

Chemoembolization in the Management of Liver Tumors

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Key Words. *Hepatocellular carcinoma · Chemoembolization · Liver metastases*

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Explain the anatomic and biologic rationale for using chemoembolization to treat tumors localized to the liver.
2. Identify appropriate candidates for this treatment based upon tumor biology and patient characteristics.
3. Anticipate and manage the toxicities and complications of chemoembolization.
4. Discuss the variability in results reported in the literature from different centers and in different tumor types.

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ABSTRACT

The dual vascular supply of the liver affords a unique opportunity to explore intraarterial therapies for hepatic malignancies. Chemoembolization is a well-established technique combining intra-arterial chemotherapy with delivery of embolic agents in order to achieve an antitumor effect due to a high local concentration and prolonged dwell time of the drug, along with select ischemia. Many tumors, such as hepatocellular carcinoma, colorectal cancer, and neuroendocrine tumors, cause symptoms and death by local growth and destruction of the liver.

While there are other methods capable of controlling small or isolated hepatic neoplasms, none are suitable for the majority of these patients. Chemoembolization can produce significant results in terms of tumor shrinkage in many of these patients, and there are studies to suggest a survival advantage in hepatocellular carcinoma. Toxicity, however, may be substantial, and patient selection is crucial in order to achieve the optimal benefit of this powerful technique for individual populations. *The Oncologist* 2003;8:425-437

INTRODUCTION

Primary and secondary cancers of the liver comprise a significant and often therapeutically frustrating oncologic problem. They are a tremendous cause of neoplastic morbidity and mortality: worldwide, hepatocellular carcinoma (HCC) is among the most frequent causes of death from malignancy [1-3], and the majority of metastatic cancers involve the liver at some point as disease progresses. Despite the presence of extrahepatic spread, many patients with liver involvement die as a consequence of local growth and tissue destruction; most deaths are due to hepatic failure

and cachexia, or to gastrointestinal bleeding from portal hypertension. Therefore, in the absence of effective systemic therapy, much hope and effort has been placed in developing and testing methods of local control in an effort to reduce hepatic deaths. In fact, focally applied liver-directed therapies have become paramount in the treatment of several tumor types. Chemoembolization has been prominent among these internationally over the past two decades as a widely used procedure to suppress intrahepatic tumor growth in an effort to palliate symptoms and perhaps even prolong survival.

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BACKGROUND

Chemoembolization involves intraarterial chemotherapy and particulate arterial embolization. Many alternative therapies may be considered for patients with liver-predominant disease. A partial list of possibilities includes surgical resection, liver transplantation, radiofrequency (or microwave, laser, or other thermal) ablation, cryotherapy, conformal radiation, intraarterial radiotherapy, percutaneous ethanol injection, and systemic or directed chemotherapy. Of course, the longer a list of potential options is, the less likely any particular choice is to be especially helpful [4]. A thorough explanation of the benefits and shortcomings of each of these modalities is beyond the scope of this review, but any one of them is generally restricted to a small subset of patients with hepatic malignancies (Table 1). Like these alternatives, chemoembolization is usually employed when standard therapy has failed or is known to be ineffective. The diseases treated with chemoembolization, in general, share the characteristics of having few options in terms of systemic therapy and not being amenable to other forms of treatment. Although frequently suggested as a possibility, chemoembolization is unlikely to be the treating physician’s first choice of therapy.

RATIONALE

Chemoembolization developed conceptually from experience with both intra-arterial chemotherapy and embolic therapy. It is well-established that both primary and secondary liver tumors derive their blood supply from the

hepatic artery [5], while approximately 50% of the oxygen supply to normal liver is from the portal system (Fig. 1) [6, 7]. Nutrient flow from the hepatic artery to a tumor is twice that from the portal vein [8], and experiments that gave chemotherapy during surgery showed a 10 times higher intratumoral concentration when it was given through the artery rather than the portal vein [9]. This makes arterially directed treatment especially attractive from both the delivery and safety points of view, since the tumor can be made ischemic while uninvolved liver is spared. Moreover, the pharmacokinetic advantage of locoregional drug administration enhances the theoretical benefit [10-12]. Many drugs exhibit preferential extraction when delivered intrahepatically and they can achieve quite favorable liver/systemic drug concentration ratios, thus minimizing the systemic toxicities associated with chemotherapy. For instance, hepatic drug exposure has been estimated to be double for doxorubicin, sevenfold greater for cisplatin, eight times greater for mitomycin, ten times greater for 5-fluorouracil, and up to 400-fold higher for 5-fluorodeoxyuridine (FUDR) when delivered intrahepatically rather than intravenously [10].

HISTORY AND DEVELOPMENT

Regional arterial infusion chemotherapy, using surgically placed catheters, was first attempted in the early 1960s [13]. Later, techniques for placement of percutaneous catheters became available [14] and were widely used for chemotherapy delivery in patients with both HCC and metastatic lesions [15-19]. Although the toxicities associated

Table 1. Available treatment options for hepatic neoplasms

Treatment modality	Limitations
Liver transplantation	Donor availability Three or fewer lesions, none >3 cm Solitary lesions <5 cm
Hepatic resection	Minimal or no cirrhosis Three or fewer lesions, geographically restricted
Thermal ablation (radiofrequency, microwave, laser)	Three or fewer lesions, each <5 cm
Cryotherapy	Small lesions Rarely done percutaneously
Conformal radiation	Solitary lesion
Proton beam therapy	Radiation-induced liver disease
Intra-arterial radiotherapy (¹³¹ I lipiodol, ⁹⁰ Y microspheres)	Radiation hepatitis, renal/pancreatic damage
Intralesional ethanol	Few, small lesions Difficulty viewing during injections Requires multiple sessions
Chemoembolization	Adequate hepatic function, patent portal vein Considerable local toxicity
Systemic or intra-arterial chemotherapy	Toxicity, lack of efficacy

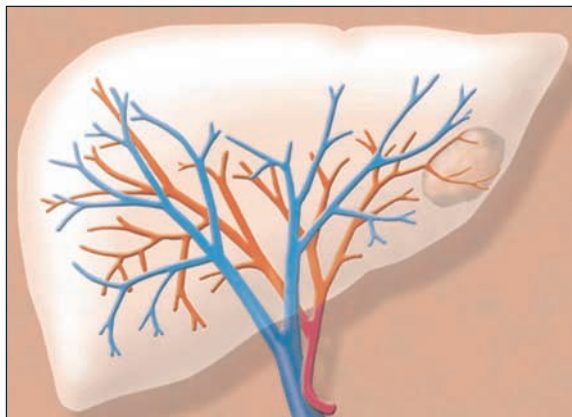


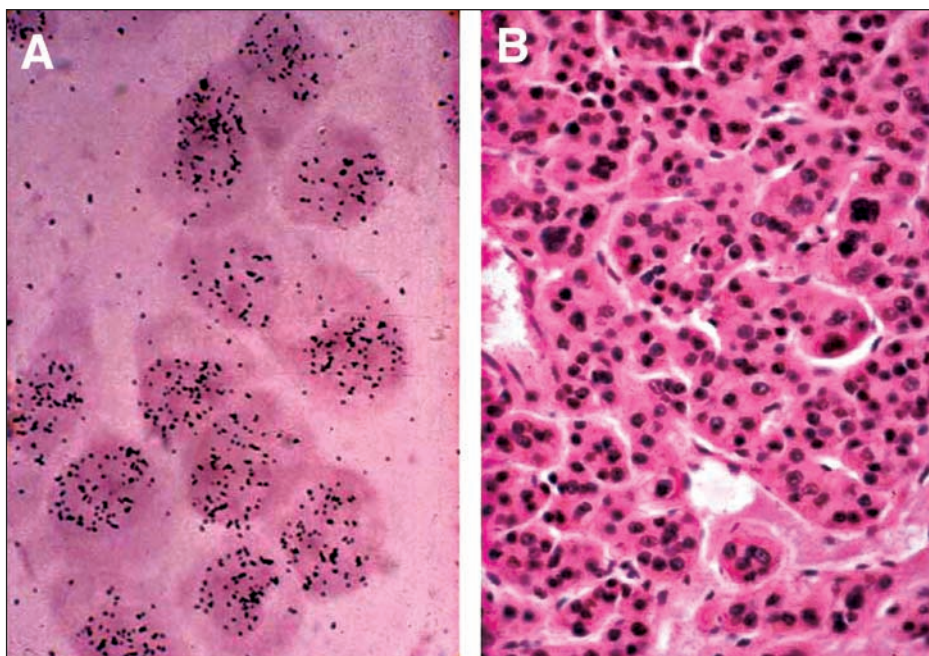
Figure 1. The dual vascular supply of the liver is demonstrated. The left lobe tumor receives arterial support alone. Illustration courtesy of Lisa Jeanne Graf.

with the various chemotherapeutic agents are relatively mild, there may be more significant problems associated with the catheter itself, such as thrombosis, infection, and leakage or malposition and infusion into an inappropriate vessel. These are apparent whether catheters are placed radiographically [14] or surgically [20]. Cost may favor the former method, if its anticipated use is for a short duration [21].

Interestingly, thrombosis of the catheter during delivery of intraarterial chemotherapy has been described as beneficial for inducing an improved tumor response. Surgical ligation or dearterialization [22] and angiographic embolization [23-25] have been used as well in the treatment of these tumors, but these methods are complicated by considerable morbidity. Tumor necrosis was readily achievable, but there was little evidence of any effect on long-term survival.

Chemoembolization represents a combination of two partially effective therapies with the aim of improving on both. There are multiple variations on the technique and ingredients, but it has evolved into a common procedure in many institutions worldwide to palliate patients with previously untreatable malignancies. Early studies

Figure 2. Greater intracellular concentration of chemotherapy under hypoxic conditions. Autoradiograph of human hepatoma cells administered ^3H -daunomycin under normoxic (A) and after 13 hours of hypoxic (B) conditions. Photomicrographs courtesy of Jonathan Kruskal, M.D.



demonstrated that extensive tumor necrosis could be produced, with radiographic tumor response rates of up to 83% [26-31]. Tissue levels of chemotherapy were found to be up to 40 times higher in the tumor than in the surrounding liver, and to persist for several months [32-35]. Moreover, there is reason to hypothesize that the ischemia resulting from the embolization component might actually enhance the cytotoxic action of the chemotherapy. Many drugs, such as doxorubicin, are actively expelled from tumor cells due to the action of the transmembrane pump P-glycoprotein, the product of the multidrug resistance (MDR) gene [36, 37]. P-glycoprotein is an ATP-dependent pump, and it is conceivable that the tissue hypoxia induced by chemoembolization inhibits the active efflux of the drug (Fig. 2). Further reports emphasized that, despite considerable local side effects, chemoembolization is relatively well tolerated in this group of patients with advanced cancer and may lead to prolonged survival [38-42].

TECHNIQUE

Chemoembolization is performed percutaneously in the angiography suite, with the patient under conscious sedation. After infiltration of local anesthetic, the Seldinger technique is used to gain access to the common femoral artery, although the brachial artery may also be used. An initial diagnostic mesenteric and hepatic arteriography is performed with the digital subtraction technique. A superior mesenteric artery injection shows any hepatic arterial supply arising from this vessel as well as any problems with patency of the portal vein. The celiac artery is then studied, followed by selective arteriography of the common and/or proper hepatic

arteries and left and right hepatic arteries. Large tumors near the periphery of the liver may be fed by adjacent parietal arteries, such as the phrenic arteries or internal mammary arteries. Occasionally, the gastroduodenal artery arises uncomfortably close to the origin of the middle or left hepatic artery or the right gastric artery may arise from the right or proper hepatic artery. Coil embolization of these vessels is then performed to protect the stomach and duodenum from potential reflux of the chemoembolic agent (Fig. 3) [43].

With the catheter lodged in the appropriate vessel supplying the tumor, the chemotherapy mixture is then injected. Many centers use a single agent, such as doxorubicin, while others add different drugs such as cisplatin, mitomycin, or 5-fluorouracil. Lipiodol (ethiodized oil), a cottonseed-oil-based contrast agent, is frequently added to form a chemoemulsion. This helps to increase the dwell-time of the chemotherapy by slowing the arterial flow as the oily mixture moves through the vessels. In addition, tiny micelles are formed that serve to embolize vessels with diameters as small as 5-10 μm [44-46]. The chemotherapeutic drugs are dissolved in a water-based contrast agent. Since these are high in iodine content, their specific gravity of about 1.6 enables the chemotherapy solution to mix more easily with the oil.



Figure 3. Postangiographic plain film demonstrating specific uptake of ethiodol within two hepatic masses and coils placed within the gastroduodenal artery.

Some centers mix larger embolic particles with the chemotherapy solution in order to deliver all agents simultaneously. However, it may produce a better result to perform the particulate embolization separately, immediately following delivery of the chemoemulsion. This allows more control over the arterial flow after one ensures the complete delivery of chemotherapy. In this way, multiple lesions may be treated simultaneously (Fig. 4). The specific agent used for embolization varies by center; plastic particles cause a permanent thrombosis, while gelatin foam particles may allow for recanalization of the vessel and retreatment if needed.

ELIGIBILITY AND COMPLICATIONS

Due to the potential toxicity of chemoembolization, especially the local effects caused by hepatic ischemia, strict criteria for eligibility for appropriate patients must be met. Generally, adequate hematologic and renal functions must be present, and hepatic function should be relatively well preserved. In our center, we have found that patients with a serum bilirubin level of over 3.0 mg/dl or a serum albumin level of under 2.8 g/dl have a significantly higher mortality rate. Obviously, since the aim is to embolize arterial flow, portal vein patency is mandatory for most patients. However, there are situations, such as a focal tumor with a discrete partial portal thrombosis, that may still be amenable to chemoembolization in a nonprotocol situation.

Patient characteristics may be used to help predict survival following chemoembolization [47]. Multivariate analysis has demonstrated the power of several factors, related not just to the tumor but to host liver function as well. Pretreatment predictors of worse survival in HCC include a serum alpha-fetoprotein (AFP) concentration >400 ng/ml (relative risk 2.8), a tumor volume $>50\%$ of liver volume (relative risk 2.6), and high Child-Pugh score (relative risk 1.3). Posttreatment predictors of worse survival include the presence of portal vein thrombosis (relative risk 2.7) and diffuse heterogeneous



Figure 4. Multifocal uptake of chemoemulsion.

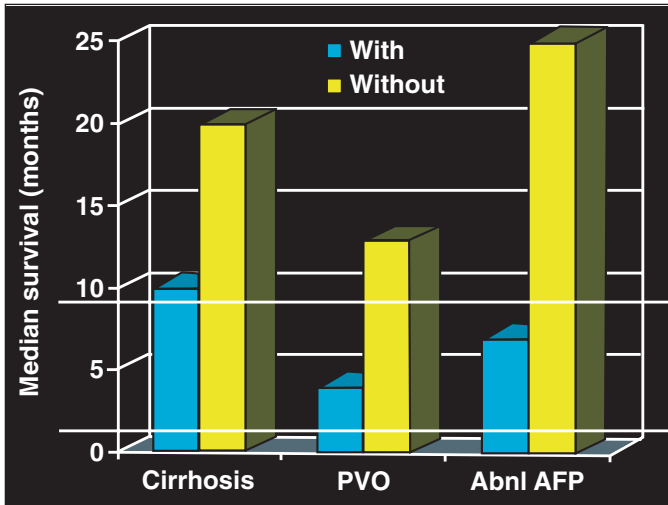


Figure 5. Variation in overall median survival depending upon the presence or absence of cirrhosis, portal vein obstruction (PVO), and elevated (Abnl) AFP.

uptake of lipiodol on computerized tomography (CT) scan (relative risk 2.4). Based on the pretreatment variables, it was found that patients with the most favorable characteristics were more likely to be alive at 12 months posttreatment than those with the least favorable characteristics (survival of approximately 70% versus 20%) [48]. In our center, median survival varies widely depending upon the presence or absence of cirrhosis, portal vein obstruction, and elevated AFP (Fig. 5). Another study found that there was no apparent survival benefit for patients with diffuse tumors, although those with focal lesions did better [49]. Of course, these factors are also descriptors of more advanced or aggressive disease and have been linked to poor survival regardless of treatment [50].

Given the combination of chemotherapy and hepatic ischemia, side effects are common. There is a postembolization syndrome of pain, fever, and malaise (due to hepatocyte and tumor necrosis). Transaminases commonly rise 100-fold; a leukemoid reaction is seen as well. Rarely, patients may develop bacteremia, pneumonia, ascites, renal dysfunction (Fig. 6), pleural effusions or arterial desaturation, or encephalopathy. Symptomatic hypothyroidism may occur as a result of the high retained iodine load [51]. Intrahepatic abscess and gallbladder ischemia (Fig. 7) are extremely rare. Rising bilirubin is a warning sign of irreversible hepatic necrosis, generally occurring in the setting of cirrhosis. In an effort to reduce the likelihood of significant hepatic toxicity, chemoembolization should be restricted to a single lobe or major branch of the hepatic artery at one time. The patient may be brought back after 1 month, once toxicities and abnormal chemistries have resolved, to complete the procedure in the opposite lobe. Retreatment of new lesions may be necessary, if patients fulfill the original eligibility criteria.



Figure 6. CT scan 1 day following chemoembolization. Note the i.v. contrast remaining within the left renal collecting system 24 hours after the procedure. This patient developed contrast-induced acute tubular necrosis.

HEPATOCELLULAR CARCINOMA

In many parts of the world, especially where the disease is very common, chemoembolization is the preferred treatment for relatively healthy patients with HCC (Fig. 8). However, due to the expense and toxicity associated with the procedure, and the poor prognosis of this patient population in general, there has been a great deal of controversy surrounding the utility of chemoembolization in prolonging survival. That it can palliate symptoms in select cases is not

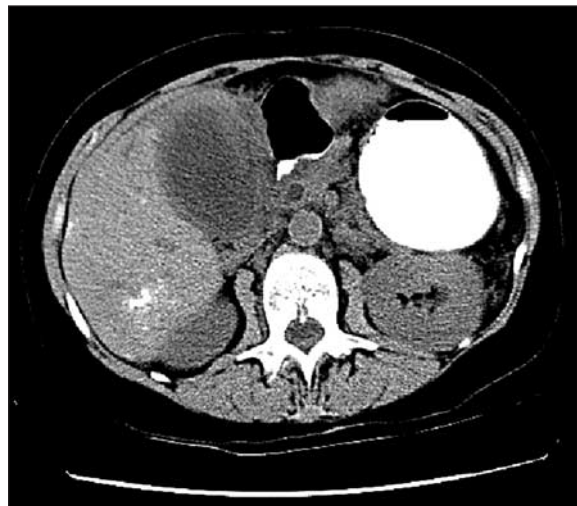


Figure 7. CT scan 1 week following chemoembolization. Note the gallbladder wall ischemia, demonstrating edema and stranding. Also note the absence of ethiodol within the gallbladder wall, illustrating that it is likely the embolic particles, rather than the chemoemulsion, were responsible.

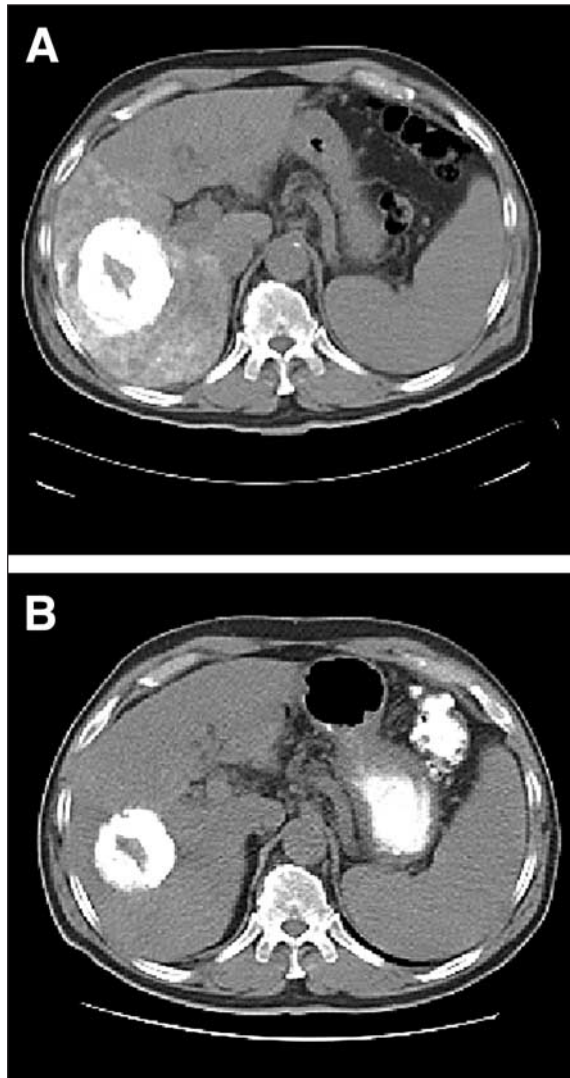


Figure 8. Nonenhanced CT scan at 1 day (A) and 1 month (B) following chemoembolization, demonstrating specific uptake and significant tumor response.

questioned, but the value of the technique in large cohorts has been questioned many times in the literature. Advocates of chemoembolization have looked to randomized trials to support their belief in its ability to help many patients. Unfortunately, the dearth of alternative treatments has meant that most data are in the form of phase II studies or comparisons with supportive care only.

Older, nonrandomized studies compared inoperable patients with HCC undergoing chemoembolization with those treated in other ways. Comparisons with embolization alone showed a difference in the 1-year survival rate, 44% versus 28% [52], and in the 2-year survival rate, 37% versus 16% [33]. Others were unable to show a clear difference, even when compared with untreated historical controls [53]. Some randomized studies have been unable to demonstrate

a significant difference in survival between patients receiving chemoembolization and those treated symptomatically [54-56]. However, the heterogeneity of approaches to the technique of chemoembolization—with each group using different drugs, various intervals between repeated treatments, and the presence or absence of lipiodol—makes generalization of these results impossible.

For instance, a relatively large trial (96 patients, who represented 12% of all potential HCC patients) conducted by the Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire in Europe demonstrated a 53% rate of tumor shrinkage. However, they could not show a statistically significant improvement in survival, although there was a trend in favor of the chemoembolization group (63% versus 44% at 1 year and 38% versus 26% at 2 years) [55]. A major criticism of that study was that most patients received repeated courses of chemoembolization every 2 months, and many of the reported causes of death were related to cirrhosis rather than tumor growth. This demonstrates both the power and the danger of chemoembolization, which is likely to cause some decompensation in hepatic function each time it is performed, as it destroys normal hepatocytes along with tumor tissue. *Uchida* and colleagues, in an examination of survival following preoperative chemoembolization, helped to underscore this paradox by showing that excess deaths from exacerbated cirrhosis may, in some instances, balance out improved tumor-related survival [57]. While chemoembolization was successful in postponing death from tumor at 1.5 years, when it preceded resection in cirrhotic patients, it led to a significantly lower survival rate at 4 years (35% versus 72%). This illustrates the mandate that chemoembolization be used judiciously and sparingly in appropriate patients [58].

Several more recent studies have convincingly demonstrated a survival advantage among carefully selected patients with HCC who receive chemoembolization. The Barcelona Clinic Liver Cancer Group performed a randomized study comparing bland embolization, chemoembolization, and conservative treatment for unresectable and untransplantable patients [59]. They found 112 (12%) suitable patients out of a group of 903 with HCC, and divided them into three approximately equal groups that were well balanced for baseline tumor and hepatic characteristics. All had cirrhosis, and hepatitis C was the cause in over 80% of the cases. More than two-thirds of patients were classified as Child-Pugh class A or Okuda stage I, and most had performance statuses of 0. The mean size of the treated lesions was about 5 cm, and almost half the patients had normal AFP levels. Therefore, this was a quite healthy group of patients, who would be expected to have relatively good prognoses regardless of treatment. Indeed, the control group had a

mean survival of 17.9 months (median approximately 14 months), which is considerably longer than the generally expected survival of untreated patients with this disease. The chemoembolization group, however, had a mean survival of 28.7 months (median about 31), with a significantly greater 2-year survival rate as well, 63% versus 27% ($p = 0.009$).

Similarly, a study of unresectable HCC in Asia randomized 80 patients to chemoembolization or symptomatic care [60]. Tumor response was significant, as expected, in the treated group. There was, however, a higher rate of death from liver failure (as opposed to death from tumor progression) among patients who underwent chemoembolization. The 2-year actuarial survival rate was significantly better in the chemoembolization group (31% versus 11%, $p = 0.002$), and the relative risk of death was 0.49. It is instructive, in evaluating differences among studies such as these, to note the major differences in survival between the two latter studies. The techniques used were quite similar, and the measurable hepatic function had comparable indicators. However, the Spanish population was primarily hepatitis C positive, while the patients in Hong Kong were mostly hepatitis B positive.

Differing etiologies change the characteristics of cirrhosis and the host liver, which may certainly alter overall prognoses and hepatic resilience to insults such as surgery or ischemia [61, 62]. Furthermore, in the U.S., the most common cause of cirrhosis is alcohol abuse, which affects older patients with other comorbid illnesses and leads to an even worse prognosis [50]. These profound differences in the underlying hepatic parenchyma make any intercontinental comparisons fraught with difficulty. Nonetheless, a recent meta-analysis of randomized trials of chemoembolization in patients with HCC demonstrated an overall slight improvement in 2-year survival (odds ratio of 0.54, $p = 0.015$) [63].

Chemoembolization has also been evaluated, and is frequently used, as an adjunct to other therapies, such as resection, transplantation, percutaneous ethanol injection [64-72], and radiofrequency ablation [73-75], in the treatment of HCC. Several uncontrolled series and at least one randomized trial have suggested that preoperative chemoembolization is associated with greater mortality [57, 76-78]. In that controlled trial, 52 patients with resectable large HCC were randomly assigned to preoperative chemoembolization or immediate surgery [78]. Patients undergoing chemoembolization had a slightly longer operative time, a higher rate of concomitant resection of adjacent organs, and a higher rate of histologic invasion into these organs. Although disease-free survival was similar in the two groups, extrahepatic cancer was more common in those who had been treated with chemoembolization (57% versus 23%), and survival was worse. Patients undergoing transplantation for HCC are also

frequently treated with chemoembolization beforehand in an effort to reduce the chance of intraoperative tumor shedding. Although this has been shown to be feasible, no survival benefit has been reported as no randomized studies have been done [79-83].

NEUROENDOCRINE METASTASES

Neuroendocrine tumors, such as pancreatic islet cell and carcinoid tumors, while rare, are a common indication for hepatic chemoembolization. These tumors frequently metastasize to the liver by the time they are discovered, and it is these liver metastases that are usually responsible for the patient's symptoms. For instance, in one analysis, 95% of patients with carcinoid syndrome had liver metastases [84]. These are also generally indolent neoplasms, so they may grow to a large size in the liver before causing symptoms due to hepatic bulk, such as pain or anorexia. Furthermore, the hepatic metastases are angiographically hypervascular, extrahepatic metastases are unusual, and systemic chemotherapy is often ineffective. All of these characteristics have led investigators to attempt both palliative and definitive treatment with chemoembolization [42, 80, 85-95].

Due to the hypervascularity of these lesions, reported response rates are as high as 70%-90%. Morbidity is generally less than in the HCC population, since cirrhosis is rarely a complicating factor. Median survival in many of these series is at least 2 years, although, given the extended natural history of these tumors, it is unclear whether this represents a significant prolongation of survival. For this reason, we generally reserve this treatment for patients whose tumors are already symptomatic or are beginning to grow at a significant rate.

COLORECTAL METASTASES

In the U.S., metastases to the liver are approximately 40 times more common than primary cancers. Colorectal cancers are the most important causes of these metastases, since other common cancers, such as lung or breast, rarely are metastatic to the liver as the only site. Conversely, patients with metastatic colorectal tumors frequently die of hepatic failure due to liver metastases. In fact, autopsy series have shown that up to 38% of patients who die from these diseases may have the liver as the sole site of metastases [96]. Surgical resection is the treatment of choice for colorectal metastases to the liver and may be curative for a number of these patients [97-99], but this approach is limited in perhaps two-thirds of potential candidates by the number or location of the lesions, hepatic function, or comorbid illnesses [100].

Intra-arterial chemotherapy has been more fully studied and is more successful for colorectal liver metastases than for HCC [15, 101-106]. Building on this work, chemoembolization

has been investigated for unresectable lesions in this population. Tumor response rates are not as high as those in HCC and neuroendocrine metastases because colorectal lesions are frequently hypovascular on arteriography [107, 108], limiting the ability to deliver adequate chemotherapy and embolic agents. Nonetheless, response rates of approximately 50% have been reported, with survival longer than would be expected in studies of systemic therapy among patients who had failed standard chemotherapy. As in neuroendocrine patients, the absence of underlying cirrhosis reduces the expected morbidity. Chemoembolization for patients with metastatic colorectal cancer appears to be a reasonable alternative for many who are not surgical candidates [109-116]. Survival may be especially enhanced in treated patients who have no extrahepatic metastases [117].

OTHER DISEASES

Cholangiocarcinoma, although frequently an isolated intrahepatic malignancy, responds to chemoembolization

less than half the time. There are few other neoplastic diseases that may sensibly be treated with a liver-directed therapy, such as chemoembolization, since most patients will die of systemic disease. Even so, in the absence of effective treatments, many investigators and frustrated oncologists have explored its possibilities [118, 119]. Soft-tissue sarcomas may involve the liver as a principal site of growing or symptomatic metastases which are frequently hypervascular, leading to the possibility of chemoembolization as helpful therapy [120]. Ocular melanoma is notorious for the appearance of late liver metastases, and chemoembolization has been used for this as well [121, 122]. Unfortunately, the liver is usually just the first site in a rapidly systemic recurrence, so hepatic treatment is unlikely to affect survival in this situation.

PERSONAL EXPERIENCE

We have been performing chemoembolization for appropriate patients at our institution since 1988 (Fig. 9). Patients

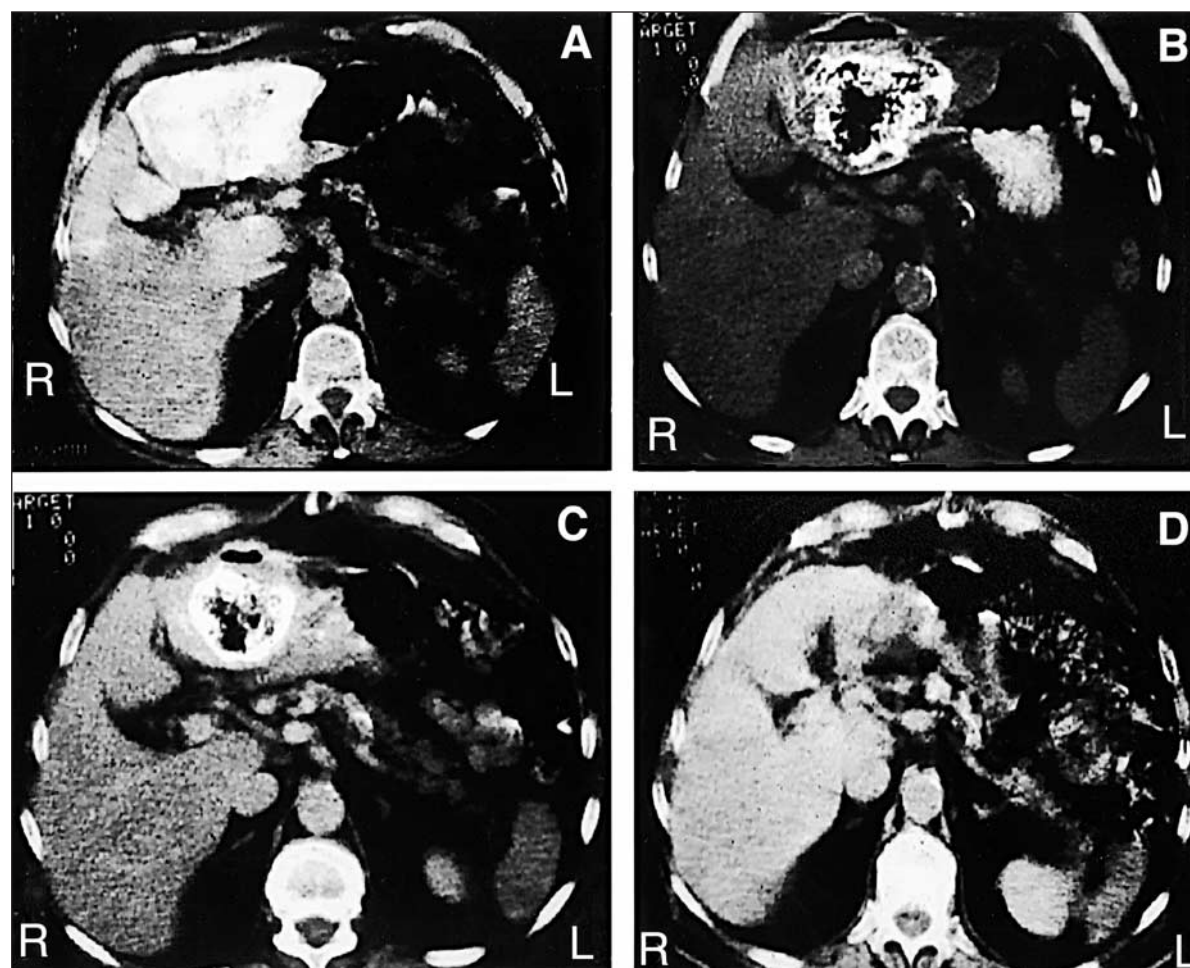


Figure 9. Sequence of CT scans day of (A), 1 week (B), 1 month (C), and 6 months (D) following chemoembolization, showing the development of intratumoral necrosis and disappearance of the treated lesion. Aspiration indicated this area was sterile.

are carefully selected to include those most likely to benefit. These are generally patients with liver-predominant disease and with symptomatic or rapidly growing tumors. They must have focal rather than diffusely infiltrative tumors. Those with fewer than three lesions, <6 cm each, generally are treated preferentially with radiofrequency ablation, if the location of the tumors makes this technically feasible. Rarely, this may be combined with chemoembolization to improve radiographic results. Any potentially resectable lesions are treated with surgery. If the patient understands the risks, has a good performance status (0 or 1 by Eastern Cooperative Oncology Group criteria), has a patent portal vein, and has a total bilirubin level ≤ 3.0 mg/dl, albumin level ≥ 2.8 g/dl, and creatinine level ≤ 2.0 mg/dl, then chemoembolization is recommended.

All patients receive hydration with normal saline and prophylactic medications including lactulose, furosemide, antibiotics, ranitidine, and narcotic analgesics. Most patients are hospitalized for a single night for pain control, hydration, and monitoring of hepatic function. Patients are followed radiographically with a noncontrast CT scan at 1 month to evaluate ethiodol remaining within the treated lesion, which is taken to indicate successful devascularization of the tumor. Beginning at 3 months, triphasic scans are ordered to look for evidence of new lesions. Both the presence of necrosis and any diminution in tumor size are interpreted as partial responses to chemoembolization. Magnetic resonance imaging may be used as well; experience with positron emission tomography scanning is limited in this setting.

Over 300 patients with HCC have been treated in this way at our institution. Most have had cirrhosis, primarily due to alcohol, and all have been unresectable. Many have had poor performance statuses or portal vein involvement. By CT criteria, over 60% had good responses, defined as persistent intratumoral accumulation of ethiodol over 1-3 months and some degree of tumor shrinkage. Median survival was approximately 10 months in this quite ill population, but among the subgroup with well-preserved hepatic function and patent portal veins, median survival was over 20 months. Patients with adverse prognostic factors, such as portal vein thrombosis or advanced Child-Pugh score (see above), are no longer offered this procedure. At the time of writing of this report, one patient remained alive and disease-free 13 years after the procedure.

Over 100 patients with colorectal metastases treated at our facility with chemoembolization had a radiographic response rate (as defined above) of over 50%. Overall median survival was 10 months, but it approached 24 months in patients with no extrahepatic disease. Approximately 90 patients with neuroendocrine metastases (about half with carcinoid tumors) have undergone chemoembolization successfully at our institute, with radiographic and hormonal response rates each of approximately 70% and a median survival of 24 months. All patients have undergone repeat procedures as needed for recurrent disease (if they were still eligible), and we always perform single-lobe embolizations due to the additional morbidity associated with whole-liver procedures.

CONCLUSION

Chemoembolization may be an effective method of controlling hepatic disease in many patients with liver-dominant neoplasms, such as HCC, colorectal metastases, and neuroendocrine tumors. Response rates are high compared with what is achievable with systemic therapy, and the procedure should certainly be considered in any appropriate patient who has symptomatic disease. The effect on survival has been difficult to demonstrate because of the difficulty in randomizing patients who may have no reasonable alternative therapy available. However, at least in HCC, recent studies have shown a true prolongation of life in several different selected populations, when compared with supportive care.

It is essential to have an experienced angiography team performing the actual chemoembolization, as the technique is quite difficult and possible hazards are beyond the standard of routine interventional radiology [43]. Furthermore, the medical team caring for the patient must be well-versed in possible complications and likely toxicities in order to help the patient during a difficult recovery [123]. Careful selection of appropriate patients should be done to restrict the procedure to those who are likely to tolerate it and benefit from such an aggressive intervention. Despite these limitations, chemoembolization has developed into a common procedure around the world and continues to evolve as a useful tool to help patient populations with limited therapeutic options.

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