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Arterial Patency after Repeated Hepatic Artery Bland Particle Embolization

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Abstract

PURPOSE: To evaluate hepatic arterial patency after serial bland particle embolization procedures in patients with hepatocellular carcinoma (HCC).

MATERIALS AND METHODS: All patients with HCC who underwent five or more hepatic artery bland embolization procedures with permanent particulate and spherical embolic agents between September 1996 and December 2007 were retrospectively reviewed. Data analyzed included patient demographics, vessels embolized, embolic agent used, and duration of arterial patency.

RESULTS: Forty-three patients were identified who underwent five or more bland embolization procedures in the same arterial distribution. Of the 43 patients examined, 83% ($n = 36$) showed no change in the hepatic arterial tree after repeated bland embolization (mean treatment period of 48 months $\pm$ 23). Six patients (13%) exhibited occlusion of a fifth-order or more distal vessel after an average of 5 embolizations $\pm$ 2 over a period of 34 months $\pm$ 27. A single case of vascular occlusion of a fourth-order vessel was observed after five embolizations over a period of 52 months.

CONCLUSIONS: Repeated bland embolization of the hepatic arteries in HCC preserves patency of the hepatic arterial vasculature despite the fact that embolization is carried out to complete stasis.

PRIMARY liver cancer is the sixth most common cancer and the third most common cause of cancer death worldwide (1). Primary hepatocellular carcinoma (HCC) accounts for 70%–95% of these cases (2). At the time of presentation, curative therapies for HCC, which include resection, transplantation, and ablative therapies, are possible in only approximately 30%–40% of patients (3), making locoregional therapies and palliative treatments a major focus of clinical care. Hepatic artery embolotherapy with chemotherapy (ie, hepatic artery chemoembolization) or without chemo-therapy (ie, hepatic artery bland embolization) has become the standard of care for unresectable HCC (4). The goal of chemoembolization and bland embolization is to devitalize the tumor while minimizing effect on the underlying liver

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parenchyma. To achieve maximal tumor response and limit disease progression, embolization can be repeated as necessary.

Hepatic artery chemoembolization can lead to vascular changes in the hepatic arterial tree that may reduce the efficacy of repeat treatment (5,6). Arterial occlusion, both proximal and distal, with subsequent development of collateral vessels (7–9), can limit the ability to repeat embolization via conventional hepatic vessels, increasing the complexity and risk of subsequent embolization procedures. Although arterial occlusion after repeated chemoembolization has been reported (10,11), arterial occlusion after bland embolization has not been examined. In this study, we retrospectively reviewed cases of patients with HCC who underwent repeated hepatic artery bland embolization to evaluate the incidence of arterial occlusion after bland particle embolization.

MATERIALS AND METHODS

A waiver of authorization was obtained from our institutional review board for this retrospective study. The database used for this review was registered and approved by our institutional review board in compliance with the Health Insurance Portability and Accountability Act.

Patient and Disease Characteristics

We retrospectively reviewed data from patients with HCC who underwent five or more hepatic artery bland embolization procedures between September 1996 and December 2007. This patient group was chosen in an effort to maximize the likelihood of seeing subsequent arterial occlusions, as the incidence of arterial occlusion is known to increase as a function of the number of earlier embolization sessions (7). During the 136-month period, 53 patients underwent five or more hepatic artery bland embolization procedures. A subset of 43 patients had five or more treatments of the same vascular territory. Patient demographics are shown in Table 1.

To exclude the possibility of a selection bias that could arise in studying patients who underwent five or more hepatic artery bland embolizations, we performed a separate analysis of patients who underwent two to four bland embolization procedures to determine if these patients received fewer embolizations because arterial occlusion limited future embolization. A total of 272 patients underwent two bland embolizations, 121 patients underwent three bland embolizations, and 51 patients underwent four bland embolizations. Of these 444 patients, only four patients could not undergo subsequent embolization as a result of a newly occluded vessel. Of these four patients, three could not undergo embolization as a result of intraprocedural catheter-related dissection or spasm resulting in arterial occlusion. Only one of the 444 patients who underwent two, three, or four bland embolization procedures could not undergo embolization as a result of vascular occlusion from previous embolization.

Bland Particle Embolization

Hepatic artery bland embolization was performed by one of eight experienced, fellowship-trained interventional radiologists according to our previously described technique (12,13). Outcomes and survival for patients with HCC treated with our technique have been

published previously (14). Visceral angiography was performed with 4- or 5-F angiographic catheters to delineate the hepatic arterial anatomy. Vessels supplying the tumor were selectively catheterized with a 3-F microcatheter. Angiography was performed before embolization for tumor targeting and after embolization for treatment monitoring and to document stasis of flow in target vessels. A total of 272 embolizations were performed. Before the availability of spherical embolic agents, patients underwent embolization with 50- μ m polyvinyl alcohol (PVA) particles; by 2002, nearly all patients received spherical embolic agents. Patients whose treatments spanned this transition period received both types of embolic agent. Five patients were embolized with PVA only (Ivalon; Cook, Bloomington, Indiana), 12 with spherical embolic agent only, and 26 with both. In the 108 patients who received PVA, embolization was usually performed with 50- μ m particles; in 12 of these 108, embolization was begun with 50- μ m PVA particles and followed by larger 100- and 200- μ m particles. The majority of patients treated with spherical embolic agents underwent embolization with tris-acryl gelatin micro-spheres (Embosphere; Biosphere Medical, Rockland, Massachusetts), usually beginning with 40–120- μ m microspheres and continuing to 300–500- μ m micro-spheres. In three patients, bland embolization was performed with acrylamide PVA macromer microspheres (Bead Block, Biocompatibles, Surrey, United Kingdom; beginning with 100–300- μ m microspheres). No chemotherapeutic agents or Ethiodol was administered as part of any bland embolization procedure.

Preexisting occlusion of an access vessel (celiac or hepatic artery) was identified in three patients on diagnostic angiography before the first embolization. In these patients, embolization was performed via collateral vessels that reconstituted the proper hepatic artery or by recanalization of the parent vessel.

Data Analysis

In the 43 patients, a total of 272 hepatic artery bland embolization procedures were reviewed, and 249 angio-graphic studies were examined to evaluate changes to the arterial tree after multiple embolization procedures. In the remaining 23 studies, the angiograms obtained before installation of our Picture Archiving and Communication System in 2000 were not available for review, and reports of these earlier procedures and angiograms of subsequent procedures were examined. A hepatic artery was considered occluded as a result of bland embolization if the vessel was present on a previous angiogram but absent on the preembolization angiogram of a subsequent session. Descriptive statistics are expressed as mean $\pm$ SD.

To examine whether the type of embolic agent was a factor in changes to the arterial tree, we compared the statistical distribution of embolic agent used for the subsets of patients in whom (i) vascular changes were observed and (ii) no changes were observed with use of a χ^2 test.

RESULTS

A total of 43 patients underwent five or more hepatic artery bland embolization procedures in the same arterial distribution: 26 patients underwent repeated right hepatic artery embolization, 10 underwent repeated left hepatic artery embolization, and seven underwent

repeated right and left hepatic artery embolization. These patients underwent a total of 272 embolization procedures, averaging 6 embolization procedures $\pm$ 2 during a mean treatment period of 47 months $\pm$ 24. The average interval between embolization treatment sessions was 8.8 months $\pm$ 8.0 (range, 0.6–59 months).

Vascular Effects of Bland Particle Embolization

Thirty-six of 43 patients (83%) showed no change in the hepatic arterial tree after repeated bland embolization (Table 2 and Fig 1). This subset of patients averaged 6 embolizations $\pm$ 2 during a mean treatment period of 48 months $\pm$ 23. The remaining seven patients showed some degree of vascular occlusion. Six patients (13%) demonstrated occlusion of a fifth-order or more distal vessel (Fig 2), occurring after an average of 5 embolizations $\pm$ 2 over a period of 34 months $\pm$ 27. A single case of vascular occlusion of a fourth-order vessel was observed, occurring after five embolizations over a period of 52 months. This patient underwent chemoembolization at an outside hospital before the session in which the occlusion was demonstrated angiographically.

In the 36 patients in whom no change was observed in the hepatic arterial tree with repeated bland embolization, 132 embolizations were performed with Embosphere microspheres, 89 with PVA only, and two with Bead Block (Table 3). In the 7 patients where occlusion was observed in the hepatic arterial tree following repeated bland embolization, 29 embolizations were performed with Embospheres, 19 embolizations with PVA only, and one embolization with Bead Block. To determine if the type of embolic agent was a factor in the vascular occlusion, we compared the statistical distribution of embolic agents used for cases with occlusion to those in which there was no change in the hepatic arterial tree. The statistical distribution of embolic agents used in these two groups was not statistically different ($P < .78$).

DISCUSSION

This study demonstrates that, when repeated hepatic artery bland embolization is performed to complete stasis with the use of “permanent” embolic agents (ie, PVA or microspheres), patency of the hepatic arterial tree is preserved in greater than 80% of patients. In cases in which occlusions did occur, the occlusions were distal within the hepatic arterial tree (ie, fifth-order or smaller vessels). These distal occlusions did not preclude repeat treatment with intraarterial methods, and were of no obvious clinical significance. As the vascular tree was nearly completely preserved despite repeated bland embolization to stasis, treatment was not limited by vascular occlusion that might prevent subsequent embolization.

In this study, the choice of embolic agent (PVA or tris-acryl gelatin micro-spheres) was not a factor in the fourth- and fifth-order branch occlusions that were observed during hepatic artery bland embolization. Similarly, with chemoembolization, it appears as if the particle embolic agent chosen does not play a major role in arterial occlusion either. Geschwind et al (5) reported that there was no significant difference in the rate of arterial patency during chemoembolization when PVA particles or Gelfoam (Pharmacia and Upjohn, Kalamazoo, Michigan) were used for embolization after administration of Lipiodol/chemo-therapeutic agent emulsion (74% with PVA vs 81% with Gelfoam pledgets). However, when PVA/

Lipiodol/chemo-therapeutic agent was administered simultaneously in a slurry, a significant difference was observed, with patency of only 56% of embolized vessels at subsequent chemoembolization procedures. Given the fact that the rate of vascular occlusion after chemoembolization is significantly higher when the chemotherapeutic agent is administered simultaneously with the embolizing agent rather than before it, one might hypothesize that the major factor responsible for vascular occlusion after chemoembolization is not the chemotherapy itself, but rather stasis of chemotherapeutic agent in large vessels. Performing chemoembolization by administering the chemotherapeutic agent, Ethiodol, and the embolic agent simultaneously could exacerbate the occlusive effect of the chemotherapeutic agent given separately by increasing the time that the agent is in contact with the vascular endothelium. The preservation of ante-grade flow and the avoidance of stasis as an endpoint during chemoembolization may serve to mitigate this occlusive effect by washing chemotherapeutic agents away from proximal inflow vessels (15).

Prolonged contact of cytotoxic agents with the vascular endothelium can certainly result in vascular changes, as is seen in patients treated with hepatic arterial infusion of chemotherapeutic agents (16). Intraarterial administration of chemotherapeutic agent alone can result in occlusion of blood vessels whether administered sporadically (17,18) or as a continuous pump infusion, in which cases arteritis and occlusion are seen in as many as 17% of patients (19). Arteritis and arterial occlusion constitute a recognized complication of chemoembolization (6,10,11). It will be informative to see what effect hepatic embolization with drug-eluting beads loaded with chemotherapeutic agent (20,21) have on the hepatic arteries. One might predict that the higher concentration of chemotherapy seen with drug-eluting beads may yield a pattern of occlusion suggesting a chemotherapy-mediated effect rather than an embolic agent-mediated effect.

By preserving patency of the native hepatic arterial tree, the complexity and concomitant risk of embolization via parasitized extrahepatic collateral vessels like the internal mammary artery or phrenic artery (9,22,23) can be reduced. Embolization of these vessels is associated with higher rates of complication and higher rates of nontarget embolization (24,25). After chemoembolization, nonhepatic tumor blood supply is seen in as many as 25% of patients (8). Although parasitic blood flow to hepatic tumors via extrahepatic collateral vessels is not unusual, the development of these vessels as the primary or only source of arterial blood supply to hepatic tumors is related to occlusion of the native hepatic arteries after chemoembolization. Chung et al (7) found that, as the number of chemoembolization sessions increased, the cumulative probability of formation of extra-hepatic collateral vessels also increased. Interestingly, in the present study, the most proximal arterial occlusion that we observed was in a fourth-order vessel, and this occurred in a single patient who underwent chemoembolization at an outside hospital before the bland embolization procedure in which the occlusion was identified. Tumor size (ie, >6 cm), location (ie, subcapsular or bare area of liver), and progression of disease were also factors which increased the chance of extrahepatic collateral vessel formation in their study (7).

Although these embolic agents are considered permanent, vessels embolized with Embosphere microspheres and PVA do recanalize over periods of weeks to months (26,27). In hepatic artery bland embolization, this late recanalization of inflow vessels should not

affect treatment efficacy, as response to treatment after bland embolization is a result of ischemia resulting in cellular death, which manifests as tumor necrosis within hours of embolization (28).

The present study has several limitations. By retrospectively identifying patients who have undergone five or more bland embolization procedures, there is a potential selection bias for patients whose tumors may be smaller or whose biology of disease may be different, resulting in longer survival and greater length of follow-up. The small numbers of patients in the different embolic agent subgroups also limit interpretation of these data. The study population was treated over a period of 136 months, during which time there was a change in practice, with greater use of spherical embolic agents over time; this has the potential to create an interaction in the subgroup analysis. Finally, in 23 of the 272 studies, reports rather than angiograms were reviewed as the Picture Archiving and Communication System did not exist at the time of initial and early embolizations, which could underestimate the true number of arterial occlusions.

In conclusion, repeated hepatic artery bland embolization does not result in any significant change in the hepatic arterial vasculature, despite the fact that embolization is carried out to complete stasis. This has important implications for patients who require repeated palliative transarterial treatment that may span several years. For patients in whom palliative treatment with transarterial therapies are the primary or only remaining therapeutic option, preservation of access to the arterial tree with techniques like bland embolization may be an important consideration in choosing a particular transarterial therapy.

Abbreviations:

HCC	hepatocellular carcinoma
PVA	polyvinyl alcohol

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55:74–108. [PubMed: 15761078]
2. Parkin DM, Ohshima H, Srivatanakul P, Vatanasapt V. Cholangiocarcinoma: epidemiology, mechanisms of carcino-genesis and prevention. *Cancer Epidemiol Biomarkers Prev* 1993; 2:537–544. [PubMed: 8268770]
3. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; 362:1907–1917. [PubMed: 14667750]
4. Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol* 2007; 30:6–25. [PubMed: 17103105]
5. Geschwind JF, Ramsey DE, Cleffken B, et al. Transcatheter arterial chemoembolization of liver tumors: effects of embolization protocol on injectable volume of chemotherapy and subsequent arterial patency. *Cardiovasc Intervent Radiol* 2003; 26:111–117. [PubMed: 12616414]
6. Belli L, Magistretti G, Puricelli GP, et al. Arteritis following intra-arterial chemotherapy for liver tumors. *Eur Radiol* 1997; 7:323–326. [PubMed: 9087350]
7. Chung JW, Kim HC, Yoon JH, et al. Transcatheter arterial chemoembolization of hepatocellular carcinoma: prevalence and causative factors of extrahepatic collateral arteries in 479 patients. *Korean J Radiol* 2006; 7:257–266. [PubMed: 17143029]

8. Miyayama S, Matsui O, Taki K, et al. Extrahepatic blood supply to hepato-cellular carcinoma: angiographic demonstration and transcatheter arterial chemoembolization. *Cardiovasc Intervent Radiol* 2006; 29:39–48. [PubMed: 16328697]
9. Soo CS, Chuang VP, Wallace S, Charnsangavej C, Carrasco H. Treatment of hepatic neoplasm through extrahepatic collaterals. *Radiology* 1983; 147:45–49. [PubMed: 6828758]
10. Bismuth H, Morino M, Sherlock D, et al. Primary treatment of hepatocellular carcinoma by arterial chemoembolization. *Am J Surg* 1992; 163:387–394. [PubMed: 1373044]
11. Xia J, Ren Z, Ye S, et al. Study of severe and rare complications of transarterial chemoembolization (TACE) for liver cancer. *Eur J Radiol* 2006; 59:407–412. [PubMed: 16621394]
12. Brown KT, Nevins AB, Getrajdman GI, et al. Particle embolization for hepatocellular carcinoma. *J Vasc Interv Radiol* 1998; 9:822–828. [PubMed: 9756073]
13. Covey AM, Maluccio MA, Schubert J, et al. Particle embolization of recurrent hepatocellular carcinoma after hepatectomy. *Cancer* 2006; 106:2181–2189. [PubMed: 16596622]
14. Maluccio MA, Covey AM, Porat LB, et al. Transcatheter arterial embolization with only particles for the treatment of unresectable hepatocellular carcinoma. *J Vasc Interv Radiol* 2008; 19:862–869. [PubMed: 18503900]
15. Lewandowski RJ, Wang D, Gehl J, et al. A comparison of chemoembolization endpoints using angiographic versus transcatheter intraarterial perfusion/MR imaging monitoring. *J Vasc Interv Radiol* 2007; 18:1249–1257. [PubMed: 17911515]
16. Charnsangavej C, Kirk IR, Dubrow RA, et al. Arterial complications from long-term hepatic artery chemoinfusion catheters: evaluation with CT. *AJR Am J Roentgenol* 1993; 160:859–864. [PubMed: 8456682]
17. Bledin AG, Kim EE, Chuang VP, Wallace S, Haynie TP. Changes of arterial blood flow patterns during infusion chemotherapy, as monitored by intra-arterially injected technetium 99m macroaggregated albumin. *Br J Radiol* 1984; 57:197–203. [PubMed: 6230133]
18. Forsberg L, Hafstrom L, Lunderquist A, Sundqvist K. Arterial changes during treatment with intrahepatic arterial infusion of 5-fluorouracil. *Radiology* 1978; 126:49–52. [PubMed: 619435]
19. Curley SA, Roh MS, Chase JL, Hohn DC. Adjuvant hepatic arterial infusion chemotherapy after curative resection of colorectal liver metastases. *Am J Surg* 1993; 166:743–746. [PubMed: 8273861]
20. Malagari K, Chatzimichael K, Alexopoulou E, et al. Transarterial chemoembolization of unresectable hepatocellular carcinoma with drug eluting beads: results of an open-label study of 62 patients. *Cardiovasc Intervent Radiol* 2008; 31:269–280. [PubMed: 17999110]
21. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol* 2007; 46:474–481. [PubMed: 17239480]
22. Chung JW, Park JH, Han JK, et al. Transcatheter oily chemoembolization of the inferior phrenic artery in hepatocellular carcinoma: the safety and potential therapeutic role. *J Vasc Interv Radiol* 1998; 9:495–500. [PubMed: 9618112]
23. Hori S, Inoue E, Narumi Y, Fujita M, Kadowaki K. Hepatic arterial embolization in cases of extensive celiac arterial stenosis. *Radiology* 1991; 178:353–355. [PubMed: 1846238]
24. Arora R, Soulen MC, Haskal ZJ. Cutaneous complications of hepatic chemoembolization via extrahepatic collaterals. *J Vasc Interv Radiol* 1999; 10:1351–1356. [PubMed: 10584650]
25. Kim HC, Chung JW, Lee W, Jae HJ, Park JH. Recognizing extrahepatic collateral vessels that supply hepato-cellular carcinoma to avoid complications of transcatheter arterial chemoembolization. *Radiographics* 2005; 25 (Suppl 1):S25–S39. [PubMed: 16227494]
26. Laurent A, Wassef M, Namur J, et al. Recanalization and particle exclusion after embolization of uterine arteries in sheep: a long-term study. *Fertil Steril* 2009; 91:884–992. [PubMed: 18321492]
27. Davidson GS, Terbrugge KG. Histo-logic long-term follow-up after embolization with polyvinyl alcohol particles. *AJNR Am J Neuroradiol* 1995; 16:843–846. [PubMed: 7611054]
28. Vossen JA, Buijs M, Kamel IR. Assessment of tumor response on MR imaging after locoregional therapy. *Tech Vasc Interv Radiol* 2006; 9:125–132. [PubMed: 17561215]

Figure 1.

(a) Initial digital subtraction angiogram of a 78-year-old man who underwent five right and one left hepatic artery bland embolizations. Black arrows point to the common hepatic artery in all four panels. (b) The hepatic arterial tree remains largely unchanged at the sixth bland embolization procedure performed 49 months later. (c) Initial digital subtraction angiogram of a 74-year-old woman who underwent nine right and seven left hepatic artery bland embolizations. (d) The hepatic arterial tree remains largely unchanged at the 12th embolization procedure performed 64 months later.

Figure 2. Digital subtraction angiogram of a 63-year-old man who underwent five right hepatic artery bland embolizations. **(a)** Initial embolization procedure. **(b)** Fifth embolization procedure performed 38 months later. Only a single fifth-order branch of the right hepatic artery that was seen at the initial procedure (**a**, black arrows) had become occluded after five bland embolizations (**b**, gray arrows).

Table 1Patient Demographics (*N* = 43)

Parameter	Value
Sex	
Male	32
Female	11
Race	
White, non-Hispanic	25
Asian	14
Black, non-Hispanic	2
White, Hispanic	2
Etiology of HCC	
Hepatitis B	16
Hepatitis C	7
Hemochromatosis	5
Alcoholic cirrhosis	3
Unknown	12
Age at first embolization (y)	
Mean $\pm$ SD	67 $\pm$ 12
Median	69
Range	22–91
No. of embolization procedures	
5 on right	26
5 on left	10
5 on both right and left	7

Table 2

Arterial Patency after Repeated Hepatic Artery Bland Particle Embolization

Vessel Status	No. of Pts.	Embolization Procedures	Treatment Time Span (mo)
No change	36	6 ± 1	48 ± 23
Occlusion			
First to fourth order	1 *	5	52
Fifth or greater order	6	5 ± 2	34 ± 27

Note.—Values expressed as mean ± SD where applicable.

* Patient underwent chemoembolization at an outside hospital before the session in which the occlusion was identified.

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Table 3
Influence of Embolic Agent on Arterial Patency after Repeated Hepatic Artery Bland Embolization

Patient Group	No. of Embolizations			P Value
	Embosphere	PVA	Bead Block	
No change (<i>n</i> = 36)	132	89	2	.78
Occlusion (<i>n</i> = 7)	29	19	1	