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Chemoembolization and Bland Embolization: A Critical Appraisal

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Hepatocellular carcinoma (HCC) is a major cause of cancer-related mortality worldwide, resulting in more than 500,000 deaths per year [1]. In the West, HCC is becoming the most frequent cause of liver-related death in patients with viral-associated cirrhosis [2]. In the United States, the incidence of HCC increased 114% between 1975 and 1998, with the fastest growing age group in recent years being those 45 to 55 years old [3]. Unfortunately, only about 30% of the patients diagnosed with HCC in surveillance programs are candidates for potentially curative therapy such as liver transplantation, surgical resection, or local ablation [4]. Without surveillance only 10% to 15% of patients are eligible for potentially curative treatment.

Palliative therapy includes options such as bland embolization, chemoembolization, and chemotherapy (intraarterial and systemic). Chemotherapy has only limited utility in HCC because of poor objective response rates (generally less than 25%) and lack of survival benefit [5,6]. Thus, chemotherapy should be offered in the setting of clinical investigation of new agents for patients with advanced stage disease [6]. Those patients with intermediate-stage disease (tumors either too large or multicentric for curative treatment and relatively preserved hepatic function) are candidates for embolization therapy [5,6]. There have been seven randomized clinical trials [7–13] comparing embolization treatment to supportive care or ineffective treatment and four systematic reviews/meta-analyses [14–17]. This article will critically evaluate the various roles for bland and chemoembolization of HCC.

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How does embolization therapy work?

The goal of embolization therapy is to disrupt the blood supply to HCC while limiting collateral damage to the nontumorous liver. In the case of chemoembolization, there is the additional delivery of a high concentration of chemotherapeutic agents that remain in contact with the lesion for a prolonged period of time. The rationale supporting the technique comes from the observation that >90% of the blood supply to HCC comes from the hepatic artery where about 80% of the blood supply to the normal liver comes from the portal vein [18]. In theory, the embolization causes ischemia of the tumor, and combined with chemotherapy, result in tumor necrosis. Greater than 95% tumor necrosis is seen on pathologic examination in 70% of small HCC after a single bland embolization, but only 44% for lager tumors [19]. The chemotherapy is usually mixed with iodized poppy seed oil (lipiodol) forming an emulsion that traps the chemotherapy and tends to concentrate in HCC [20]. The concentration of chemotherapy in the tumor may be 10 to 100 times greater than if given systemically [21]. Additionally, the embolization induces tumor ischemia, which blocks transmemebrane pumps and directly limits the chemotherapy from washing out of the tumor cells [20]. Despite these observations, the true mechanism of producing tumor necrosis remains unknown [20].

Technique

There are local variations in the techniques of embolization therapy. Generally, the patient enters the angiography suite following an overnight fast. After volume loading with normal saline, administration of sedatives and prophylactic antibiotics (not all centers give prophylaxis), a visceral angiogram is performed to identify the arterial anatomy of the liver, the size and locations of the tumors, and their feeding vessels and portal venous potency. A catheter is advanced beyond the gastroduodenal artery (to avoid extrahepatic embolization), and depending on tumor location to lobar, segmental, or subsegmental branches feeding the target lesion(s). Chemotherapy, in combination with lipiodol (for chemoembolization), and embolization materials (gelatin sponges) such as Gelfoam (Pharmacia and Upjohn, Kalamazoo, Michigan) or Ivalon (M-PACT Worldwide Inc., Eudora, Kansas) or polyvinyl alcohol particles are injected sequentially [20]. The gelatin sponges cause only temporary thrombosis lasting about 2 weeks, whereas polyvinyl alcohol is more permanent [20]. Patients are admitted for continued volume loading, antibiotics, and pain management for 24 to 48 hours [22].

The choice of chemotherapeutic agents used with embolization generally includes cisplatin [8,10,13], doxorubicin [11,12], and epirubicin [23,24]. Two studies compared doxorubicin to epirubicin and found no differences in overall survival [24,25]. Doxorubicin was compared with cisplatin in nonrandomized studies, with two showing improved overall survival with cisplatin [26,27] and

one showing no differences [28]. In addition, one of the strongly positive randomized controlled trials (RCTs) assessing chemoembolization therapy used doxorubicin [11] and the other used cisplatin [10]. Thus, there is no convincing evidence that one agent is better than another, and an RCT comparing doxorubicin to cisplatin is warranted.

The dose of chemotherapeutic agents for chemoembolization varies among centers. Chen et al demonstrated in a randomized trial that for Child A patients high-dose lipiodol chemoembolization (epirubicin 50 $mg \cdot m^{-2}$, mitomycin C 8 $mg \cdot m^{-2}$, and iodized oil mean dose 28 mL) sometimes followed by resection resulted in better survival compared with a standard dose [29]. No differences in survival were found by another group who assessed conventional (mitomycin C 10 mg, epirubicin 40 mg, and carboplatin 300 mg) versus low-dose (mitomycin C 2–8 mg, epirubicin 0–10 mg, carboplatin 0–100 mg based upon tumor diameter) lipiodol chemoembolization in a nonrandomized study [30].

Most centers repeat chemoembolization based upon response assessed by imaging, hepatic reserve, and a planned interval usually every 2 to 4 months [9–11,13]. One nonrandomized study suggested improved survival with repeated treatments based upon response and hepatic reserve alone [31].

Complications

The most common toxicity (32–80%) from embolization therapy is a self-limited postembolization syndrome consisting of fever, abdominal pain, vomiting, and sometimes elevations in alanine aminotransferase (ALT) [8,10,13,32]. Postprocedural pain may be limited by administration of lidocaine during the procedure [33,34]. Other complications occurring in generally <10% of cases include new or worsening ascites, gastrointestinal bleeding from varices or ulcers, leukopenia, and worsening hepatic function [8,10,11,13,32]. Rare but significant complications include death, cholecystitis, ischemic hepatitis, liver abscess, bacteremia, hepatic failure, and renal failure [11,13,35]. Persistent renal failure is associated with Child-Pugh class B and diabetes mellitus [35]. Long-term oral supplementation with branched chain amino acids resulted in significant improvements in postchemoembolization albumin, bilirubin, and quality of life, reduced complications including ascites and edema, but no effects on survival [36].

Efficacy for primary treatment of hepatocellular carcinoma

The "gold standard" to assess the efficacy of any therapy is to rely on the results of large RCTs comparing treatment to no treatment in a well-defined and uniform group of patients [15,37]. No large RCTs are available for embolization therapy, but the literature contains seven smaller RCTs [7–13]. Meta-analysis

is generally considered the next best level of proof of efficacy, and combines the results of several smaller RCTs to usually overcome the lack of statistical power of individual studies [15,37]. It relies upon uniformity of the combined trials with regard to treatments and patient populations. Even if the combined trials have adequate statistical uniformity, meta-analyses may disagree with large RCTs 10% to 23% of the time [37]. Many nonrandomized trials, some with controls, are available to assess the efficacy of embolization therapy, but without randomization there are bound to be significant biases, which are likely to have a major impact on the end point assessed.

Efficacy of treatment for HCC should be defined by survival differences rather than tumor-free survival or objective tumor responses because of the generally high mortality. In these patients, survival is clearly dependent upon both tumor progression and hepatic failure [5]. Although some therapies may effectively treat the tumor, the collateral damage to the liver may result in shortened survival due to liver failure. Additionally, because even with therapy the mortality remains high, quality of life should be part of the assessment of treatment. Thus, embolization therapy is generally limited to patients who are not candidates for curative therapy and who are thought to have adequate reserve to undergo the procedure.

Llovet et al [38] studied the natural history of a group of patients with these characteristics who were randomized to no treatment arms of two clinical trials. They showed that performance status, constitutional syndrome (weight loss, malaise, and anorexia), invasion of the portal vein, and extrahepatic spread of tumor were independent predictors of mortality [38]. Presence of any one of these parameters changed 1-, 2-, and 3-year survival from 80%, 65%, and 50%, respectively, to 29%, 16%, and 8% [38]. Another study of a similar group of untreated patients with HCC found that the presence of a variant estrogen receptor transcript and bilirubin levels were the best predictors of survival [39]. They found 1-, 2-, and 3-year survival of 94%, 66%, and 52% with the wild-type estrogen receptor, and 51%, 21%, and 16% with the variant estrogen receptor, respectively [39]. Although these predictors of survival need further validation, the magnitude of their apparent effects is much larger than any of the results from the RCTs of embolization therapy. Other factors such as Child-Pugh score, tumor morphology, α-fetoprotein level, and portal vein thrombosis, which make up the Cancer Liver Italian Program and Okuda staging systems, are also predictive of survival in treated patients with HCC [40,41]. Clearly, with and without treatment many factors relating to both the tumor and the underlying liver disease can drastically alter the survival of patients with HCC. Thus, only randomized trials should be relied upon for overall assessment of embolization therapies.

Additionally, differences in treatment protocols including number of cycles and addition of chemotherapeutic agents may alter outcomes. There may also be interaction between the effects of embolization treatment and the amount of hepatic reserve where patients with limited hepatic reserve may have worse survival with treatment and those with more reserve may have better survival.

A careful examination of these issues will help explain the differences in the outcomes of the RCTs for embolic therapy. Llovet et al [15] performed a meta-analysis of seven RCTs including 545 patients assessing primary treatment of HCC not amendable to potentially curative treatment. Bland embolization or chemoembolization were compared with no treatment or ineffective treatment (tamoxifen or intravenous 5-fluorouracil) as a control [15]. There was a significant improvement in 2-year survival (odds ratio [OR], 0.53, 95% confidence interval [CI], 0.32–0.89) in the six trials that reported 2-year results (Fig. 1) [15]. The missing trial [12] had 22% of patients with end-stage disease, Okuda III, compared with none in the other trials. When all seven trials were assessed for 1-year survival there was only trend toward favoring treatment (OR, 0.64, 95% CI, 0.41–1.01) [15]. Sensitivity analysis showed significant benefit of treatment versus no treatment, treatment for the five high-quality trials, and chemoembolization versus control, but no benefit of embolization versus control (Fig. 2) [15]. The strength of Llovet et al's [14,16,17] analysis over all the previous analyses is inclusion of all the available RCTs published to date. The analysis shows a strong suggestion of benefit for chemoembolization.

So why were three of the studies clearly negative [9,12,13] and two clearly positive [10,11]? Statistical testing for heterogeneity between the trials was negative, but the patient populations differed substantially, with 1- and 2-year survival in the control groups ranging from 13% to 80% and 11% to 50%, respectively. The control group survival in the positive Western study [11] was

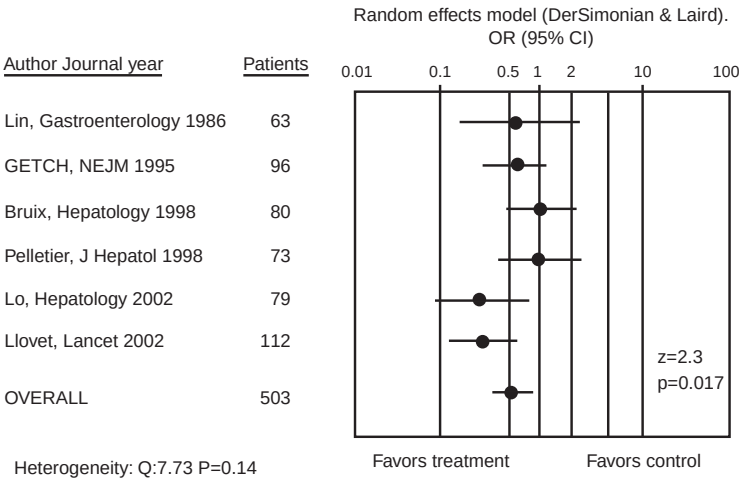

Fig. 1. Meta-analysis of RCTs comparing embolization therapy versus consevvative or ineffective treatments. Random effects model (OR, 0.53; 95% CI, 0.32–0.89; $P = 0.017$. (*From* Llovet J, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatol 2003;37:429–42. Copyright ©2003 The American Association for the Study of Liver Diseases; reprinted with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

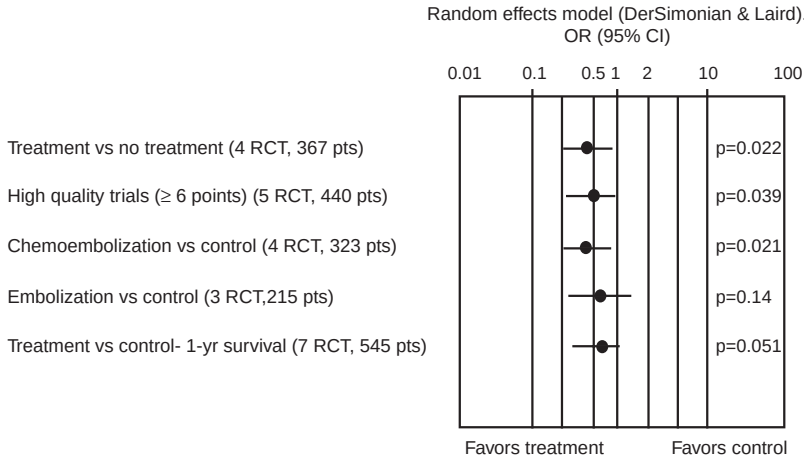

Fig. 2. Sensitivity meta-analysis of 6 RCTs reporting 2-year survival assessing embolization therapy versus conservative therapy (four RCTs), embolization therapy versus conservative or suboptimal therapy in high-quality trials (five RCTs), chemoembolization versus conservative or suboptimal therapy (four RCTs), bland embolization versus conservative or suboptimal therapy (three RCTs) ,and embolization therapy versus conservative or suboptimal therapy 1-year survival (7RCTs). (*From* Llovet J, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003;37:429–42. Copyright; 2003. The American Association for the Study of Liver Diseases; reprinted with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

among the best, whereas in the Asian trial [10] it was among the worst. These two trials generally differ from the rest by being more recent, and thus have better catheter technology to achieve more selective embolization of the tumors, using doses of chemotherapy based upon tumor size or hepatic function, using lipiodol, and repeating treatments in responders as long as hepatic function did not deteriorate. The Asian study had more advanced tumors with 25% with portal vein branch thrombosis, which probably explains their low control group survival rate [10]. There was no evidence that the patients with portal vein thrombosis benefited from treatment [10]. All the negative studies lacked at least one of these factors—selective embolization [7,8,12,13], chemoembolization [7,9], dose adjustment for chemotherapy [8,12], repeated treatments [9], and repeated treatments based upon tumor response or liver function [8,12].

Repeated chemoembolization and bland versus chemoembolization have been assessed carefully in other trials. A sequential nonrandomized assessment of every 2-month repeated chemoembolization versus retreatment based upon response found better survival with the latter [42]. The choice between bland embolization and chemoembolization is controversial. There are two RCTs comparing bland to chemoembolization from the 1980s and early 1990s that showed no survival differences between the therapies [43,44]. The most recent meta-analysis of embolization therapy versus control found that chemoembolization and not bland embolization improves survival [15]. Only one of the

studies [11] made a direct comparison that showed no statistical difference in survival between chemoembolization and bland embolization, but the study was underpowered to compare the procedures. It found a definite survival benefit for chemoembolization, and suggested a possible benefit of bland embolization. Thus, the evidence supporting a benefit for chemoembolization therapy is stronger than bland embolization.

Predictors of survival

Multiple studies have tried to assess predictors of survival in patients undergoing embolization therapy. Predictors of survival include unilobar portal vein thrombosis, performance status, ascites, bilirubin, α-fetoprotein, Child-Pugh class, Cancer Liver Italian Program score, Model for End-Stage Liver Disease score, and tumor size [8,10,45–48]. Exact cutoffs for the predictors are not readily available, and even some patients with poor predictors can achieve 5-year survivals [48]. Most centers, including those that performed the two positive RCTs, suggest not treating patients with main or lobar portal vein thrombosis, Okuda III, poor performance status, and extrahepatic disease [5,10,11]. There are limitations of these studies, because without a large RCT, it is difficult to separate independent predictors of survival that should relate to the underlying liver disease, tumor biology, the treatment and interaction between all these factors.

Efficacy before surgical resection

The data regarding the efficacy of embolization therapy before planned resection of HCC is limited by being predominately retrospective and sometimes relying upon disease-free survival rather than the more valid overall survival. Embolization therapy before resection is performed to prevent long-term recurrence of tumor, and sometimes to downstage a previously unresectable tumor. There are two Asian RCTs that attempt to prevent recurrence of tumor by preoperative embolization. The first compares preoperative chemoembolization versus direct resection in 52 patients with tumors >10 cm and generally preserved hepatic function (50% noncirrhotic) [49]. It showed worse overall survival with chemoembolization [49]. The study results may have been compromised because the chemoembolization group had a much higher rate of invasion of adjacent organs, although the high rate may have been a result of the mean 18-week delay to surgery while getting chemoembolization [49]. The second compares preoperative bland embolization versus direct resection in 97 patients with tumors 3 cm to 5 cm, and showed no difference in cancer-free or overall survival [50]. The remaining studies in the literature are

retrospective, nonrandomized, with only one [51] with a carefully matched control. It included 48 patients with mean tumor size 7.8 cm, and showed no differences in cancer-free or overall survival [51]. Recent large series with no overall survival or tumor-free survival benefits included 889 Asian [52–57] and 76 Western patients [58] with generally large tumors. Three of the series [54,55,57] suggested that large or advanced tumors did receive a survival benefit, and one [58] suggested that 10% of previously unresectable patients were downstaged by chemoembolization. Di Carlo et al showed overall survival benefit compared with control in a group of 100 patients with tumors <5 cm [59]. Gerunda et al showed improved tumor-free but not over all survival in 40 patients with mean 4-cm tumors [60]. Many chemoembolization patients never made it to resection and were excluded, thus negating the conclusions [60]. Overall, there is no convincing evidence to recommend preresection chemoembolization. A randomized controlled trial of chemoembolization preresection for patients with large tumors including potentially unresectable tumors in patients with preserved hepatic function would be welcome, but these patients are rare in North America.

Efficacy before orthotopic liver transplantation

Orthotopic liver transplantation (OLT) is a highly effective treatment for HCC because it provides the widest possible resection margins and replaces the damaged liver [5]. By following the Milan criteria (solitary lesion <5 cm or two to three lesions each <3 cm and no extra hepatic spread or vascular invasion) [61], multiple series have demonstrated >70% long-term survival for patients with HCC treated by OLT, which is nearly identical to outcomes in patients without HCC [61–64]. These excellent results occurred at a time when mean waiting times were <6 months [38]. Unfortunately, the dropout rate for patients with HCC on OLT waiting lists can exceed 20% [65,66]. Thus, intention to survival is markedly reduced because nearly all of the dropouts have very poor survival.

Graziadei et al [67] showed that chemoembolization in patients meeting the Milan criteria while waiting for OLT could eliminate waiting list dropouts and produce 5-year survival rates of 94% despite a waiting time of a mean of 178 days (range 28–459). Harnois et al [68] evaluated a similar chemoembolization protocol including patients with up to three HCC nodules each <5 cm. The pre-OLT drop out rate was 7%, with a waiting time of a mean of 167 days (range 28–548). Survival in those transplanted was 84% at 2 years despite having 37% of the patients exceeding the Milan criteria, and there was no recurrence of HCC [68]. A longer term assessment of pre-OLT chemoembolization from the same group involving many of the same patients showed a cumulative probability of dropout due to a tumor progression of 15% at 6 months and 25% at 12 months [69]. Post-OLT 5-year survival was 74%, but it decreased to 61% if assessed by intention-to-treat analysis [69].

Complications resulting in lost opportunity to proceed with transplant or death from pre-OLT chemoembolization are rare [67–69]. Posttransplant complications also appear to be rare [67–69], and one series addressing the issue of hepatic artery complications did not show increased rates compared with other OLT patients [70]. Thus, chemoembolization may have a role in controlling HCC while a patient is waiting for OLT especially if the waiting time is likely to be 6 or more months. There does not appear to be a significant detrimental effect of chemoembolization on these patients provided that they have adequate hepatic reserve. Chemoembolization has not been compared with other options such as ethanol or radiofrequency ablation in this setting. Fortunately for patients with HCC in the United States, pre-OLT treatments may be unnecessary given the currently short waiting times with the special exception listing for HCC in the Model for End-Stage Liver Disease organ allocation system. Thirty- and 90-day transplantation rates are 26% and 44% for <2 cm lesions and 47% and 76%, respectively, for other lesions meeting the Milan criteria [71]. The criteria were recently changed to giving additional advantage only to patients with the larger or multiple tumors, but waiting times should continue to remain low [72].

Some have proposed expanding the Milan criteria to permit OLT in more patients with HCC [25,67,73]. Chemoembolization may be able to downstage these patients. Roayaire et al [25] assessed 80 patients with tumors >5 cm who underwent attempted downstaging. They were unable to downstage 46%, but the remaining who went on to OLT had a survival of 44% at 5 years [25]. The decreased survival compared with the >70% long-term survival found in other series was generally due to tumor recurrence, and could be reduced by restricting transplant to tumors <7 cm and without vascular invasion [25]. Another group performed a similar assessment of chemoembolization for advanced tumors and had a 27% dropout rate and a 41% 4-year survival [67]. Thus, overall intention-to-treat survivals in these patients are poor, but some patients appear to have long-term benefit. Downstaging with chemoembolization before OLT should be limited to research protocols attempting to find predictors of better long-term success.

Efficacy in combination with local ablative therapy

Percutaneous ethanol ablation is a standard treatment for small HCC [5]. Combination of chemoembolization followed by ethanol ablation for tumors <3 cm compared with chemoembolization alone has been evaluated and found not to significantly affect long-term survival, but may reduce recurrence [74,75]. Similar therapy for large tumors assessed by nonrandomized comparisons suggested improved long-term survival [76–78]. A randomized trial of chemoembolization plus local ablative therapy versus chemoembolization alone is warranted.

Summary

Bland embolization and chemoembolization are commonly used therapies for patients with HCC who are not candidates for curative treatment. Thus, their role is palliative, and should be applied to patients with larger or multiple tumors who have sufficient hepatic reserve. The ability of chemoembolization as primary treatment to prolong survival has recently been demonstrated by meta-analysis. The evidence for efficacy of bland embolization is weaker. The role of embolization therapy before resection or OLT is controversial, and warrants assessment by RCT.

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