Editorial

Optimizing transcatheter therapies for hepatocellular carcinoma: invited editorial regarding "Roles played by chemolipiodolization and embolization in chemoembolization for hepatocellular carcinoma: single-blind, randomized trial"

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Submitted Mar 07, 2013. Accepted for publication Apr 09, 2013.
doi: 10.3978/j.issn.2224-5820.2013.04.03
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Shi *et al*. recently published a 3 arm randomized study comparing efficacy and safety of 3 different modes of intra-arterial chemotherapy infusion and embolization (1). This study adds to the growing, yet sometimes confusing literature regarding transcatheter therapies for hepatocellular carcinoma (HCC). Although the literature is growing, unfortunately randomized and prospective trials are relatively sparse.

This particular randomized study compares triple drug chemoembolization with iodized oil and gelatin sponge, single drug chemoembolization with iodized oil and gelatin sponge, and triple drug chemotherapy infusion with iodized oil but without additional gelatin sponge embolization. Specificity regarding the type of embolization or infusion performed is very important as the terminology vary widely. The Society of Interventional Radiology published recommendations to standardize reporting in 2009 (2).

The current practices in major academic referral centers vary widely between bland embolization alone, chemoembolization with iodized oil, and drug eluting bead chemoembolization, the latter two with or without additional bland embolic. Further variation includes the level of arterial embolization, the chemotherapeutic agents used and their dosage, and the type and amount additional bland embolic used. This wide variability is confirmed in a recent survey published in the *American Journal of Roentgenology* (3).

The study by Shi and co-workers was designed with laudable goals; however, there are some glaring but perhaps unavoidable limitations. As the authors state, the level 1 evidence to support specific transcatheter techniques is lacking and much of practice is based on two randomized studies from 2002 showing survival benefit of chemoembolization over supportive care (4,5). The techniques used in these landmark studies were chemotherapy (doxorubicin in one and cisplatin in the other) mixed with iodized oil followed by gelfoam embolization. Furthermore, patient selection was very strict, thus limiting the study population to patients with early stage HCC. Since those reports, the number of reported techniques has grown and the patient population being targeted for treatment with transcatheter therapies has broadened.

Not only are techniques and patient selection widely variable, but the effectiveness of each element of the treatment regimen remains unclear. The aim of this study was to further elucidate what portion of current techniques leads to tumor response and prolonged survival. Proposed theories include the cytotoxic effects through achieving high intra-tumoral concentration of chemotherapy, the ischemia induced by the bland embolization, or both. Animal models suggest that the mechanism of inducing tumor necrosis in drug eluting bead chemoembolization is related to the high concentration of doxorubicin eluting from the beads rather than the mechanical effects of cessation of blood flow as with bland embolization (6). On the other hand, the mechanism from chemoembolization with iodized oil and bland embolic may relate to both the cytotoxic effects of the

chemotherapy and iodized oil combined with the ischemic effect of the additional embolic.

The study population comprised patients with relatively large median tumor size (10.9 cm), significant percentage with vascular invasion (34.5%), and advanced Barcelona cancer liver clinic (BCLC) stage. In much of the chemoembolization literature, evidence of vascular invasion is considered a relative contraindication and these patients have often been excluded from other studies (4). The current treatment recommendation for advanced BCLC stage patients is sorafenib, although there is growing data supporting use of radioembolization and possibly chemoembolization in this population (7-9).

As would be expected, large tumor size, portal vein tumor thrombus, and advanced stage were significantly associated with poor survival in this study. This limits some of the comparison to the existing literature evaluating treatment in patients with a less advanced stage. It also leads to the unanswered question of where to draw the line with patient selection for transcatheter therapies. When advanced stage patients are targeted in a randomized study, a control arm with sorafenib has been suggested given current treatment recommendations (10). However, to their credit, Shi *et al.* did account for BCLC stage in the multivariable analysis.

Initially, 365 patients enrolled and randomized into each arm with only one significant difference in the number of patients with Hepatitis B. Unfortunately, 30 patients withdrew, 33 stopped due to undefined "technical problems", and 59 stopped due to "contraindications" to chemoembolization.

The methods regarding follow-up and allocation for further treatment is not clearly defined. This lack of standardization is a significant drawback of the trial. Several patients received further chemoembolization off protocol, resection, radiofrequency ablation (RFA), and sorafenib or antiviral therapies [as showed in the second table of the article (1)]. There was a significant difference in the number of on protocol treatment sessions between Arm 1 and Arm 3. Furthermore, there were 58 chemoembolization treatments done off study, which accounts for 10% of the treatments. 14% [33] of the chemoembolization treatments in Arm 1 were off study versus 8% [15] in Arm 3.

Patients thought to be amenable to resection at initial evaluation were excluded from the study. Yet, 33 resections were performed in 34 patients and 59 RFAs were performed, both potentially curative treatments. The authors do not specify how many patients were recipients of the 59 RFAs. While downstaging to curative therapies does occur in practice, including these patients in the study significantly limits the conclusions drawn. The authors concede this fact when stating "if the trial had included patients with less-advanced HCC, a considerable number of patients might have been downstaged to undergo curative treatment (11). The survival of these patients would be largely influenced by the choice of subsequent resection or ablation".

However, 47 potentially curative treatments were still performed in Arm 1. Assuming all treatments were in different patients (not specified in the study) this represents 39% of the patients in Arm 1 versus only 12% (15 treatments) in Arm 3. This difference is explained by "better treatment response" in Arm 1 by the authors, but is only speculative. While the authors stratify patients based on a single tumor versus multiple, the decision to proceed with potentially curative treatment options is complex and often influenced by exact tumor location. The real decisions behind proceeding with resection or RFA are not known.

The authors do concede these limitations in the discussion. Interestingly, patients who received potentially curative therapies were excluded from the time to progression (TTP) analysis, but not from survival outcomes. In their multivariate model, "there was no statistically significant difference in TTP among these three arms". However, it is unclear if the study would have been powered enough or what the results would have been should these patients have been excluded from survival analysis.

Another limitation mentioned by the authors was the relatively large size of the gelatin sponge used, 500-1,000 microns. Smaller particles are typically favored in the United States (3). The authors state they "might be too large and cause only temporary thrombosis." Also, embolization was performed to the point of stasis in the tumor-feeding artery. It should also be mentioned that the endpoint of embolization is also a matter of contention (12,13) with some experts suggesting achieving complete stasis may increase mortality.

In summary, the authors conclude that triple drug chemoembolization with iodized oil and gelatin sponge was more efficacious than single drug with iodized oil and gelatin sponge based on survival, but not superior to triple drug chemoembolization with iodized oil without gelatin sponge. This finding would suggest that the effect of type and/or amount chemotherapy is more important in treatment rather than the embolic effect. The hypothesis is supported by an earlier report from Japan. In that study, however, the chemoembolic agent was zinostatin stimalamer (ZSS), which is a lipophilic drug that forms a stable

solution in iodized oil (14). ZZS may behave in a fashion similar to drug eluting beads, achieving higher intra-tumoral concentrations than other agents mixed with iodized oil. Conversely, an earlier meta-analysis refutes the conclusions of the current study. In that analysis, chemoembolization "was not more effective than [bland embolization], which suggests that the addition of the chemotherapeutic agents currently used does not improve the benefit of therapy and emphasizes the need for more effective anticancer drugs." (15) .

The conclusions should be approached with caution given the significant limitations regarding patient selection, off protocol transcatheter therapies, and potentially curative treatments received by the study population. Clearly, patient BCLC stage and portal vein invasion are independent predictors of poor survival. However, the optimal chemoembolization technique remains unclear. Given many variables in patient selection, drug choice, embolic choice, and technique, we have just begun to scratch the surface of potential research in this rapidly growing area.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Kogut M, Valji K. Optimizing transcatheter therapies for hepatocellular carcinoma: invited editorial regarding "Roles played by chemolipiodolization and embolization in chemoembolization for hepatocellular carcinoma: single-blind, randomized trial". Ann Palliat Med 2013;2(2):56-58. doi: 10.3978/j.issn.2224-5820.2013.04.03

