as poor predictors of disease-free survival and patient survival. In patients who do not have any of these negative prognostic indicators (solitary lesions less than 5 cm without vascular invasion and a negative surgical margin of more than 1 cm), the 5-year survival rate after resection has been reported^{46,51,52} to be as high as 78%. Adjuvant intra-arterial injection of 131-iodine labeled lipiodol is a positive predictor of outcome as it has been shown in one study of French patients with HCC to significantly decrease tumor recurrence rates after curative hepatic resection in a retrospective case-control study.⁵³

As an adjunct to liver resection in patients with evidence of decreased hepatic reserve where tumor is confined to one side of the liver, portal vein embolization (PVE) with a variety of agents has been used to induce hypertrophy in the other lobe.⁵⁴ A prospective nonrandomized trial in 55 patients with primary or secondary tumors of the right lobe of the liver compared outcomes in patients who underwent

Table 2. Survival rates after resection of HCC in recent studies Overall survival/disease - free survival when available

Author	Yr	N	Operative mortality (%)	1 yr* (%)	3 yr* (%)	5 yr* (%)	8 yr* (%)	10 yr* (%)
De Carlis et al. ¹⁷³	2003	154	5	NR	NR	47/NR	NR	28/NR
Daniele et al. ¹⁷⁴	2003	17	NR	82/NR	63/NR	NR	NR	NR
Ercolani et al. ⁴⁸	2003	224	NR	83/70	63/43	43/27	NR	NR
Sim and ooi ¹⁷⁵	2003	81	5	79/59	59/30	NR	NR	NR
Wei et al. ¹⁷⁶	2003	155	8	NR	NR	NR	NR	NR
Kanematsu et al. ¹⁷⁷	2002	303	2	84/75	67/41	51/27	NR	20/11
Regimbeau et al. ¹⁷⁸	2002	34	6	NR	NR	35/26	6/0	NR
Limited								
Regimbeau et al. ¹⁷⁸	2002	30	7	NR	NR	54/45	45/21	NR
Anatomic								
Poon et al. ¹⁷⁹	2002	135	4	90/74	76/50	70/36	NR	35/22
(Milan criteria)								
Grazi et al. ⁴³	2001	107	9	NR	53/49	32/28	NR	NR
Pre-1992								
Grazi et al. ⁴³	2001	157	1	NR	72/49	49/28	NR	NR
Post-1992								
Zhou et al. ¹⁸⁰	2001	1000	2	91/NR	77/NR	65/NR	NR	46/NR
< 5 cm								
Zhou et al. ¹⁸⁰	2001	1366	4	76/NR	48/NR	37/NR	NR	29/NR
> 5 cm								
Hanazaki et al. ⁴⁹	2000	386	4	NR	51/37	34/23	NR	11/8
Buell et al. ¹⁸¹	2000	26	0	75/NR	60/NR	38/NR	NR	NR

*NR = not recorded.

right hepatectomy with or without preoperative PVE.⁵⁵ In patients with Child A cirrhosis that underwent resection, PVE-induced hypertrophy of future liver remnant volumes in 86% of patients was associated with a significantly lower incidence of complications and led to decreased length of stay compared with those without PVE.

Despite earlier detection, safer operations, and more aggressive treatment of HCC, disease recurrence is likely. The liver is the most common site of tumor recurrence as a result of either multicentric carcinogenesis or intrahepatic metastases derived from primary HCC. Nearly 10% of patients with recurrent tumor undergo repeat resection. Repeat surgical resection provides good long-term benefits in appropriately selected patients; a poor prognostic indicator for these patients is tumor recurrence within 12 months of the first resection.^{52,56}

Transplantation

In the past, liver transplantation was performed for patients with HCC who were not candidates for curative resection due to tumor size and/or inadequate hepatic reserve. This approach resulted in high rates of early tumor recurrence. However, it was recognized in this early transplant experience

that subsets of patients with small tumors (often those with incidental tumors) and those with the fibrolamellar variant could potentially benefit from transplantation with success rates similar to those in patients transplanted for nonmalignant disease.

Liver transplantation is the only treatment that ensures complete removal of all hepatic foci of tumor as well as tissue with high oncogenic potential for tumor recurrence. Until 1990, the survival rates for patients undergoing liver transplantation for HCC ranged from 15%–35% at 5 years and were strikingly different from patients transplanted for other reasons.^{57–60} Bismuth et al.⁶⁰ demonstrated that subpopulations of patients with less than 3 tumor nodules, of a size smaller than 3 cm, and no tumor thrombus in the portal vein derived more benefit from transplantation. The Milan criteria described by Mazzaferro et al.⁶¹ cited 4-year survival rates of 85% and disease-free survival of 92% when transplant criteria consisted of either one tumor less than 5 cm or ≤3 tumors with none larger than 3 cm.

In addition to tumor size and number, survival outcomes may also be defined by other prognostic factors. Iwatsuki and Starzl⁶² found that patients who received orthotopic liver transplant for HCC fared no better than those that received resection unless the HCC patients had concomitant cirrhosis.

In multivariate analyses from a retrospective study of 125 patients with HCC, Philosophe et al.⁶³ reported that hepatitis B virus (+) status was predictive of recurrent HCC after transplantation. This finding was supported by Hemming et al.,⁶⁴ who also demonstrated the prognostic importance of vascular invasion. Molmenti and Klintmalm⁶⁵ reported data collected from the International Tumor Registry on 790 patients transplanted for HCC. There was significantly higher survival probability for patients with incidentally discovered tumors, no vascular invasion, negative nodes, tumor size ≤ 5 cm, and better histologic grade.

The United Network for Organ Sharing currently follows the Milan criteria and allocates organs based on the model of the end-stage liver disease scoring system,⁶⁶ but several groups have described the success of transplantation in patients who are outside these criteria. Marsh and colleagues⁶⁷ studied factors predictive of recurrence in 307 patients who underwent liver transplantation for HCC from 1981 to 1997. Their analysis showed that the current TNM classification system neither correlated with tumor-free survival nor showed homogeneity in outcomes of patients within the same pTNM category. Yao et al.⁶⁸ advocated expanding transplant criteria to a single tumor less than 6.5 cm or ≤ 3 tumors with the largest no greater than 4.5 cm and total tumor diameter of ≤ 8 cm, because this group of patients showed 1- and 5-year survival rates of 90% and 72.5%.⁶⁹ A summary of survival outcomes after transplantation is provided in Table 3, A–C.

To help mitigate the shortage of suitable organs for patients with HCC and to help expand indications, transplantation using split-liver cadaveric or adult living donors is becoming more common. Kaihara and colleagues⁷⁰ describe 56 patients with HCC that underwent living related right lobe liver transplantation, with an overall survival of 73% at 1 year and 55% at 3 years. An important finding was 15 of 20 patients outside the Milan criteria were alive and disease free at follow-up.

Improved long-term survival in patients undergoing transplantation is aided by improving

Table 3A. Survival rates after liver transplantation for HCC based on stage^{58,59}

	1 yr	2 yr	3 yr	5 yr
Overall (n = 105)	66%	49%	39%	36%
State I	75%	75%	75%	75%
State II	80%	70%	60%	60%
State III	60%	40%	40%	40%
State IVA	50%	30%	15%	10%

Table 3B. Survival rates after liver transplantation for HCC based on T classification³⁹

Group	N	Median survival (mo)	5-yr survival (%)
T1	44	58	50
T2	178	68	56
T3	201	35	31
T4	108	16	21

immunosuppression.⁷¹ Neoadjuvant or adjuvant chemotherapy protocols have improved survival for some patients^{72–74} Carr et al.⁷² reported a series of patients with advanced HCC who first underwent at least three cycles of intra-arterial chemotherapy before liver transplantation. At 1 year, the survival rate was 91% in the treated groups compared with 43% in those not receiving chemotherapy. Graziadei et al.⁷⁵ routinely treated HCC patients with neoadjuvant TACE while on the waiting list. Their 1- and 5-year survival rates for 41 patients transplanted based on Milan criteria were 98% and 93%, respectively, with tumor recurrence in only one patient (2%). TACE was also used to downstage 15 of 36 patients with advanced stage HCC; 10 of those 15 underwent liver transplantation with subsequent 1- and 4-year survival rates of 82% and 41%, respectively. Roayaie et al.⁷⁶ studied the effects of preoperative TACE and adjuvant chemotherapy in 80

Table 3C. Survival rates after liver transplantation for HCC based on current common transplantation criteria

Name	Criteria	N	1 yr (%)	5 yr (%)
Milan ^{61,†}	Within	35	—	85*
	Outside	13	—	50*
UCSF ^{69,‡}	Within	60	90	75
	Outside	10	50	—
CLIP ^{182,§}	0	62	92	67
	1	65	80	17
	2	48	52	0
	3	45	37	0
	4	27	4	0
	5	7	0	0
	6	3	0	0
Okuda ^{182,}	1	132	82	35
	2	111	36	0
	3	14	14	0

*4 year survival rate.

†Milan: single tumor < 5 cm or ≤ 3 tumor nodules all < 3 cm.

‡UCSF: single tumor nodule < 6.5 cm or ≤ 3 tumor nodules all < 4.5 cm and total diameter < 8 cm.

§CLIP: points based on aggregate score determined by Child-Pugh class, tumor morphology, AFP level, and macrovascular invasion.

||Okuda: based on number of following present: tumor size $\geq 50\%$, ascites, albumin ≤ 30 g/L bilirubin ≥ 3 mg%.

patients with HCC greater than 5 cm diameter. Patients received subselective arterial chemoembolization before transplant, followed by intraoperative doxorubicin and systemic doxorubicin postoperatively. An overall survival rate of 44% at 55 months was observed in the 43 patients that proceeded to transplantation; 40% of the patients undergoing transplantation had no evidence of disease recurrence at last follow-up.

Thermal Ablation

Radiofrequency ablation. Because resection is not possible in the majority of patients with HCC because of poor hepatic reserve or comorbid conditions, other less physiologically demanding therapies have been developed to control hepatic tumors. These ablative therapies can also be used in conjunction with resection for secondary, smaller, distant tumors. Radiofrequency ablation (RFA) involves the delivery of energy created by radiofrequency waves to tumors by means of ultrasound-guided electrodes. This energy induces thermal damage with coagulative necrosis of the tumor. The electrodes are insulated along all but the distal portion of the shaft and can be introduced into the tumor at celiotomy or by image-guided laparoscopic or percutaneous techniques. Preliminary studies with radiofrequency-based ablation indicate that this procedure is safe in patients with compensated cirrhosis and small HCC. A 10-minute application of RF thermoablation has been shown to result in complete necrosis of a 3 cm tumor.⁷⁷

Numerous studies compare outcomes with RFA to other previously established therapies for HCC. In a prospective randomized study of 86 patients with compensated cirrhosis and small HCC, RFA was superior to percutaneous ethanol injection (PEI) in terms of complete tumor necrosis (90% vs. 80%) and number of required treatments (1.2 vs. 4.8 sessions) but caused more complications (10% vs. 0%).⁷⁸ Pearson et al.⁷⁹ compared RFA to cryoablation in 146 patients, 41 with HCC. They determined that treatment-related complications, including one death, were higher (41% compared with 3%) in the group receiving cryoablation, and a recurrence rate with cryoablation of 22% compared with 3% for RFA. These findings were mirrored by a retrospective review of 64 French patients, 36 of whom were diagnosed with HCC.⁸⁰ There was a nonsignificant trend toward higher recurrence rates in patients with HCC treated with cryoablation (38% vs. 17% with RFA).

The utility of RFA becomes limited as tumor size increases. It has traditionally been advocated in treatment of tumors less than 3 cm. However, several

studies describe techniques by which this method can be employed in treatment of larger tumors with similar results. Hansler et al.⁸¹ used a saline perfusion device to elicit a complete response in 85% of patients with a mean tumor size of 3.1 cm, including 8 with tumors between 3 and 4.5 cm. Technological advances, including increasing larger arrays are theoretically able to handle increasing larger lesions satisfactorily, but data are sparse. Yamakado et al.⁸² used TACE before RFA. The rationale was that elimination of blood flow increased the volume of thermal ablation. They treated 108 tumors in 64 patients within 2 weeks of chemoembolization. Complete necrosis was achieved in all tumors, including 43 greater than 3 cm (3.1–12 cm). No local recurrences were detected in 97 tumors less than 5 cm and only 2 of 11 tumors greater than 5 cm. Temporary venous occlusion during RFA was used in 10 consecutive tumors measuring greater than 35 mm or located adjacent to large vessels in patients with either metastases to the liver or HCC.⁸³ These authors report a larger zone of coagulative necrosis and complete necrosis in 90% of tumors when compared with patients undergoing RFA alone. Yamasaki et al.⁸⁴ report a retrospective review of 31 patients with 42 HCC lesions less than 4 cm in greatest dimension. There were no differences in number of treatments, duration of treatments, or needle insertions between the 12 patients treated with balloon occlusion and RFA compared with the 19 patients treated by RFA alone. However, they also reported a larger area of coagulative necrosis (37 mm × 30 mm) in patients treated with RFA during temporary balloon occlusion. Together, these data suggest that lesions between 3 and 5 cm may be amenable to RFA if lesions are located away from large vessels or temporary blood flow is halted by either TACE or balloon occlusion.

Cryosurgical ablation. Cryosurgical techniques have been used as an adjunct to secure adequate tumor margins or as an alternative to surgical resection in patients with limited hepatic reserve or with multiple, bilobar, or recurrent primary liver tumors. Cryosurgery is based on the principle that rapid freezing and thawing of tissue causes cell death. Under the guidance of intraoperative ultrasound, a probe with recirculating liquid nitrogen is placed in the tumor and two or more freeze/thaw cycles are initiated. The zone of destruction is monitored until the leading edge of the ice ball is 1.0 cm beyond the margin of the tumor. The advantage of cryosurgery is that single or multiple tumors can be treated locally without resection of surrounding liver parenchyma in patients with marginal hepatic reserve. The most serious, though relatively uncommon,

complication of cryotherapy is the development of cryoshock syndrome (1% of patients), characterized by disseminated intravascular coagulation and multi-organ failure. Hemorrhage from cracking of the liver, renal dysfunction, biliary disruption with bile leakage, and acute respiratory distress syndrome are seen occasionally as well.⁸⁵

Table 4 reports the outcomes of cryoablation for HCC in recent major series. Zhou et al.⁸⁶ reported 167 patients with HCC treated by cryosurgery, with an overall 5-year survival rate of 32%. Patients with small, solitary tumors had a 48% 5-year survival rate. Wren et al.⁸⁷ showed cryosurgery was more beneficial when the aim was curative as opposed to palliative. Clavien et al.⁸⁸ performed a prospective study focusing on complications and outcomes in 15 patients treated with TACE before cryosurgery who had cirrhosis and unresectable HCC. Complications occurred in 4 of 15 patients, including one death. However, the 5-year actuarial survival was 79% with only three recurrences after a median follow-up period of 2.5 years. Cryoablation seems to be progressively less favored for ablative treatment due to the need for laparotomy and the comparatively increased incidence of complications.

Chemical Ablative Therapy

Percutaneous interstitial treatments under ultrasound guidance are effective in achieving palliation and tumor reduction. Ethyl alcohol (ethanol), acetic acid, hot saline, and chemotherapeutic agents have been used with differing degrees of success. PEI remains a very popular option and the best studied of the chemical ablative techniques. It causes sclerosis and extensive necrosis of tumor cells and thrombosis of tumor vessels. Advantages of PEI over other forms of ablative therapy include the relative ease in regards to outpatient administration, the inexpensive costs compared with other techniques, the lack of special technological equipment other than CT or ultrasound

for guidance, and the large number of tumors that may be treated with minimal morbidity at any given session. Disadvantages of this treatment have included difficulty in monitoring completeness of a treatment session, requirement for multiple sessions, and limitations of treating tumors larger than 3 cm.

Several studies have demonstrated complete coagulative necrosis in up to 75% of lesions treated by PEI, with 68%–80% survival at 3 years after initiation of therapy depending upon the size and number of tumors.^{89,90} Table 5 reviews the results of percutaneous ablative techniques cited in the recent literature. In a review of 746 patients with HCC and cirrhosis, PEI treatment was associated with a 3- and 5-year survival rate of 68% and 40%, respectively, when tumor nodules were single and ≤ 3 cm. That survival data declined as tumor size or number of nodules increased.⁹¹

PEI is more successful for small, encapsulated, hypovascular tumors that can trap injected ethanol. In patients with well-compensated cirrhosis, larger tumors (greater than 5 cm) can also be treated with PEI but require larger volumes of ethanol and general anesthesia.⁹² Several studies have described techniques whereby PEI can be used in larger tumors with satisfactory results. Tanaka et al.⁹³ first described a combination of TACE and PEI to treat patients with solitary HCC lesions greater than 3 cm. Together, the complete response rate was 83% compared with 20% with TACE alone. This was followed by a randomized, controlled study by Bartolozzi et al.⁹⁴ that confirmed a higher complete response, longer survival, and decreased tumor recurrence in the arm of patients treated with both PEI and TACE. The 5- and 7-year survival rates for these patients has been reported to be 35% and 14%, respectively, with stage of cirrhosis and size of largest lesion identified as independent risk factors for survival.⁹⁵

In a large multicenter study of PEI use in patients with cirrhosis and HCC less than 5 cm, the 5-year

Table 4. Cryosurgery for treatment of HCC in recent series

Study	Yr	N	Child class (n)	Morbidity/mortality	1 yr survival (%)	3 yr survival (%)	5 yr survival (%)	Other treatments
Adam et al. ⁸⁰	2002	18	A 7 B 6 C 3 None 2	NR	66			TACE and/or resection
Clavien et al. ⁸⁸	2002	15	A 11 B 4	27/7	93	79	79	TACE
Wren et al. ⁸⁷	1997	12	A 7 B 4 C 1	8/0				
Zhou et al. ¹⁸³	1988	27	NR	0/0	33	13	4	TACE, HA ligation

TACE = Transcatheter arterial chemoembolization; HA = hepatic artery; NR = not recorded.

Table 5. Use of percutaneous chemical ablation for treatment of HCC in recent series

Study	Year	N	Child class (n)	M/m	1 yr survival (%)	3 yr survival (%)	5 yr survival (%)	Other treatments
Leugn et al. ⁹⁹	2003	51	A 13 B 38	NR	79	14	NR	Use of cis-epi gel for palliation
Gournay et al. ⁹⁷	2002	55	A 37 B 8	38/2	≤30 mm: 88/DF: 82 >30 mm: 73/DF: 45	70/DF: 38 34/DF: 5	44/DF: 15 17/DF: 5	Compared PEI to resection
Koda et al. ¹⁸⁴	2001	PEI: 26 TACE/PEI: 26	A 14 B 8 A 19 B 5	0/0 0/8	91 100	66 81	38 40	All patients with 1–3 tumors, <3 cm
Lencioni et al. ¹⁸⁵	1998	86	A 48 B 38	0/0	92	69	47	TACE then PEI for tumors > 3 cm
Tanaka et al. ⁹⁵	1998	83	A 48 B/C 35	0/0	100 100	82 48	46 21	TACE followed with PEI
Ohnishi et al. ⁹⁸	1998	PEI: 29 PAI: 31	A 21/B 8 A 26/B 5	NR	PEI: 82, DF: 59 PAI: 100, DF: 83	NR	NR	None
Bartolozzi et al. ⁹⁴	1995	26	A 14 B 12	0/0	100	72	NR	TACE followed by PEI
Livraghi et al. ⁹¹	1995	462	A 293 (ONE TUMOR, <5 CM)	NR	A : 98	DF : 52 A : 79	A = 47 B : 29	Also compared by stage and tumor number
Horiguchi et al. ¹⁸⁶	1994	10 (<1.5 cm) 6 (1.5–3 cm)	C 20 NR	NR	C : 64 <1.5 cm: 90 1.5–3 cm: 82	C : 0 NR	C : 0 NR	Compared PEI to resection or TACE

NR = not recorded; TACE = transcatheter arterial chemoembolization; DF = disease-free survival; M = mortality; m = morbidity; Cis-ept- cisplatin-epinephrine injectable gel; PEI = percutaneous ethanol injection; PAI = percutaneous acetic acid injection.

survival of patients with Child A cirrhosis ($n = 293$) was 47% compared with 29% for patients with Child B cirrhosis ($n = 149$) and 0% for patients with Child C cirrhosis ($n = 20$).⁹¹ Life expectancy of Child A patients with a small tumor treated by PEI appeared to be as good as that of similar patients treated with hepatic resection.⁹⁶ In fact, Gournay et al.⁹⁷ found that PEI was more effective than resection in patients with HCC and a single nodule less than 3 cm in terms of cost and comfort to the patient, with no difference in survival or disease-free survival. Those differences did not translate to patients with larger tumors. In most patients that failed therapy, a second primary tumor was detected (64%–100%). PEI was associated with low risk of severe complications and mortality (0.1%). Major complications with PEI are unusual, but fever and discomfort are not uncommon. Occasionally, peritoneal hemorrhage or hemobilia, biliary sclerosis, or major liver infarction may occur.

Acetic acid has also been used as an agent in percutaneous therapy for HCC. It offers the advantage of better tissue penetration and possibly higher rates of complete response. In a randomized, controlled trial, Ohnishi et al.⁹⁸ compared 31 patients treated with percutaneous acetic acid injection to 29 patients treated with PEI. They found that all original tumors were treated successfully with both agents. However, only 8% of tumors treated with percutaneous acetic acid injection recur compared with 37% with PEI. In addition, the 1- and 2-year survival rates were significantly better with percutaneous acetic acid injection (100% and 92%, respectively, compared with 83% and 63%, respectively).

Yet another option for percutaneous treatment of HCC is injection of active chemotherapeutic agents into the tumor. In the past, this technique had not proven successful due to rapid drug diffusion into surrounding normal parenchyma and the systemic circulation. Recent attempts to minimize this limitation have met with some success. Leung et al.⁹⁹ described results in 58 patients treated with a gel-based cisplatin–epinephrine mixture. They found 53% of patients responded with either partial or complete response, but median survival was only 27 months, with 3-year survival rates of 14%.

Chemotherapeutic Approaches

Transcatheter arterial chemoembolization. TACE can be used before resection to improve resectability, before transplantation to maintain curability while awaiting a graft, in conjunction with other methods of ablation, or alone as a palliative measure. TACE provides a means of achieving regionally elevated levels of chemotherapeutic agents in the liver while

avoiding concomitant systemic toxicity. Concentrated chemotherapeutic agents, such as doxorubicin, cisplatin, or mitomycin C, can be delivered via angiography. Typically, gelatin foam or other inert substances are used to induce embolization that may be temporary or permanent. This serves to increase local chemotherapeutic dwell time and induce tumor ischemia. In addition, lipiodol, an ethiodized poppy seed oil that selectively remains in tumors for long periods may enhance the antitumor effect.

Chemoembolization can be applied to one major branch of the hepatic artery or selectively to individual hepatic segments. TACE takes advantage of relatively selective tumor arterial vascularization. HCC tumors derive approximately 80%–85% of their blood supply from the hepatic artery; normal hepatic parenchyma has a dual blood supply with 80%–85% supplied by the portal vein and the remainder from the hepatic artery.

Relative contraindications of TACE include thrombosis of the portal vein, renal failure, extrahepatic metastases, or advanced liver dysfunction. Child class A and B patients tolerate the procedure well, but mortality rates as high as 40% have been reported in patients with Child class C cirrhosis treated with TACE.¹⁰⁰ TACE has been shown to be of little use in patients with diffusely infiltrating or multifocal tumors.¹⁰¹

A decrease in tumor size has been noted in 16%–61% of patients treated with TACE, though the duration of response is variable.¹⁰² The best outcomes with TACE have been observed in patients with encapsulated tumors, small tumors, solitary lesions, and with repeated treatments. Overall results with TACE in Western and Eastern studies, however, have been difficult to interpret, partly due to patient selection and the intent to treat for cure versus palliation. Median survivals, subgroups, and statistical analysis of the predominant series are presented in Table 6, divided according to type of study design. The outcomes in patients with unresectable HCC from prospective randomized trials are mixed with two studies^{103,104} showing no improvement in overall survival and two studies suggesting higher survival rates.^{105,106}

There is widespread debate about the applicability and validity of these trials.^{107,108} Pelletier et al.¹⁰³ reported in 1990 a decreased median survival to 4 months in 21 patients receiving TACE compared with a 6-month median survival in patients receiving supportive care only. This is the only study in the Western literature that reports a decreased survival with TACE for patients with HCC. The Group d'Etude et de Traitement du Carcinome Hépatocellulaire¹⁰⁴ reported in 1995 their results with 50 patients undergoing TACE in 24 institutions. Although no

Table 6. TACE for HCC

Author	Yr	Therapy	N	Median survival (mo)	P
Prospective randomized					
Pelletier et al. ¹⁰³	1990	Dox + gel	21	4	NS
		Supportive care	21	6	
French Study Group. ¹⁰⁴	1995	Cis + lip + gel	50	19	NS
		Supportive care	46	8	
Pelletier et al. ¹⁸⁷	1998	Cis + lip + gel + tamoxifen	37	13	NS
		Tamoxifen	36	12	
Llovet et al. ¹⁰⁵	2002	Dox + lip + gel	40	29	0.009
		Supportive care	35	18	
Lo et al. ¹⁰⁶	2002	Cis + lip + gel	40	12	0.002
		Supportive care	40	6	
Retrospective, matched historical controls					
Vetter et al. ¹⁰⁹	1991	Dox + lip + gel	30	12	<0.001
		Supportive care	30	3	
Bronowicki et al. ¹¹⁰	1994	Dox, cis, or epi + lip + gel	127	18	<0.0001
		Supportive care	127	5	
Stefanini et al. ¹¹¹	1995	Dox + lip + gel	69	21	<0.001
		Supportive care	64	3	
Retrospective, Non matched controls					
Bronowicki et al. ¹¹²	1996	Dox, cis, or epi + lip + gel	42	36	<0.0001
		Supportive care	33	11	
Stuart et al. ¹¹³	1996	Dox + lip + gel	137	14	<0.01
		Supportive care	81	2	
Marcos-Alvarez et al. ¹¹⁴	1996	Dox + lip + gel	30	13	<0.05
		Supportive care	22	5	
Ryder et al. ¹¹⁵	1996	Dox + lip + gel	67	9	N/A
		Non surgical therapy	118	3	
Rose et al. ¹¹⁹	1999	Dox + lip + gel	35	9	<0.0001
		Supportive care	31	3	

Dox = doxorubicin; Cis = cisplatin; epi = epirubicin; lip = lipiodol; gel = gelatin-foam particles or power; NS = not significant; N/A = not applicable.

statistically significant difference was noted in survival when compared with supportive care only, median survivals were increased from 8 to 19 months, and the estimated relative risk of death was 1.4 in the conservatively managed group compared with the chemoembolization group. Llovet et al.¹⁰⁵ used TACE as palliative treatment in a prospective, randomized controlled trial published in 2002 on 112 patients with intermediate stage HCC not felt to be candidates for other therapies. The patients were allocated between an embolization only group, a chemoembolization group, and a supportive care only group. A significant increase in survival for the chemoembolization group was observed when compared with controls (82% and 63%, 1- and 2-year survival, respectively, compared with 63% and 27%). In a study of 80 Asian patients also published in 2002, Lo et al.¹⁰⁶ found that chemoembolization resulted in a survival advantage compared with untreated controls (57% and 26%, 1- and 3-year actuarial survival rates, respectively, compared with 32% and 3%).

The remainder of the studies listed in Table 6 are retrospective, with either historically matched or nonmatched controls. Of note, all of these studies demonstrate a significant improvement in overall patient survival when compared with patients receiving supportive care only.¹⁰⁹⁻¹¹⁵ Examination of the median survivals of these studies shows a consistent threefold improvement in survival in those patients undergoing TACE.

Variations of TACE exist, including transcatheter arterial chemotherapy and transcatheter embolization alone. These techniques were used more widely in the past but have given way to TACE, given the findings of recent studies. The most significant study with transcatheter embolization alone was a randomized controlled trial in 80 patients conducted by Bruix et al.¹¹⁶ They found that transcatheter embolization alone slowed tumor growth but did not impact the survival of patients with advanced stage HCC. Madden et al.¹¹⁷ studied transcatheter chemotherapy with epidoxorubicin suspended in a lipiodal

suspension in 25 patients with advanced unresectable HCC. There was no significant difference between the treated and control groups (median survival of 48 days vs. 51 days, respectively) in terms of survival, but treated patients spent more time in the hospital and received no symptomatic improvement compared with controls.

TACE is typically well tolerated with most patients requiring only an overnight observation. Lopez et al.¹¹⁸ reported an experience with TACE in unresectable hepatic malignancies and found only transient adverse side effects associated with the post-embolization syndrome. Similar results were seen in the series of Rose et al.¹¹⁹; overall, we find TACE to be a safe procedure in properly selected patients. Complications of the procedure reported in one series from 1992 include cholecystitis (10%), vasculitis (14%), hepatic decompensation with ascites (14%), jaundice (12%), and renal insufficiency (13%).¹⁰⁰

Investigations are underway to determine the impact of TACE in the preoperative management of patients undergoing liver resection or transplantation. In a recent report,¹²⁰ downstaging or total tumor necrosis was induced by TACE in 62% of patients and was associated with an improved disease-free survival both after liver resection and transplantation. Patients initially excluded from transplantation because of tumor size who respond favorably to TACE have been shown to have a disease-free survival after transplantation that is similar to patients with smaller tumors.

Hepatic arterial infusion chemotherapy (HAI).

Given the dual blood supply of the liver, regional chemotherapy has been considered an attractive treatment option because of decreased systemic effects of chemotherapeutic agents. In fact, regional approaches to chemotherapy have produced more encouraging results than systemic chemotherapy for HCC, although these results are still far from optimistic. Several agents including doxorubicin, cisplatin, mitomycin C, floxuridine and α -interferon have produced objective responses of 30%–50% in patients with HCC.^{121–125} These responses appear to be three-fold greater than in patients receiving systemic therapy, and there are reports of a few month survival advantage. However, patients treated with HAI are selected for their ability to tolerate an operation and tend to have a better overall performance status than the average patient with unresectable HCC.

HAI therapy has been used to downstage unresectable tumors so that patients may undergo surgical resection. Meric et al.¹²⁶ performed a retrospective analysis on their patients initially treated with HAI. Twenty-five patients with HCC were included; four of these patients (16%) were able to undergo further treatment consisting of either surgical

resection or RFA. None of these four patients showed any evidence of disease recurrence after a mean follow-up of 16 months. Clavien et al.¹²⁷ examined the effect of preoperative HAI therapy in 28 patients with unresectable liver tumors, including five patients with HCC. After a mean follow-up of 33 months, four of five patients with HCC had been downstaged to the point that resection was possible. Curative resection was achieved in three patients, and the 3-year actuarial survival was 60%, with the other two patients alive for more than 2 years after resection. Despite these findings, other treatment modalities such as TACE seem like a more pragmatic approach for downstaging.

HAI is well tolerated without the usual systemic toxicities of chemotherapy, but it is associated with an increased risk of regional toxicities such as biliary sclerosis, chemical hepatitis, and acalculous chemical cholecystitis, necessitating weekly biochemical observation. Additional complications associated with hepatic artery infusion include arterial injury, gastric or duodenal malperfusion, infection, and thrombosis of the infusion catheter or hepatic artery.

Systemic chemotherapy. Systemic chemotherapy has been widely used to treat inoperable HCC, but response rates are low (near 20%). The possible explanations include tumor heterogeneity or overexpression of a multidrug resistance gene. Of all the neoplastic agents, doxorubicin is thought to have the most potent activity. However, in the only randomized controlled trial, doxorubicin not only failed to prolong survival but also caused fatal complications due to cardiotoxicity.¹²⁸ Numerous other agents including etoposide, cisplatin, eniluracil, 5-fluorouracil, gemcitabine, and epirubicin, have been unsuccessful in producing response rates greater than 30%.^{129–132} Current combination regimens based on doxorubicin or 5-fluorouracil demonstrated response rates of 20%–30%.

No single agent or combination of agents given systemically leads reproducibly to greater than 20%–25% response rates. A meta-analysis of randomized and nonrandomized controlled trials¹³³ showed no survival benefit to adjuvant chemotherapy after resection. Because there has been no demonstrable beneficial effect of systemic chemotherapy on survival rates, the risks of chemotherapy must be balanced against the potential gains.

Other Approaches

Hormonal and immunotherapy. The possible sex hormone dependence of HCC and the presence of tumor hormone receptors have suggested a potential for hormonal manipulation of tumor growth,

particularly by using antiestrogens. Although some of the early smaller trials suggested a survival benefit for the use of tamoxifen, several larger trials have subsequently determined that treatment with tamoxifen does not improve survival compared with placebo.^{134,135} Several antiandrogens,¹³⁶ including cyproterone acetate¹³⁷ and ketoconazole,¹³⁸ have also been ineffective.

Systemic interferon therapy has a response rate of only 7%–10%.^{139–141} Combinations of systemic chemotherapy¹⁴² or intrahepatic arterial chemotherapy¹⁴³ combined with interferon had only marginal effects in patients with locally advanced disease. However, a decrease in recurrence of HCC after ablation by other methods may be possible with the use of interferon^{144,145} or with polyphenolic acid.¹⁴⁶ Interferon therapy was shown to increase survival in a group of patients with hepatitis C virus (HCV)-induced HCC after surgical resection.¹⁴⁷ Additionally, eradication of HCV-RNA by use of interferon therapy may decrease the recurrence rates of HCC after curative treatment when compared with contemporaneously matched controls with continued HCV viremia.¹⁴⁸ Interferon therapy used in combination with granulocyte macrophage-colony stimulating factor has shown some ability to prolong survival in a select subset of patients deemed unresectable but positive for the human leukocyte antigen-DR cell marker.¹⁴⁹

Newer approaches have included the use of somatostatin, a hormone with antimitotic activity. In a study of 58 patients with advanced HCC,¹⁵⁰ subcutaneous octreotide was shown to significantly reduce AFP and possibly increase median survival time (13 months vs. 4 months) as compared with patients receiving placebo. Several studies assessed the role of interleukin-2 (IL-2) and other cytokines as part of various chemotherapeutic regimens; all showed low response rates.^{151–153} Palmieri et al.¹⁵⁴ recently showed that ultralow dose IL-2 was associated with a complete response in 2 of 18 patients for 35 and 46 months, and was associated with a mean overall survival of 25 months. Further studies to compare this effect in a controlled, randomized setting are needed.

Radiotherapy. The conventional method of palliative external radiotherapy for pain reduction is not effective in HCC. Proton irradiation provides good effects but is expensive and available in few medical centers. With this method, a large amount of radiation is focused on the tumor, minimizing the exposure of the surrounding liver. An analysis of 83 patients treated with proton radiotherapy showed that 19% had a complete response, 50% a partial response, and 31% no appreciable benefit. The quality of life was unaffected in most patients, and only three patients developed liver failure.¹⁵⁵

Since reporting the application of conformational three-dimensional radiotherapy in pilot studies of unresectable HCC, Cheng et al.¹⁵⁶ have continued to modify the delivery mechanisms of radiotherapy to prevent or reduce the associated radiation-induced organ damage prone to occur with local high-dose radiation.¹⁵⁷ Although this technique is not widely used, further work in this field may lead to more widespread availability of radiotherapy for unresectable tumors and add at least one more option for control of locally advanced disease.

The advent of selective intra-arterial radiation therapy offers an alternative delivery of radiation that may prove useful. ⁹⁰Yttrium microspheres are glass-based microspheres with a mean diameter of 25 μm with a variety of dose activity from 81 mCi to 540 mCi delivered transarterially via the hepatic artery. In an excellent review of this technique, Salem et al.¹⁵⁸ report median survival of 23 months for 54 patients with Okuda stage I disease and 11 months for patients with Okuda stage II disease. In an earlier report by Dancey et al.,¹⁵⁹ 22 patients with unresectable HCC were treated with an average of 104 Gy. They report an overall 20% response rate, with a median survival of 54 weeks in nine patients with Okuda stage 1 and 11 patients with Okuda stage 2 disease.

Multimodality Approach

The vast majority of patients with HCC will not be candidates for liver resection or transplantation. The above-mentioned treatment modalities may provide temporary local control of tumors, but recurrence is common due to the high oncogenic potential of the cirrhotic liver. Though an initial treatment may prove successful, physicians must remain vigilant for disease recurrence and open to implementation of other treatment modalities as clinical circumstances change. Takano et al.¹⁶⁰ described this approach in the treatment of 600 patients with HCC from a single Japanese institution. Although 54% of patients were treated with initial hepatic resection, recurrence was observed in 49% of those patients, and additional treatments included reresection, TACE, PEI, and regional chemotherapy. As discussed previously, patients may be candidates for therapy such as TACE or RFA before transplantation as a means of local control while awaiting organ availability. Reresection of recurrent lesions is applicable in some patients with suitable anatomy and clinical performance, but ablation techniques are more commonly applied as the liver disease progresses.

Table 7. Treatment options for HCC

Operative risk	Liver function	Tumor extent				Applicable treatment options
		Mets	Numbers	Volume	Size	
Good	Normal function	0	Limited (≤ 4)	$\leq 3/4$		Resection up to trisectionectomy
Good	Child A or MELD ≤ 9	0	Limited	$\leq 1/2$		Resection up to lobectomy
Good	Child B or MELD 10–11	0	Limited	$< 1/4$		Resection up to segmentectomy
Good	Normal, Child A or B	0	Limited		< 3 cm	Resection, RFA, PEI, or cryosurgery
Good	Normal, Child A or B	0	Limited		< 4 cm	Resection, PEI, or cryosurgery
Good	Normal, Child A or B	0	Limited		< 6 cm	Resection or cryosurgery
Good	Child A or B	0	Multiple	Extensive		Chemoembolization and/or PEI
Fair, poor	Child B or C or MELD > 11	0	1 3		≤ 5 cm or ≤ 3 cm	Transplantation
Good	Child A or B	+	Any	Any	Any	Systemic chemotherapy or clinical trial
Poor	Child C	+	Any	Any	Any	Supportive care

Patient performance, liver function as assessed by Child class or MELD, and extent of tumor (shown in the first 3 columns) together influence the choice of treatment (shown in the last column). MELD = model of end-stage liver disease.

ON THE HORIZON

Gene Therapy

Advances in genetic engineering promise opportunities for novel treatments of HCC. Several strategies have been proposed including transfection of tumor cells with gene-encoded viruses or synthetic vectors. These could potentially facilitate cell suicide, enhance expression of tumor specific antigens, augment cytokine-mediated immunity, alter oncogene and tumor-suppressor activity, or enhance responsiveness to chemotherapeutic agents.¹⁶¹ One such attempt at treating HCC by using gene therapy focused on the delivery of the suicide gene herpes simplex virus thymidine kinase via an HIV vector.¹⁶² Others have focused on the induction of apoptosis using adenoviral vectors to transduce the TRAIL (tumor necrosis factor related apoptosis-inducing ligand) gene¹⁶³ to avoid the risk of hepatitis associated with soluble TRAIL.¹⁶⁴ Tumor necrosis in addition to active secretion of cytotoxic agents by transfected tumor cells has been reported by Tran et al.¹⁶⁵ in trials using plasmid encoded metalloproteinase inhibitors. Results from these studies are encouraging, but highlight the difficulty in translating this research to common practice given the variable uptake in tumor cells, potential for damage to surrounding normal hepatocytes, and application to a diversity of patients potentially with biologically different tumors. Numerous problems must be resolved before the successful clinical application of gene therapy for HCC. Key developments will include more efficient gene delivery systems with better tumor specificity and prolonged transgene expression.

Tagged Antibodies

Intrahepatic arterial infusion of ¹³¹I-labeled anti-HCC monoclonal antibody (Hepama-1 mAb) has been studied as a method of cytoreduction for the treatment of unresectable HCC. In a comparison of 32 patients receiving infusion of monoclonal antibody (Hepama-1 mAb) via the hepatic artery and 33 patients treated with only intrahepatic-arterial chemotherapy, the post-treatment resection rate was 53% compared with 9%, with an overall 5-year survival rate that was significantly higher in the antibody-treated group (28% vs. 9%).¹⁶⁶

Isolated Perfusion

Although systemic drug exposure is limited after HAI, hepatobiliary toxicity has prevented dose escalation. To circumvent this problem, several groups have developed techniques, both operative and percutaneous, for isolating the venous outflow of the liver to allow delivery of increased dosages of drugs while reducing systemic exposure.^{167,168} Ku and colleagues¹⁶⁹ have developed a single catheter technique for percutaneous isolated liver chemoperfusion. A quadruple lumen-balloon catheter is used to isolate and capture total hepatic venous outflow and direct filtered blood to the right atrium to administer high-dose regional therapy. Using an intra-arterial infusion of high-dose doxorubicin in single or multiple treatments, a significant response rate of 63% was observed in 28 patients with advanced HCC. These authors recently reported their

experience with a phase II study of patients with advanced HCC by using reductive resection of tumor and locally positive nodes followed by isolated hepatic perfusion with doxorubicin. Of 25 patients enrolled in the prospective study, 22 were able to undergo hepatic perfusion, with 86% achieving some objective tumor response for an overall actuarial survival rate of 42% at 5 years.¹⁷⁰

Immunotherapy

Use of the body's natural defense mechanisms for tumor destruction theoretically offers a safe, effective mechanism to induce tumor necrosis or maintain disease stability. Some researchers are attempting this feat with the use of autologous cells to battle HCC. Cytotoxic T-lymphocytes are efficient destroyers of other cell types when triggered by antigen stimulating cells. Ladhams et al.¹⁷¹ are utilizing dendritic cells derived from patient sera and pulsing these cells with tumor markers derived from their own HCC tumors. They describe two patients with unresectable, untreatable disease managed in such a way; one died 3 months into treatment, whereas the other was alive over 3 years after therapy.

Conclusions

Treatment options for patients with HCC must be selected on the basis of number and size of hepatic tumors, underlying hepatic function, patient condition, and available resources. One approach is summarized in Table 7, showing the corresponding choice of treatment under given clinical circumstances. Regardless of the specific therapy, patients with well-preserved hepatic function and a single, small incidental tumor identified during screening programs have better outcomes than patients with advanced liver disease and/or large tumors. As a result of efforts in early detection, resection, transplantation, and cytoreduction with sequential resection or ablation, some patients with HCC are living longer. However, recurrence and metastasis together with decreased underlying liver function remain the major obstacles to prolonged survival.

Currently, there is no standard therapy for advanced hepatocellular carcinoma. Many options exist and a response rate has been reported with interstitial therapies such as TACE, HAI chemotherapy, and PEI. The choice of individual treatment options is largely dependent upon patient factors, facility resources, and physician experience.

Future management of HCC will, in part, rely on preventative strategies, including immunization to hepatitis B in at-risk patients as well as efforts to decrease cirrhosis of any origin. Vaccination of

high-risk populations has been shown to result in a decline in the incidence of hepatitis B-related liver cancer.¹⁷² In addition, we must continue to elucidate the genetic events leading to hepatocarcinogenesis in an effort to ultimately interrupt the cascade of events leading to hepatocellular carcinoma.

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