Society of Interventional Radiology Position Statement on Chemoembolization of Hepatic Malignancies

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Abbreviation: HCC = hepatocellular carcinoma

PRIMARY and secondary malignancies in the liver present one of the most challenging problems in clinical oncology. Hepatocellular carcinoma (HCC) is one of the most common fatal malignancies worldwide, with more than 530,000 new cases diagnosed annually (1). The prevalence of hepatoma in the United States is rapidly increasing as a result of the spread of chronic infection with hepatitis C. Currently 10,000–15,000 cases of HCC are diagnosed annually in the United States. It is estimated that this number will more than double to 34,000 cases of HCC per year by 2019 (2). Colorectal cancer is the second leading cause of cancer-related death in the United States, with liver metastases accounting for approximately half these deaths. More than 56,000 patients died from colon cancer in 2002 and it is predicted that there will be more than 145,000 new cases of colorectal cancer diagnosed in the United States in 2005 (3). Other tumors that frequently develop fatal hepatic metastases despite a treatable primary tumor include ocular melanoma, neuroendocrine tumors, and gastrointestinal sarcoma.

Chemoembolization combines hepatic artery embolization with simultaneous infusion of a concentrated dose of chemotherapeutic drugs followed by embolization particles. Hepatic artery embolization refers to infusion of particles into tumor-feeding arteries without chemotherapeutic agents. Embolization by either technique renders the tumor ischemic, depriving it of nutrients and oxygen. When chemotherapy is used, tumor drug concentrations are one to two orders of magnitude greater than are achieved by infusion alone, and the dwell time of the chemotherapy agent is markedly prolonged, with measurable drug levels present as long as 1 month later (4–7). Because most of the drug is retained in the liver, systemic toxicity is reduced (8).

Embolization and chemoembolization lead to ischemia of the tumor by blockade of the nutrient supply. An advantage of embolization is that the ischemia induced by embolization helps to overcome drug resistance by causing metabolically active cell membrane pumps to fail, thereby increasing intracellular retention of the chemotherapeutic drugs (9). Recent research has demonstrated that ischemia can increase angiogenesis in tumor cells, possibly spurring tumor growth (10–12). These molecular changes raise questions about whether chemoembolization or hepatic arterial embolization is the better method to perform endovascular hepatic arterial therapy. To date, no study has demonstrated a difference in survival between the two techniques (10,13).

RESULTS IN SPECIFIC DISEASES

HCC

Surgical resection remains the gold standard for HCC. However, fewer than 20% of patients with HCC are candidates for surgery (14). Even in a highly preselected group, postoperative mortality is a significant potential risk, with incidences ranging from 1.3% to 7% (15). The potential benefits of surgery are prolonged survival and maintenance of a disease-free state. Patients undergoing curative surgery have a 34%–59% 5-year survival rate, and at 5 years, 13%–40% are disease-free (15). The majority of patients are not surgical candidates and other options are considered. Appropriate patients with limited tumor burden are considered for transplantation (16,17). Chemotherapy is largely ineffective. Doxorubicin is the most commonly described agent for systemic therapy for HCC; however, it does not appre-

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Table 1
Cancer Liver Italian Program Scoring System

Variable	Points		
	0	1	2
Child-Pugh stage	A	B	C
Tumor morphology	Uninodular	Multinodular	Massive (>50% of liver)
α-Fetoprotein level (ng/mL)	<400	>400	NA
Macrovascular invasion	No	Yes	Yes

Table 2
Okuda Staging

Variable	Points	
	0	1
Tumor size	<50% of liver	>50% of liver
Ascites	No	Yes
Albumin level (g/dL)	≥3	<3
Bilirubin level (mg/dL)	<3	≥3

Note.—Okuda Stage 1 = 0 points; Okuda Stage 2 = 1–2 points; Okuda Stage 3 = 3–4 points.

ciably affect survival and responses are rare (18).

Chemoembolization is accepted worldwide as an effective treatment for patients with unresectable HCC and adequate preservation of liver function. Even in patients who are potential candidates for resection, chemoembolization results in similar projected 5-year survival rates compared with surgery (26% for chemoembolization vs 42% for surgery; $P = .556$) for patients with a Cancer Liver Italian Program score of 1 or higher (**Table 1**) (19). A metaanalysis was performed of randomized controlled trials between 1978 and 2002 with a combined total of 545 patients with unresectable HCC treated palliatively with embolization or chemoembolization (20). This review also analyzed systemic therapies with tamoxifen, which was used to target estrogen receptors on the primary tumors ($N = 898$). Arterial treatments led to a significant increase in 2-year survival rate compared with patients who received tamoxifen (odds ratio, 0.53; $P = .017$). Survival was found to vary directly with oil uptake and retention and inversely with tumor volume, Okuda stage (**Table 2**), and Child class.

Recent experience supports the effectiveness of chemoembolization in the United States population. Among 38 patients who underwent chemoembolization in the study of Solomon et al (21), 62% of whom had Okuda stage 2 disease, median time to progression was greater than 1 year and survival rates were 60%, 41%, and 16% at 1, 2, and 3 years. Another study of 81 patients by Brown et al (22) demonstrated 61%, 42%, and 32% survival rates at 1, 2, and 3 years after chemoembolization. Survival outcomes in both trials were comparable to those in Asian studies. In contrast, survival rates among a contemporary series of 618 European and North American patients with hepatoma who were not treated with chemoembolization were 31%, 19%, and 13% at 1, 2, and 3 years (23).

Randomized trials in HCC.—Despite the large volume of single-institution experiences with chemoembolization of hepatoma published during the past two decades, few randomized controlled trials have been reported. Early randomized trials were published during the evolution of the procedure and are fraught with structural flaws that limit the value of information obtained from each. It is important to recognize that none of these early trials reflect the treatment of hepatoma as practiced in the United States. Common flaws in these trials included the exclusion of patients who would be considered treatment candidates in the United States. Treatment of only patients with minimal disease and normal hepatic function does not represent the presentation of the majority of patients with HCC in the United States, so no generalized conclusions can be drawn from the results (24).

The randomized trial reported by Pelletier et al (25) in 1990 was similarly limited by excessive exclusion of patients and insufficient treatment in the chemoembolization arm relative to current practice. The more recent report from Bruix et al (26) in 1998 reported the use of gelatin sponge and coils for hepatic artery embolization as the only treatment, which are ineffective devascularization techniques in the liver that would not be expected to have any durable antitumor effect. These trials also were underpowered, limiting the ability to draw conclusions as a result of small sample sizes (27). Despite these limited outcomes, chemoembolization continued to be performed worldwide given the lack of options. Criticism of these older trials is well-documented and led to calls for new randomized trials (27,28).

The two most recent prospective randomized trials are the best structured to date to evaluate treatment of HCC with chemoembolization. Both trials demonstrated significantly longer survival with chemoembolization. The first, by Lo et al (29), compared survival outcomes with chemoembolization versus symptomatic management, with 40 patients per group. One, 2-, and 3-year survival rates in the study group were 57%, 31%, and 26% compared with 32%, 11%, and 3% in the control group ($P = .02$). On univariate analysis, chemoembolization remained a significant predictor of survival (odds ratio, 0.49; $P = .006$). The second study, by Llovet et al (30), included 112 patients in three arms and compared outcomes with chemoembolization versus embolization alone versus symptomatic treatment. The trial was stopped when a significant survival benefit was demonstrated with chemoembolization (survival rates, 82% at 1 year and 63% at 2 years) versus symptomatic treatment (63% at 1 year and 27% at 2 years; $P = .009$). At the time the trial was halted, there was not a survival benefit identified with embolization alone (75% at 1 year and 50% at 2 years)

versus symptomatic treatment, although the difference may have reached significance with continuation of the trial. The only variable associated with prolonged survival was assignment to the chemoembolization group (odds ratio, 0.45; $P = .02$).

The dearth of randomized controlled trials for HCC in the United States reflects the reality that patients seeking treatment at cancer centers are not willing to be randomized to receive no therapy, especially as chemoembolization is a widely accessible treatment with a 20-year track record for this disease. Additionally, survival in well-constructed trials from Asia and Europe during the past few years has demonstrated a significant benefit to treatment. For these reasons, it is highly unlikely that there will ever be a prospective randomized controlled trial of chemoembolization for HCC in the United States. Decisions regarding the merits of this therapy must be made based on the best available data. Approval for treatment by third-party payers should not be withheld based on the absence of randomized controlled trial data that will never be produced.

Case-control trials for HCC.—Many publications report comparisons of chemoembolization versus control groups that are concurrent or historical, with varying degrees of matching for disease state and other important risk factors. These publications are limited by the statistical weaknesses associated with their design. Strengths are more realistic patient selection and treatment regimens and substantial numbers in some series.

A French multicenter trial (31) of 127 patients with more typically advanced disease, such as is diagnosed in unscreened populations in the United States (62% Okuda stage 1 or 2 disease), showed survival rates in the chemoembolization arm of 64% and 38% at 1 and 2 years, with survival rates in a matched concurrent untreated control arm of only 18% and 6%, respectively ($P < .0001$). A more recent trial compared outcomes of 110 patients with HCC treated with chemoembolization versus 83 patients treated with symptomatic management (32). The two groups were matched by their demographic characteristics and clinical characteristics of disease. The group treated with chemoembolization had a 54% survival rate at 2 years, compared with 26% in untreated control subjects. Mean survival in the treatment group was 26 months, compared with 10 months for the control group ($P = .0001$). These and several similar reports from the 1990s consistently show a two- to three-fold increase in median survival after chemoembolization compared with untreated control subjects, with a high degree of statistical significance.

Chemoembolization as a bridge to transplantation.—Patients on liver transplant lists are at risk to have or develop HCC while awaiting a graft. Patients with small HCC are prioritized on the transplant list (33). However, the demand for organs remains greater than the supply. Because of the long wait for donor livers, uncontrolled growth of HCC can render the patient ineligible for transplantation. Conversely, transplantation is the ideal therapy for HCC, with higher long-term survival rates than seen with resection. Therefore, prevention of progression of the HCC until a donor liver becomes available is in the patient's best interest. Chemoembolization plays a critical role in permitting eventual cure in this patient subset by inhibiting tumor growth so patients can remain on the transplant list (34).

Neoadjuvant/adjuvant chemoembolization.—Tumor regression after chemoembolization can render selected cases resectable that were previously excluded from surgery (21). The impact of pre- or postoperative chemoembolization on recurrence rates is controversial, with no preponderance of data indicating a benefit.

Chemoembolization combined with percutaneous ablation.—Image-guided tumor ablation is another option for patients with small neoplasms depending on size, number, and location of the tumor(s), as well as local expertise. One of the limitations of thermal ablation therapy is that the maximal zone that can consistently be created is approximately 3–4 cm (35). One factor that limits creation of the zone of ablation is blood flow to the tumor. Chemoembolization can also be combined with thermal ablation therapy to induce a larger sphere of ablation. Perfusion of the tumor limits the ability to reach tumoricidal temperatures, and elimination of arterial flow has improved the ability to reliably achieve zones of necrosis as large as 6.5 cm (36,37). Additionally, treatment of a single HCC as large as 7 cm in diameter with a combination of chemoembolization and thermal or chemical ablation led to similar survival compared with surgical resection (1-, 3-, and 5-year survival rates of 97%, 77%, and 56% for chemoembolization plus ablation vs 81%, 70%, and 58% for surgery; $P = .22$) (38). Embolization to supplement thermal or chemical ablation is a potentially useful tool.

Colorectal Metastases

The only chance of cure for patients with liver metastases from colon carcinoma is resection. Unfortunately, fewer than 30% of patients have resectable disease (39). Even in optimal resection candidates, recurrence is frequent, with a 5-year survival rate of only 35%. Negative predictors of survival include a short interval between diagnosis of the colonic primary tumor and the liver metastases, number of metastases, carcinoembryonic antigen level greater than 10 ng/mL, extrahepatic disease, and the ability to obtain a negative resection margin (40).

The majority of patients with hepatic metastases from colon cancer undergo systemic chemotherapy. There are a variety of novel chemotherapeutic agents are being used to treat metastatic colorectal cancer. Cytotoxic agents such as irinotecan and oxaliplatin, as well as the monoclonal antibodies cetuximab and bevacizumab, have shown promising results in early trials. Combination therapy with bevacizumab in addition to irinotecan, 5-fluorouracil, and leucovorin has improved survival to a mean of 20.3 months (41). Similar survival was identified with addition of oxaliplatin to 5-fluorouracil and leucovorin (42). However, even with these agents, progressive disease, particularly in the liver, occurs at a mean of 9–10 months. At this point, palliative therapies such as chemoembolization are considered.

Phase II studies of chemoembolization for metastatic colorectal cancer have been reported by several centers in the United States. Patients enrolled in these trials are usually individuals in whom systemic and/or intraarterial infusion chemotherapy has failed. Abramson et al (43) devised a spreadsheet model to determine cost-effectiveness thresholds for palliative chemoembolization for colorectal metastases. A mean

survival time of 12 months or greater was demonstrated to be necessary for chemoembolization to be considered a cost-effective method of treatment. Lang et al (44) used a combination of superselective segmental and selective lobar injections of a doxorubicin/iodized oil emulsion in the treatment of 46 patients. The actuarial survival rates were 68% at 1 year and 37% at 2 years. In the study of Sanz-Altamira et al (45), 40 patients received chemoembolization with 5-fluorouracil, mitomycin-c, iodized oil, and gelatin sponge. The median survival time after the first chemoembolization procedure was 10 months. A number of prognostic factors predictive of longer survival were identified. Patients with an Eastern Cooperative Oncology Group performance status of 0 or 1 had a median survival of 24 months, versus 3 months among patients with a performance status of 2. Patients with extrahepatic disease at the time of initial chemoembolization had a median survival of 3 months, versus 14 months for those with isolated liver metastases. Among patients with good performance status and no extrahepatic disease, the survival rates were 73% at 1 year and 61% at 2 years after chemoembolization. In the study of Tellez et al (46), 30 patients underwent chemoembolization with cisplatin, doxorubicin, mitomycin-c, and bovine collagen. Median survival times were 8.6 months from first chemoembolization and 29 months from diagnosis. In a study by Soulen (47), 51 patients underwent chemoembolization with cisplatin, doxorubicin, mitomycin-c, iodized oil, and polyvinyl alcohol. Actuarial survival rates from diagnosis with liver metastases were 86%, 55%, and 23% at 1, 2, and 3 years, with a median of 24 months. Outcomes in patients with isolated liver metastases who were treated with chemoembolization by Salman et al (48) were similarly encouraging, with a mean survival time of 15 months versus 8 months among patients with extra-hepatic disease. The results in these extensively pretreated patients are promising, but high early response rates do not necessarily cause an improvement in survival. A consistent trend toward survival times longer than 12 months after initial therapy has also been demonstrated, suggesting that chemoembolization for colorectal metastases is a cost-effective method of treatment for patients with good performance status and disease isolated to the liver. To best determine absolute survival benefit, a multi-center phase II/III trial was initiated by the American College of Radiology Imaging Network. The purpose of the trial was to compare outcomes with chemoembolization combined with systemic therapy versus systemic therapy alone. This trial was stopped because of the evolution of new agents and the resultant paradigm shift regarding the standard of systemic therapy.

Neoadjuvant/adjuvant chemoembolization for colorectal metastases.—Tumor regression after chemoembolization allowing more complete treatment with image-guided laser-induced thermotherapy has been described (49). In this publication, patients with four or fewer tumors measuring no larger than 80 mm underwent chemoembolization. In those individuals in whom maximum tumor diameter after chemoembolization was 50 mm, laser-induced thermotherapy was performed. Overall, 51% of patients showed an adequate response to allow laser therapy to be performed. Mean survival time of patients who underwent sequential chemoembolization and thermal ablation was 26.2 months, versus 12.8 months for patients who underwent chemoembolization alone. Because thermal ablative therapies are limited by the maximum size of the zone of necrosis, combination therapies as described by this study show significant potential.

Ocular Melanoma

The liver is the initial site of metastatic disease in approximately 50% of patients with ocular melanoma (50). More than 90% of patients with metastatic ocular melanoma will develop liver metastases (51). When liver metastases develop, involvement is rapidly widespread and aggressive, with median survival times of 2–6 months (50). A review of a variety of treatment methodologies in 201 patients by Bedikian et al (52) demonstrated longer survival with chemoembolization versus any other treatment method, including intraarterial and systemic chemotherapy, leading the authors to state that patients with isolated liver metastases from ocular melanoma should undergo hepatic arterial chemoembolization as a primary therapy. Mavligit et al (53) reported 30 patients treated by serial chemoembolization with cisplatin and polyvinyl alcohol particles. There was one complete response at follow-up imaging, and 46% of patients had a partial response (>50% tumor destruction at follow-up imaging). Median survival time was 11 months (14 months for patients whose disease responded vs 6 months those who showed no response), with an actuarial survival rate of approximately 33% at 1 year. We are aware of no other large series for this tumor.

Neuroendocrine Tumors

Embolization has an established role in the palliation of these hypervascular tumors and typically produces symptom-free intervals in 90%–100% of patients. Two reports that initially evaluated chemoembolization of neuroendocrine tumors (54,55) found a duration of response after chemoembolization of nearly 2 years. Brown et al (56) described objective responses in 96% of patients treated with hepatic arterial embolization without chemotherapy. Treatment for pain as the primary indication had less-durable results (6.2 months) than when embolization was performed for hormonal symptoms with or without the presence of pain (16–17.5 months). Gupta et al (57) reported outcomes in 81 patients treated with embolization alone (n = 50) or chemoembolization (n [H11005] 31). The time to symptomatic progression after arterial therapy was 19 months and the mean survival time for the patient group was 31 months.

Sarcoma

Mavligit et al (58) reported major regression of metastatic leiomyosarcoma in 10 of 14 patients treated with cisplatin/gelatin sponge chemoembolization followed by a 2-hour vinblastine infusion into the hepatic artery, with a median duration of response of 1 year. Disease in 10 of 16 patients treated with cisplatin, doxorubicin, mitomycin-c, iodized oil, and polyvinyl alcohol particles by Rajan et al (59) showed a response, with extensive tumor necrosis on computed tomography in all cases. Three patients became candidates for surgical resection after treatment. Because systemic chemo-therapy and radiation therapy are ineffective against

metastatic sarcomas in the liver, chemoembolization appears to be the most effective treatment for unresectable disease.

Cholangiocarcinoma

Burger et al (60) reported a median survival of 23 months after chemoembolization in 17 patients with unresectable cholangiocarcinoma. Two patients had their disease downstaged enough after chemoembolization to become resectable. Historic survival for patients with unresectable cholangiocarcinoma is 5–8 months. Even candidates for surgical resection have limited survival rates of 20%–56% at 3 years. Complication rates for this group (60) were in keeping with those for treatment of other tumor types. Chemoembolization appears to be a viable treatment option for well-compensated patients with unresectable cholangiocarcinoma.

Other Metastases

Liver metastases from lung, breast, pancreas, stomach, small bowel, kidney, bladder, thymus, ovary, or thyroid tumors, as well as those from unknown primary tumors, have been treated with chemoembolization (61–63). The published reports lump together patients with different tumor types, making interpretation of the results difficult. Overall, mixed metastatic lesions treated with chemoembolization are associated with a 60%–75% objective response rate and median patient survival times of 8–11 months.

TOXICITY AND RISK

Embolization of the liver has been performed for decades for a variety of indications and is well-tolerated. Embolization of solid organs causes a self-limited postembolization syndrome in the majority of patients, consisting of varying degrees of pain, nausea, vomiting, and fever. This is independent of chemotherapeutic drug use, reason for embolization (eg, bleeding, tumor), and the organ treated (eg, liver, kidney, spleen, uterus). With current medical care (eg, hydration, antiemetic therapy, and pain control), postembolization syndrome is well-tolerated, and 50% of patients can be discharged from the hospital the day after chemoembolization. The average length of stay is 1.5 days. Liver function is transiently affected with an increase in liver aminotransferase levels. These values usually peak 3–5 days after therapy and return to baseline levels by 10 –14 days after embolization. There is no sustained degradation of liver function in properly selected patients who do not meet the well-established exclusion criteria for hepatic artery occlusion, even in the presence of cirrhosis (64). Because most of the injected drug is retained in the liver, systemic toxicity is minimized, with little bone marrow suppression. The cumulative toxicity is far more limited than is experienced with systemic chemo-therapy, which requires protracted drug exposure for an indefinite period of time. Serious adverse events occur after approximately 5% of chemoembolization procedures. The most common serious adverse events are liver abscess or liver infarction, which occur in approximately 2% of cases each. The 30-day mortality rate is 1% (21,22,65,66).

SUMMARY

Hepatic arterial chemoembolization is a safe, proven, and effective technique for the treatment of a number of malignancies, including HCC, neuroendocrine tumors, ocular melanoma, cholangiocarcinoma, and sarcoma. It has a palliative role for patients with colon carcinoma. It may be useful with patients who have hepatic-dominant metastatic disease from other primary malignancies. The benefit of chemoembolization for these individuals should be evaluated on a case-by-case basis.

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