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Current Treatment Modalities for Hepatocellular Carcinoma

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Objective

This study evaluated the currently available treatment modalities for hepatocellular carcinoma (HCC).

Summary Background Data

One of the most common tumors worldwide, HCC has several known risk factors. Untreated HCC typically has a dismal prognosis. Early detection remains the key to successful treatment of this malignancy. Surgical resection has been the mainstay of treatment for HCC, but newer modalities have been recently introduced.

Methods

The authors evaluated the treatment modalities for HCC.

Results

Surgical resection affords 5-year survival rates as high as 45% with more favorable subgroups having 1) small tumors, 2) well-differentiated tumors, 3) unifocal tumors, 4) lack of vascular invasion, 5) absence of cirrhosis, and 6) the fibrolamellar variant (FL-HCC). Resection has been limited primarily by low resectability rates and recurrent disease. Newer therapeutic modalities that appear the most promising are transarterial chemoembolization and percutaneous ethanol injection. Neither therapy has been evaluated in a prospective randomized manner. Combination chemotherapy and surgical intervention may provide the best results, but randomized controlled trials with long-term follow-up are needed. As single-treatment modalities, radiation therapy, intravenous chemotherapy, intra-arterial chemotherapy, and immunotherapy play limited palliative roles.

Conclusions

Surgical resection in the form of partial or total hepatectomy is the preferred treatment for HCC. The early detection of tumors by screening high-risk populations is crucial. Randomized trials of combinations of chemotherapy and surgical resection are needed to demonstrate their potential utility for treatment.

Primary hepatocellular carcinoma (HCC), one of the most common tumors worldwide, has an incidence which varies from 30 per 100,000 men per year in high-risk regions, such as Southeast Asia and sub-Saharan Africa, to less than 2 per 100,000 men per year in low-risk regions, such as Northern Europe and North America.[1–4] Several risk factors associated with the development of HCC have been identified from epidemiologic studies. Men have a three to eight times greater risk.[1–4] Sex hormones and hepatotoxins, such as alcohol,

Thorotrast, and aflatoxin B_1, have been associated with HCC.[4–6] Hepatic cirrhosis, particularly the macronodular variety, has been found in up to 90% of patients with HCC.[5] A strong epidemiologic link between infection with hepatitis B or C, cirrhosis, and the development of HCC has been demonstrated repeatedly.[4–7] In addition, metabolic conditions, such as hemochromatosis, alpha$_1$-antitrypsin deficiency, porphyria cutanea tarda, tyrosinemia, glycogen storage diseases, and Wilson's disease, may also increase the risk.[4–6] However, the association between these factors and HCC is purely epidemiologic. A demonstration of direct casual relationships is forthcoming.

The diagnosis of HCC is usually based on a combination of clinical and laboratory features together with radiographic and histopathologic findings. Since the introduction of serum alpha-fetoprotein testing in 1963,[8] this simple marker has been used as the primary screening test for HCC.[4,9,10] However, the alpha-fetoprotein assay is limited by a lack of specificity and, except when extremely elevated, a sensitivity of only 70%.[4] To overcome these limitations, newer refinements in alpha-fetoprotein assays are being developed.[11,12]

Real-time ultrasonography, computed tomography, and angiography are used commonly to detect early hepatic tumors, with sensitivities for tumors less than 3 cm ranging from 80% to 85%.[13] Newer radiographic techniques, including intraoperative sonography, iodized oil computed tomography, and portal angiography are more sensitive.[13] Together, improvements in the alpha-fetoprotein assay and radiographic imaging are leading to the detection of earlier and smaller HCC lesions.

A pathologic analysis of smaller lesions identified a putative preneoplastic lesion for HCC, which has been demonstrated to undergo neoplastic transformation.[14,15] Efforts are currently underway to evaluate precancerous and early cancerous lesions further, using oncogene molecular analysis, chromosomal rearrangement analysis, and staining of extracellular matrix antigens and Mallory bodies.[6,9,16]

Pathologically, HCC may be unifocal, multifocal, or diffuse, with or without encapsulation.[17] Tumors have been divided into several histopathologic types, including trabecular, pseudoglandular, compact, scirrhous, pleomorphic, or clear cell.[4,9] The FL-HCC variant, in particular, has distinct epidemiologic, histopathologic, and prognostic characteristics.[17,18] Staging and prognosis are based on histopathologic criteria that includes the size of the primary tumor, the number and lobar distribution of the tumors, the presence of vascular invasion, lymph node involvement, and distant metastasis.[19]

HCC remains difficult to treat and, in the past, has had a poor prognosis, with most series reporting a 3- to 6-month median survival after the onset of symptoms.[2,3,20] Until further research is able to delineate the specific interactions between environmental factors, hepatic injury, hepatic regeneration, and malignant transformation (leading to specific preventive and treatment interventions), the control of HCC will continue to rely on modifications of currently available treatment modalities. Even so, the results of newer treatments suggest that some improvements may already be available. The current treatment status is the focus of this review.

PARTIAL HEPATIC RESECTION

Surgical resection remains the mainstay for treatment for HCC and provides the only consistent long-term tumor-free survival. As outlined in Table 1, most recent series report a 1-year survival rate between 55% and 80% and a 5-year survival rate between 25% and 39%.[17,21–31] Several factors have a major impact on the patient's eligibility for surgical resection.

Cirrhosis is present in up to 90% of all patients with HCC,[5,22,23] and it has been shown to alter patient demographics. In a study from the Mayo Clinic of 124 patients with HCC, a unimodal age distribution was noted in patients with cirrhosis, whereas a bimodal age distribution was noted in those without cirrhosis.[32] Furthermore, the 3:1 male predominance in cirrhotic patients diminished to nearly 1:1 in noncirrhotic patients.

Surgical resections in the presence of hepatic cirrhosis are associated with higher intraoperative and perioperative morbidity and mortality rates. Cirrhosis (which is usually associated with compromised hepatic function, thrombocytopenia, and coagulopathy) increases intraoperative blood loss and can lead to postoperative hepatic decompensation and failure.[2,25,27] The operative mortality rates were less than 3% for noncirrhotic patients and between 7% and 25% for cirrhotic patients.[2,22,23,25,32] Long-term survival may also be adversely affected by cirrhosis,[2,25,32] but this remains controversial.[26,28]

Tumor multiplicity has an impact on the outcome of HCC. Pichlmayr et al.[2] found that, in patients undergoing hepatic resection, multifocal tumors had a statistically significant negative influence on survival compared with unifocal tumors. In their experience, the 1- and 3-year survival rates were approximately 70% *versus* 95% and 38% *versus* 75%, respectively. Ikeda et al.[29] also demonstrated a higher recurrence rate and lower survival time in patients with multiple tumor nodules. Other authors reported similar findings.[25,28]

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Table 1. SURGICAL RESECTION FOR HEPATOCELLULAR CARCINOMA

Center	Year	No. of Patients	No. with Cirrhosis	30-Day Mortality (%)	Recurrence (%)	1-Yr Actuarial Survival (%)	2-Yr Actuarial Survival (%)	3-Yr Actuarial Survival (%)	5-Yr Actuarial Survival (%)
University of Pittsburgh[21]	1987	67	—	8	—	76	68	49	25
Kanazawa Medical University, Japan[22]	1983	35	35	14	33	57*	47*	—	—
P. Brousse Hospital, Villejuif, France[23]	1984	35	35	14	57	62	37	22	—
Cleveland Clinic, Cleveland, Ohio[24]	1984	23	—	8	—	—	—	50	33
Red Cross Hospital, Hiroshima, Japan[25]	1985	94	94	8	—	76	61	41	—
Chang Gung Memorial Hospital, Taipei, Taiwan[26]	1987	120	55	4	—	55	40	—	—
Keio University, Tokyo, Japan[27]	1988	119	80	9	—	80	65	47	39
Tokyo University, Tokyo, Japan[28]	1985	94	71	11	56	73	—	42	25
Toranomon Hospital, Tokyo, Japan[29]	1990	83	76	0	54	—	—	—	—
Liver Cancer Study Group of Japan[30]	1977	222	153	27	—	33	—	20	12
Mayo Clinic[31]	1986	87	26	9	—	—	—	—	27
1974 Liver Tumor Survey[17]	1974	109	23	21	—	—	—	—	34*

Results from series using partial hepatectomy to treat hepatocellular carcinoma.
* Cumulative survival expressed as a percentage of total patients.
All other survivals are expressed as actuarial survival in percent as calculated by the Kaplan-Meier method.

Tumor size is also an important factor. In a series of 94 patients with HCC undergoing resection, Nagao et al.[28] demonstrated superior survival rates in patients with smaller tumors. The 2-year survival rates in patients with tumors less than 5 cm compared with those who had tumors greater than 5 cm were 80% and 40%, respectively. Chen et al.[26] reported similar findings. In their series of 120 patients, 2- and 5-year cumulative survival rates were 60% and 60% in patients with the smaller tumors compared with 40% and 10% to 30%, respectively, in patients with larger tumors. Tumor size may also affect resectability. Kinami et al.[22] found the resectability rate to be 89% in patients with tumors less than 5 cm compared with 41% in those with tumors greater than 5 cm. Nagasue et al.[25] reported a similar experience.

Some additional features of HCC that have been found to influence the outcome of surgical resection favorably include tumor location, well-differentiated histologic grade, presence of a tumor capsule, lack of vascular invasion,[26,28,29] and FL-HCC variant.[18,20,21,33] Still, only 3% to 30% of patients have disease that is completely resectable,[1,3,27] and in those patients who undergo resection, the tumor recurrence rate is as high as 57%.[23,28]

LIVER TRANSPLANTATION

The role of orthotopic liver transplantation (OLT) in the treatment of primary hepatic diseases is now widely accepted.[34–36] For patients with HCC and cirrhosis, the low resectability, high recurrence, and perioperative morbidity rates associated with partial hepatectomy has stimulated interest in total hepatectomy and liver transplantation. The results of liver transplantation for the treatment of HCC are outlined in Table 2. More than 300 patients have been reported on since 1963. The ranges of the 1- and 5-year actuarial survival rates are 42% to 71% and 20% to 45%, respectively.[37–42] However, recurrence rates are as high as 65%. Several factors have an impact on survival and recurrence.

The incidental finding of HCC during hepatectomy or subsequent pathologic analysis is known to be associated with a more favorable prognosis. Iwatsuki et al.[43] reported a 0% recurrence rate and 12 of 13 patients alive from 4 months to 13 years after OLT for incidental HCC. This finding has been confirmed by others.[41,42,44]

The histopathologic division of HCC into FL-HCC and non-FL-HCC variants has prognostic importance. Iwatsuki et al.[43] noted that patients with FL-HCC had a longer disease-free survival time and prolonged survival after recurrence than did those with non-FL-HCC. O'Grady et al.,[38] from King's College in London, also report a 100% 1-year survival rate in their 7 patients with FL-HCC and have 3 of 7 patients alive and disease-free

Table 2. LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

Center	Year	Patients	30-Day Mortality (%)	Recurrence (%)	1-Year Survival (%)	2-Year Survival (%)	3-Year Survival (%)	5-Year Survival (%)
University of Pittsburgh, Pittsburgh, PA[37]	1988	80	13*	37	64	—	45	45
King's College Hospital, London, UK[38]	1987	50	23–32*	65	42–48	37–38	—	—
Queen Elizabeth Hospital, Birmingham, UK[39]	1989	21	38	29	45	21	21	21
Medizinische Hochschule, Hannover, Germany[40]	1990	87	13–24	—	55	40	30	20
Massachusetts General Hospital, Boston, MA[41]	1990	24	17	25	71	56	42	—
UCLA, Los Angeles, CA[42] †	1992	44	16	30	63	48	30	30

Results from recent series using liver transplantation for the treatment of hepatocellular carcinoma.
* Indicates the 90-day mortality expressed as a percent of the total number of patients.
† UCLA data that combines previously published[42] and unpublished data.
Survival is calculated as actuarial survival percentages using the Kaplan-Meier method.

from 3 months to 4.5 years after OLT. Similar results have also been published by other groups.[39,42,44,45]

Several groups examined the impact of cirrhosis on short- and long-term survival after OLT. O'Grady et al.[38] found the 3-month survival rate for patients with cirrhosis to be 68.5% and that for noncirrhotic patients to be 77.4%, with more than 40% of the deaths in the cirrhotic group attributable to postoperative hemorrhage. However, the same group did not find any significant difference in survival rates after 3 months. Similarly, Pichlmayr et al.[40,46] found a higher 30-day mortality rate in cirrhotic compared with noncirrhotic patients (23.7% *vs.* 12.5%) but no difference in long-term survival. By contrast, Haug et al.[41] compared 16 patients with HCC and cirrhosis with 8 patients with HCC and normal liver parenchyma and found higher 6-month and 1-, 2-, and 3-year actuarial survival rates in the noncirrhotic group. However, the patient numbers are small, making this study difficult to interpret conclusively. Most authors found the presence of cirrhosis to have a negative impact on the short-term prognosis after OLT, but there was no significant difference in long-term survival.[45,47]

Tumor size and number are predictors of tumor recurrence and survival after OLT for HCC. In a study of 71 patients with non-FL-HCC, Yokoyama et al.[37] found that the 33 patients with tumors less than 5 cm in diameter had a mean survival time of 55 ± 8 months, whereas those with tumors 5 cm or larger had a mean survival time of 24 ± 6 months. Although the patient numbers were small, Haug et al.[41] and Penn[44] reported similar findings.

Other factors, such as vascular invasion, degree of tumor differentiation, extrahepatic disease, and lymph node metastases, appear to have a negative impact on survival.[37–40,48] The pathologic tumor–node–metastasis (pTNM) staging system (Table 3), which accounts for tumor size, multiplicity, hepatic lobar involvement, lymph node involvement, and extrahepatic disease, also correlates with patient survival after OLT.[19,40,42,48]

Overall, it appears that patients with pTNM stage I, II, III, and possibly, IVa HCC associated with severe hepatic dysfunction may benefit from OLT. These conclusions were drawn from a retrospective study from the University of Pittsburgh comparing 76 patients with HCC

Table 3. pTNM STAGING SYSTEM FOR HEPATOCELLULAR CARCINOMA[19]

Primary tumor (T)
- Tx: Cannot be assessed
- T0: No evidence of primary tumor
- T1: Solitary tumor ≤2 cm, no vascular invasion
- T2: Solitary tumor ≤2 cm, with vascular invasion or
  Multiple tumors, one lobe, ≤2 cm, no vascular invasion or
  Solitary tumor >2 cm without vascular invasion
- T3: Solitary tumor >2 cm with vascular invasion or
  Multiple tumors, one lobe, ≤2 cm, with vascular invasion or
  Multiple tumors, one lobe, >2 cm, with/without vascular invasion
- T4: Multiple tumors, more than one lobe or
  Any tumor(s) invading major branch of portal or hepatic veins

Regional lymph nodes (N)
- Nx: Cannot be assessed
- N0: No regional lymph node metastases
- N1: Regional lymph node metastases

Distant metastases (M)
- Mx: Cannot be assessed
- M0: No distant metastases
- M1: Distant metastases

Stage
- I: T1 N0 M0
- II: T2 N0 M0
- III: T1 N1 M0
  T2 N1 M0
  T3 N0 M0
  T3 N1 M0
- IVa: T4 any N M0
- IVb: Any T any N M1

treated by partial hepatic resection with 105 patients with HCC treated by OLT.[47] The overall 1- to 5-year survival rates for both groups were similar and correlated well with the pTNM classification. The presence of cirrhosis significantly decreased the survival time in the resection group but not in the OLT group. The recurrence rates were similar in both groups (43% and 50%). Ringe et al.[49] examined 192 patients with HCC who underwent either surgical resection (n = 131) or OLT (n = 61). The major difference between the groups was that 67% of patients undergoing resection did not have coexisting liver disease or cirrhosis, whereas 62% of those undergoing OLT did. The early mortality rate was similar and the presence of coexisting liver disease was associated with a higher mortality rate in both groups. The disease-free survival time was superior after resection (13.3 *vs.* 5.2 months, respectively) as were the 1- and 5-year survival rates. However, the two groups are not comparable because of the nature of patient selection.

It can be concluded that both partial and total hepatectomy offer the potential for long-term disease-free survival. Partial hepatectomy should be reserved for patients with focal disease and minimal-to-moderate underlying hepatic dysfunction. Because HCC is usually a multifocal disease or associated with cirrhosis, total hepatectomy and OLT will be the more frequent consideration. Severe hepatic dysfunction, multifocal tumors, bilobar tumors, or centrally located tumors are the strongest factors favoring total hepatectomy and OLT over partial hepatectomy. Patients with extrahepatic disease should not be treated by either surgical method, and a thorough search for extrahepatic disease must be undertaken before operative interventions.

CHEMOTHERAPY

Systemic chemotherapy as a primary treatment modality for HCC has limited value because only a small portion of patients will obtain meaningful palliation. Falkson et al.[50] outlined the experience of the Eastern Cooperative Oncology Group with intravenous chemotherapy for HCC. Between 1973 and 1984, 432 patients were treated on four consecutive randomized chemotherapeutic protocols, which included combinations of 5-fluorouracil (5-FU), streptozotocin, semustine, doxorubicin, zinostatin, amsacrine, and cisplatin. This group found that the median survival time for all patients was 14 weeks, with only 14% surviving more than 1 year. The worst results were obtained with oral 5-FU alone (median survival, 6 weeks), and the best results were obtained with a combination of intravenous 5-FU and semustine (median survival, 24 weeks). Doxorubicin alone or in combination was also more effective than was oral 5-FU. Several factors were associated with a improved outcome, including higher entrance performance status, female sex, North American heritage, and age. These results are similar to those published by Ihde et al.[51] from the National Cancer Institute and reviewed by Ramming,[52] Nerenstone et al.,[3] and Wanebo et al.[1] (Table 4). Overall, it appears that systemic intravenous chemotherapy is less effective than surgical resection, and only occasionally, is it meaningfully palliative as a solo therapy.

The poor results with intravenous chemotherapy prompted trials of hepatic arterial infusion chemotherapy (HAI) in an attempt to achieve higher local levels of agents with lower systemic toxicity. Ramming[52] reviewed the results obtained using HAI for HCC. Of the 19 studies cited, the overall response rate to fluorinated pyrimidine therapy was 42% (median survival, 8.5 months). Having previously shown a response rate of 14% to HAI with combination of doxorubicin and mitomycin C (MMC), Nakamura et al.[53] published a study of 45 patients with unresectable HCC who received HAI with either doxorubicin plus MMC (n = 19) or doxorubicin plus degradable starch microspheres (n = 26). There were 4 complete responses and 16 partial responses with no difference between the two groups (41% and 50% response rates, respectively) and an overall median survival of 7 months. Nerenstone et al.[3] reviewed HAI and concluded that it is more effective than intravenous chemotherapy but does not demonstrate a definite survival advantage. This conclusion was also drawn by Ramming.[52]

TRANSARTERIAL CHEMOEMBOLIZATION (TAE)

The rationale for treating HCC by arterial embolization or ligation evolved from the observation that, by contrast with normal hepatic parenchyma, almost 100% of the blood supply to the tumor is derived from the hepatic artery.[54] Several studies from the early 1970s using hepatic artery ligation for hepatic neoplasms demonstrated symptomatic palliation without a substantial impact on survival.[55–57] The limited success of hepatic artery ligation may have been attributable to the development of arterial collaterals, which subsequently, supplied the tumor.[58] More recently, Lai et al.[59] published a randomized controlled trial in which 33 of the 166 patients with unresectable HCC confined to the liver underwent hepatic artery ligation. Compared with a similar control group of 37 patients who received no treatment, the ligation group had a higher 7-day mortality rate (33% *vs.* 6%) and a lower median survival time (34 days *vs.* 58 days). These results led to the development of other techniques in an attempt to improve the outcome.

Currently, the technique of TAE involves the use of interventional angiography to embolize the tumor arte-

Table 4. CHEMOTHERAPY FOR HEPATOCELLULAR CARCINOMA

Treatment Mode	No. of Patients	Response Rate (%)	Median Survival (mos)	1-Year Survival (%)	3-Year Survival (%)
5-FU intravenous[1]	45	7	2–5	—	—
Doxorubicin[1]	484	16	3–4	—	—
Doxorubicin[50]	82	—	3–4	13	—
m-AMSA[1]	118	4	3	—	—
m-AMSA[50]	24	—	3	8	1
Cis-platinum[50]	33	—	3	21	—
5-FU intravenous + MeCCNU[1]	55	13	<3	—	—
5-FU intravenous + MeCCNU[50]	50	—	6	24	—
Doxorubicin + 5-FU intravenous[1]	38	13	3	—	—
Streptozotocin + 5-FU intravenous[50]	42	—	3–4	10	—
Doxorubicin + MeCCNU[1]	21	14	3	—	—

Results from reviews of chemotherapeutic trials for hepatocellular carcinoma.
5-FU = 5-Fluorouracil.

rial supply with gelatin sponge particles, chemotherapeutic agents, and oil.[60] Yamada et al.[61] reported the treatment of 793 patients with unresectable HCC treated by TAE with gelatin sponge particles soaked with MMC and doxorubicin. Seventy-five per cent of patients had a partial or complete response, and the 1-, 2-, and 5-year survival rates were 51%, 24%, and 6%, respectively. Fever and abdominal pain were the most common problems encountered. Bismuth et al.[62] reported their experience with TAE of 291 patients using iodized oil, doxorubicin, and gelatin sponge. Decreases in tumor size were noted in 29% of the patients. The 60-day mortality rate was only 7% in patients with normal hepatic function, but it was 37% in patients with severe cirrhosis. The overall median survival was 13 months and correlated strongly with hepatic function. In fact, the 12- and 24-month survival rates for noncirrhotic patients were 62% and 26%, respectively, compared with 18% and 9%, respectively, for cirrhotic patients. Hsieh et al.[63] treated 100 patients with TAE using iodized oil, MMC or doxorubicin, and gelatin sponge particles and obtained overall 1-, 2- and 3-year survival rates of 57%, 31%, and 21%. Similar results (Table 5) were reported by others.[60,64–66]

TAE and surgical resection were compared in several studies. Yoshimi et al.[67] retrospectively compared 66 patients who underwent partial hepatectomy with 29 patients who underwent TAE using iodized oil, MMC, and gelatin sponge particles. The TAE group had a higher proportion of multiple tumors and advanced-stage tumors (TNM stage III and IV) as would be expected in a nonrandomized study. Even so, the TAE group fared as well as the resection group, as shown by equivalent cumulative survival rates. Monden et al.[66] compared 140 resected and 173 TAE-treated patients in which the TAE group again had a higher frequency of multiple tumors (65% *vs.* 26%). The survival rates for the resection group were superior, but the hospital mortality rate was higher than in the TAE group (4.3% *vs.* 0.6%).

In summary, TAE appears to be a potentially valuable treatment modality for unresectable HCC. However, the study design in the two retrospective comparisons of TAE and resection do not permit any conclusions to be drawn. There are no published studies comparing TAE with intravenous or intrahepatic arterial chemotherapy without embolization or OLT. Prospective randomized studies of patients stratified for tumor stage will be needed before definitive conclusions about TAE can be drawn. Nevertheless, TAE appears promising and deserves further study.

PERCUTANEOUS ETHANOL INJECTION THERAPY (PEI)

The marginal response rate of HCC to most chemotherapeutic protocols has led to the development of PEI. This technique uses ultrasound guidance to direct a percutaneously placed needle into a intrahepatic tumor; then, a volume of absolute (99.5%) alcohol is injected. Levraghi et al.[68] reported on a series of 23 patients with 32 tumors less than 4.5 cm in diameter who were treated with 3 to 24 injections. With a follow-up of 6 to 27 months, all lesions were reported smaller by radiographic criteria and had normal histopathologic findings by fine-needle aspiration biopsy. Four patients subsequently underwent lobectomy with no pathologic evidence of residual tumor, 15 patients are disease-free, and in 4, diffuse HCC developed. Ebara et al.[69] reported on a series of 95 patients with 120 unresectable tumors less than 3 cm in diameter who were treated with PEI. Sixty-seven of the 120 tumors were identified by the authors

Table 5. TRANSARTERIAL CHEMOEMBOLIZATION (TAE) OR PERCUTANEOUS ETHANOL INJECTION (PEI) THERAPY FOR HEPATOCELLULAR CARCINOMA

Treatment	No. of Patients	Complete Response (%)	Partial Response (%)	No Response (%)	Progressive Disease (%)	Recurrence (%)	Median Survival (Mos)	1-Year Survival (%)	3-Year Survival (%)
TAE[61]	793	—	75*	—	—	—	—	51	12
TAE[62]	291	2	27	16	0	—	13	—	—
TAE[63]	100	—	—	—	—	—	14	57	21
TAE[64]	51	0	24	24	26	—	10	—	—
TAE[65]	21	0	10	57	0	88	—	68	0
TAE[66]	173	—	—	—	—	—	—	65	30
PEI[68]	23	—	100	—	—	17	—	—	—
PEI[69]	95	42	58	—	—	48	49	93	65
PEI[70]	29	—	—	—	—	8	—	—	75†

Results of published series using transarterial chemoembolization (TAE) or percutaneous ethanol injection therapy (PEI) as a single modality to treat hepatocellular carcinoma.
* The percentage of complete and partial responses combined.
† The 2-year survival expressed as a percentage of the number of patients.

as "main" lesions and followed for the purpose of data presentation. Local pain, fever, and elevated transaminase levels were the most frequently encountered side effects. All main lesions shrank in size, and 42% of these became undetectable by ultrasonography. The median survival time was 4.1 years, with 1-, 2- and 5-year actuarial survival rates of 93%, 81%, and 28%, respectively. No recurrence of the originally treated tumors was found, but in 48% of the patients, new lesions developed. Others reported similar findings (Table 5).[70,71]

Therefore, PEI appears to be an effective therapy for small tumors. PEI cannot be recommended for larger tumors because of technical difficulties with injection and poor survival rates.[65] There are no published comparisons of PEI with other treatments. Even so, PEI appears to be a promising technique worthy of further investigation.

OTHER TREATMENT MODALITIES

Cryosurgery uses an intraoperatively placed probe with circulating liquid nitrogen to produce tumor destruction. Traditionally, it has been applied only to easily accessible tumors of the skin or gastrointestinal tract. Newer applications for this treatment modality have included metastatic hepatic malignancies as outlined by Ravikumar et al.[72] Zhou et al.[73] recently treated 60 patients with histologically proved HCC by using cryosurgery. The patients were staged according to a clinical system: stage 1, subclinical disease (35%); stage 2, between stages 1 and 3 (55%); and stage 3, evidence of jaundice, ascites, or metastases (10%). Forty-five per cent underwent cryosurgery alone, 30% underwent cryosurgery plus hepatic artery ligation/perfusion, 10% underwent resection of the main tumor mass and cryosurgery of the residual tumor, 8.3% underwent cryosurgery plus resection, and 6.7% underwent cryosurgery for recurrent HCC. No operative deaths and no major postoperative complications were reported. The actual 1-, 3-, and 5-year survival rates for all groups were 52%, 21%, and 11%, respectively. Survival rates for patients with tumors less than 5 cm were 76%, 50%, and 37.5%, respectively, and for patients who underwent cryosurgery alone, they were 33%, 12.5%, and 4.3%, respectively. Overall, this study suggests that cryosurgery may be a useful adjunct to surgical resection or a palliative treatment, but the results are difficult to interpret in light of the unique staging system and the multiple treatment modalities applied.

Radiation therapy has been of limited value in treating primary HCC, mostly because of the tumor's radioresistance and radiation-induced hepatitis.[1,3] A recent study by Chen et al.[74] examined the effect of radiotherapy in a dose of 3000 to 5600 cGy applied to 7 patients with HCC confined to the liver. Two of the patients had tumor shrinkage, and the other five had no response or stationary disease by radiographic criteria. Two died within 6 months of treatment, 4 were alive from 4 to 10 months after treatment, and 1 patient was lost to follow-up. These results led the authors to conclude that radiation therapy provided a valuable palliative treatment modality of primary hepatic tumors. Nerenstone et al.[3] and others[1] reviewed the use of external-beam radiotherapy for HCC and found that it did not improve the survival rate over systemic chemotherapy. The overall poor results indicate that radiation therapy should be used as a palliative treatment only in carefully selected patients.

With advancements in tumor immunology, the application of immunotherapy to the treatment of HCC has

Table 6. COMBINED MODALITIES FOR HEPATOCELLULAR CARCINOMA

Modalities	No. of Patients	Partial Response (%)	No Response (%)	Recurrence (%)	Median Survival (Mos)	1-Year Survival (%)	3-Year Survival (%)
TAE + Hyperthermia[79]	30	17	—	—	10	—	—
TAE + PEI[65]	22	45	9	56	—	100	85
TAE + OR[80]	8	—	—	25	—	—	—
TAE + OR[81]	30	—	—	17	—	89	77
TAE + OR[82]	31	—	—	46	—	75	31
XRT/CHEMO + OR[83]	14	100	—	43	57	—	75*
CHEMO + OLT[84]	20	—	—	30	—	70	59
CHEMO + OLT†	17	—	—	18	—	73	61

Results from series utilizing combination therapies to treat hepatocellular carcinoma.
TAE = transarterial chemoembolization; PEI = percutaneous ethanol injection therapy; OR = partial hepatectomy; XRT = radiation therapy; CHEMO = chemotherapy; OLT = liver transplantation.
* 24-month survival expressed as a percentage of the number of patients.
† Unpublished data from UCLA.

been attempted. Sachs et al.[75] reported a study in which 16 patients with unresectable HCC were treated with intermediate- to high-dose recombinant leukocyte alpha-interferon for 12 weeks (12 to 50 $\times$ 10^6 units/m^2 intramuscularly 3 times per week). Only 2 of the 16 patients were able to complete the treatment course because of side effects. The treatment was considered to have contributed to the early deaths of nine patients. The mean survival time was 7.9 weeks with little or no efficacy of alpha-interferon therapy demonstrated. Gamma-interferon has produced similar results.[76] Matsuhashi et al.[77] reported on five patients with HCC who were treated with interleukin-2 (10^6 units of per day) plus lymphokine-activated killer cells administered into the hepatic artery. Two of the five patients had a partial response (mean survival time, 9.3 months), and the longest survival was 34 months. Order et al.[78] reported on 105 patients in which radiolabeled antibodies against ferritin were used in association with chemotherapy and radiation therapy. A 48% partial tumor response rate and median survival of 10.5 months were obtained. Further investigation will be required to determine the role of immunologic therapies.

COMBINED MODALITY THERAPIES

Surgical resection (partial or total hepatectomy) remains the only treatment option for HCC that produces consistent disease-free survival. Because other treatments yield partial responses, attempts to increase the responsiveness of HCC by combining therapies have been a logical outgrowth of monotherapy (Table 6). Tanaka et al.[79] reported a study of 30 patients with unresectable HCC treated with TAE plus hyperthermia. A response rate of 16.7% was obtained, and the average duration of survival was 10.1 months. In the group of patients with a maximum tumor temperature greater than 42 C, the average survival was not statistically prolonged (13.5 months). Together, these results led the authors to conclude that further refinements in the technique of hyperthermia were necessary before additional use is warranted.

Combination TAE and PEI was examined by Tanaka et al.[65] in a randomized study in which patients with unresectable HCC greater than 3 cm were treated with TAE alone (n = 21) or with TAE and subsequent PEI (n = 22). The partial response rate of those patients undergoing combination therapy was significantly better (45% *vs.* 10%), as were the 1-, 2-, and 3-year survival rates (100% *vs.* 68%, 85% *vs.* 37%, 85% *vs.* 0%, respectively). These results suggest that in patients with large unresectable HCC, TAE followed by PEI may be more beneficial than TAE alone.

Combination TAE and surgical resection has been evaluated in several studies. Hwang et al.[80] examined the outcome of 8 patients who underwent preoperative TAE followed by surgical resection and 25 patients who underwent resection alone. Preoperative TAE did not reduce the mean operative time or blood loss and, in fact, contributed to operative complications by predisposing the patient to tumor rupture, gangrenous gallbladder, and hepatoduodenal adhesions. Likewise, no impact on the recurrence rate was seen (25% *vs.* 12%). Yu et al.[81] reported the use of preoperative TAE in 30 patients with HCC greater than 5 cm. The patients underwent a mean of 2.9 preoperative TAE sessions, and the mean interval between treatment and resection was 2.4 months. Tumor diameters were reduced by an average of 31.6%, and adhesions between the liver, diaphragm, gallbladder, and hepatoduodenal ligament were found at surgery but did

not significantly complicate the resection. The 1-, 2-, and 3-year survival rates were 89%, 77%, and 77%, respectively. Nagasue et al.[82] retrospectively studied 31 patients with HCC who underwent TAE before surgical resection and compared this group with 107 patients who underwent surgical resection alone. The intra-abdominal complications resulting from TAE made the surgical resection more difficult, and preoperative TAE did not improve the recurrence or survival rates. Given the potential for complications from TAE and the absence of proof that TAE improves resection results, further investigations must be reported before preoperative TAE can be advised.

The use of radiation therapy or chemotherapy in addition to surgical resection may have clinical utility as shown by Sitzmann et al.[83] Fourteen patients with unresectable HCC, based on the presence of extrahepatic spread of the tumor, major vascular invasion, or four-segment hepatic involvement, underwent preoperative neoadjuvant therapy with external-beam radiation, intravenous chemotherapy (5-FU and doxorubicin), and polyclonal antiferritin ^{131}I-conjugated antibody. All patients had a reduction in tumor size and a complete resolution of metastases lasting 3 months. The patients then underwent surgical resection. By comparison with a contemporary group of 21 patients with resectable HCC who did not receive neoadjuvant therapy, the adjuvant group had a similar complication rate (40% *vs.* 35%) and a longer median survival (57.4 *vs.* 41.9 months). The tumor recurrence rate for the adjuvant therapy group was 43%. This provides evidence that neoadjuvant therapy in the form of external-beam radiation, intravenous chemotherapy, or immunotherapy may be an effective combined modality for HCC.

Stone et al.[84] studied neoadjuvant chemotherapy combined with total hepatectomy and OLT in 20 patients with unresectable HCC confined to the liver. The patients received 1 to 3 preoperative courses of doxorubicin at a dose of 10 mg/m^2 and 1 intraoperative course at a dose of 10 mg/m^2. Approximately 7 to 19 days after surgery, doxorubicin therapy was resumed for a total dose of 200 mg/m^2. All patients had pTNM stage II disease or greater, 11 had stage IVa tumors, and 17 had tumors greater than 5 cm. As of publication, nine patients were alive without evidence of tumor, three patients were alive with recurrent tumors, five patients died of recurrent tumors, and three patients died of recurrent hepatitis B infection. The actuarial 1-, 2-, and 3-year survival rates were 70%, 66%, and 59%, respectively. At the University of California Los Angeles (UCLA), a protocol of 6 months of intensive adjuvant chemotherapy consisting of continuous infusions of 5-FU and intermittent cisplatin and doxorubicin in previously untreated patients with HCC undergoing OLT was begun. Since December 1989, 17 patients have undergone this adjuvant chemotherapy regimen and were compared with 27 patients who had previously undergone OLT at UCLA for HCC and received either low doses of chemotherapy or no treatment. Excluding operative deaths, the recurrence rate was 37% for historic controls and 18% for patients receiving adjuvant chemotherapy after OLT. In addition, the 1-, 2-, and 4-year survival rates for patients receiving adjuvant chemotherapy were superior to the historic control rates (73% *vs.* 55%, 61% *vs.* 40%, and 61% *vs.* 22%, respectively). These results suggest a possible role for neoadjuvant or adjuvant chemotherapy, and further studies are encouraged.

CONCLUSIONS

In 1986, a National Institutes of Health consensus conference was held on HCC and concluded that surgical resection offers the only chance of cure for HCC; liver transplantation has become an increasingly acceptable treatment for unresectable HCC confined to the liver; doxorubicin alone appears to offer the best response rate and is recommended as the first chemotherapeutic treatment option; and the results from HAI, radiation therapy, and immunotherapy are less effective.[76] Since that conference, new options for the treatment of HCC are evolving, and we offer the following summary.

1. A full evaluation of the tumor stage and a search for extrahepatic disease should be undertaken before the initiation of treatment. The evaluation should include an assessment of tumor size, location, and multiplicity by abdominal computed tomography or ultrasonography, of vascular patency by hepatic duplex or visceral angiography, of the histologic type of the tumor and the extent of parenchymal pathologic findings by a liver biopsy, and of the extent of extrahepatic disease, using abdominal and chest computed tomography, bone scan, cytologic analysis of ascitic fluid, and exploratory laparotomy, if necessary.
2. High-risk lesions include those that are greater than 5 cm, nonencapsulated, multifocal, or associated with vascular invasion. Unresectable lesions include those with extrahepatic spread and those with lymph node involvement.
3. Partial and total hepatectomies remain the only treatments that provide consistent disease-free survival.
4. Standard subtotal hepatectomy should be used in patients with unifocal tumors, multifocal tumors confined to one lobe, and mild-to-moderate (Child's class A or B) hepatic dysfunction or normal-hepatic function.

5. Total hepatectomy combined with liver transplantation should be used in patients with centrally located tumors, tumors unresectable by conventional techniques but confined to the liver, multifocal tumors in more than one lobe, and patients with limited hepatic reserve (Child's class B or C function). Patients with portal vein thrombosis secondary to tumor invasion should not undergo OLT.
6. Patients with resectable high-risk lesions should be considered for multimodality therapy. Peri- and postoperative chemotherapy, and TAE, may be appropriate. Although a definitive treatment regimen cannot be recommended until prospective randomized clinical trials comparing the various modalities are completed, high-risk lesions considered resectable by partial hepatectomy should be treated with preoperative TAE with or without perioperative chemotherapy. High-risk lesions considered resectable by total hepatectomy and OLT should be treated with peri- and postoperative chemotherapy. In this latter group, preoperative TAE should also be considered.
7. Lesions considered unresectable by either partial or total hepatectomy should be treated with either TAE alone or combination TAE and PEI. Lesions that respond to treatment with considerable tumor shrinkage may be considered resectable and should be treated as a high-risk lesion, as outlined earlier.
8. Transarterial chemotherapy, systemic chemotherapy, and radiotherapy should not be used as a primary treatment modality, except in cases of metastatic HCC where palliation is the only treatment goal.
9. Further investigation into immunotherapy and cryosurgery is needed before their clinical use can be recommended.

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