in vivo *34*: 2763-2768 (2020)
doi:10.21873/invivo.12100

Combination of 1st and 2nd Week Dosing of Glass Yttrium-90 Microspheres for Superselective Radioembolization

HYO-CHEOL KIM[1], MYUNGSU LEE[1], JEONG-HOON LEE[2], JIN CHUL PAENG[3], YOON JUN KIM[2] and JIN WOOK CHUNG[1]

[1]Department of Radiology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [2]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Department of Nuclear Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea

Abstract. *Background/Aim: The aim of this study was to address the feasibility of combination of 1st and 2nd week dosing of glass microspheres in the setting of selective radioembolization for large hepatocellular carcinoma (HCC). Patients and Methods: Yttrium-90 radioembolization was performed in 53 patients with single nodular hepatocellular carcinomas larger than 5 cm. A total of 32 patients underwent radioembolization with glass microspheres from a single calibration date (single-dosing group), and 21 patients were treated with a combination of 1st and 2nd week dosing of glass microspheres (combined-dosing group). In the combined-dosing group, the lobar hepatic arteries and subsidiary tumor-feeding arteries were commonly treated with 1st and 2nd week dosing of glass microspheres, respectively. Results: The combined-dosing group tended to have a lower frequency of pain requiring analgesics without statistical significance (p=0.085). The objective response rate at 3 months in single-dosing group and combined-dosing group was 46.9% (15 out of 32) and 66.7% (14 out of 21), respectively. Conclusion: The combined 1st and 2nd week dosing of glass microspheres demonstrated an acceptable toxicity and tumor response when both a lobar hepatic artery and a small tumor-feeding artery need to be treated in one session.*

Correspondence to: Hyo-Cheol Kim, MD, Department of Radiology, Seoul National University Hospital, #101 Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea. Tel: +82 220722584, Fax: +82 27436385, e-mail: angiointervention@gmail.com

Key Words: Radioembolization, hepatocellular carcinoma.

Radioembolization with yttrium-90 microspheres is a safe and potent treatment for patients with hepatocellular carcinoma (HCC) (1). Glass microspheres (TheraSphere, Boston Scientific, Natick, MA, USA) and resin microspheres (SIR-Spheres, Sirtex Medical, Lane Cove, Australia) are the two yttrium-90 radioembolization products that are commercially available. Glass microspheres have a higher activity per sphere and require fewer particles than what is the case with resin microspheres (2). With standard glass microsphere dosimetry, patients are commonly treated 3~5 days after calibration date, (i.e., using late 1st week dosing). Radiation segmentectomy delivers an ablative dose of radiation to the affected segment, which results in improved progression-free survival compared to selective chemoembolization (3, 4). Radiation segmentectomy is commonly adopted for small HCC involving one or two segments (3, 4). Even for large HCC, boosted radioembolization in selective fashion can provide a promising outcome and acceptable toxicity (5). However, large tumors are commonly fed by multiple hepatic arteries as well as extrahepatic collateral arteries (6, 7). In addition, since perfused tissue volume of each tumor-feeding artery may have an extremely wide range between dozens to hundreds of milliliters, glass microspheres of both extremely low activity for small tumor-feeding branches and high activity for main tumor-feeding branches may be beneficial. In such situations, a combination of 1st and 2nd week dosing of glass microspheres may be suitable to adjust the activity where needed. The purpose of this report was to assess the feasibility of combination of 1st and 2nd week dosing of glass microspheres in the setting of selective radioembolization for large HCCs.

Patients and Methods

Patients. The institutional review board approved of this retrospective study and permitted the waiving of informed consent. From November 2015 to September 2020, 242 patients with HCC underwent yttrium-

Table I. *Baseline characteristics of 53 patients with hepatocellular carcinoma.*

	Total 53 patients	Single dosing group (n=32)	Combined dosing group (n=21)	*p*-Value
Gender				
Male	45	27	18	1.0
Female	8	5	3	
Age, mean±SD (year)	65.8±11.9	66.7±10.3	64.7±14.5	0.59
Etiology				
HBV	29	17	12	1.0
HCV	4	3	1	
Non-viral	20	12	8	
Albumin, mean±SD (g/dl)	4.0±0.5	4.0±0.5	4.0±0.5	0.82
Total bilirubin, mean±SD (mg/dl)	0.7±0.3	0.7±0.4	0.7±0.2	0.86
INR, mean±SD	1.02±0.08	1.04±0.08	0.99±0.07	0.01
Platelet, mean±SD (billion/l)	218.6±95.4	203.8±84.6	240.6±107.7	0.17
Child-Pugh class				
A5	42	27	15	0.31
A6	10	4	6	
B9	1	1	0	
Tumor size				
mean±SD (cm)	9.6±3.4	8.7±2.8	11.1±3.8	0.01
Size <5 cm-≤10 cm	29	22	7	
Size >10 cm	24	10	14	
Tumor extent				
Unilobar	39	27	12	0.054
Bilobar	14	5	9	
Extrahepatic collateral arteries				
Present	18	5	13	0.001
Absent	35	27	8	
AFP				
≤200 ng/ml	39	21	18	0.12
>200 ng/ml	14	11	3	
Total liver volume (ml)	1,612±547	1457±359	1850±693	0.024
Treated liver volume (ml)	1014±525	890±379	1204±657	0.031
Administered activity (GBq)	4.71±2.10	3.92±1.55	5.92±2.27	0.001
Target tissue dose (Gy)	236.8±104.6	215.1±85.3	269.9±123.5	0.061

AFP, Alpha-fetoprotein.

90 radioembolization using glass microspheres at the Authors' Institution. Inclusion criteria for this study were: i) single nodular tumor and ii) tumor diameter larger than 5 cm. Exclusion criteria for this study were: i) infiltrative tumor or multinodular tumor, ii) tumor diameter of 5 cm or less, iii) BCLC stage C or D, and iv) previous treatment for HCC. Among the 242 patients, 53 (21.9%) patients (45 men and 8 women; mean age of 65.8 years; range=33-85 years) met the inclusion and exclusion criteria (Table I and Figure 1). The median tumor diameter was 9.2 cm (mean=9.6 cm; range=5.1-18.4 cm).

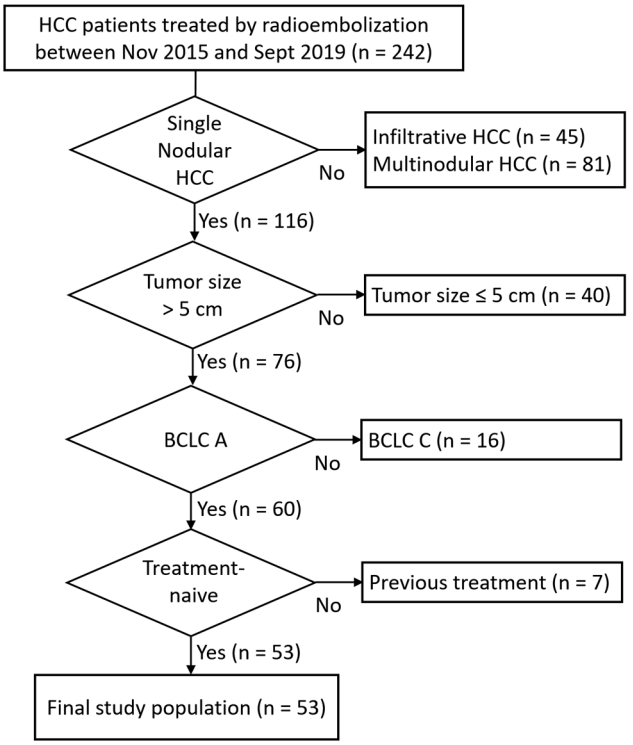

Figure 1. *Flowchart of the study population.*

Yttrium-90 radioembolization. The protocols of radioembolization have been described in previous studies (5, 8, 9). All the procedures were performed by two interventional radiologists (H.C.K with 12 years of experience in interventional oncology, M.L. with seven years of experience). When there was no small tumor-feeding branch requiring treatment in a selective fashion, the patients were commonly treated with late 1st week dosing or early 2nd week dosing of glass microspheres from a single calibration date (single-dosing group). When the operator decided to treat a small tumor-feeding branch in a superselective fashion, the patients were usually treated with combination of late 1st week and late 2nd week dosing of glass microspheres (combined-dosing group). Whereas the main tumor-feeding arteries and lobar hepatic arteries were commonly treated with late 1st week dosing of glass microspheres, subsidiary tumor-feeding arteries and extrahepatic collateral arteries were usually treated with late 2nd week dosing of glass microspheres (Figures 2 and 3). The segmental and subsegmental arteries were commonly catheterized using a 1.7-Fr microcatheter (Carnelian 1.7; Tokai Medical Products, Kasugai, Japan), 1.8-Fr microcatheter (Carnelian 1.8), or 1.9-Fr microcatheter (Radiostar; Taewoong Medical, Gimpo, Republic of Korea), and the lobar arteries using a 2.4-Fr or 2.8-Fr microcatheter.

The dose calculation was based on the medical internal radiation dose (MIRD) method recommended by the manufacturer of glass microspheres. Total liver volume and treated tissue volume were measured by volume analysis software (IntelliSpace Portal, version 7, Philips Healthcare, Cleveland, OH, USA).

Analysis. Two radiologists (H.C.K. and M.L.) retrospectively reviewed imaging studies until January 2020 independently and

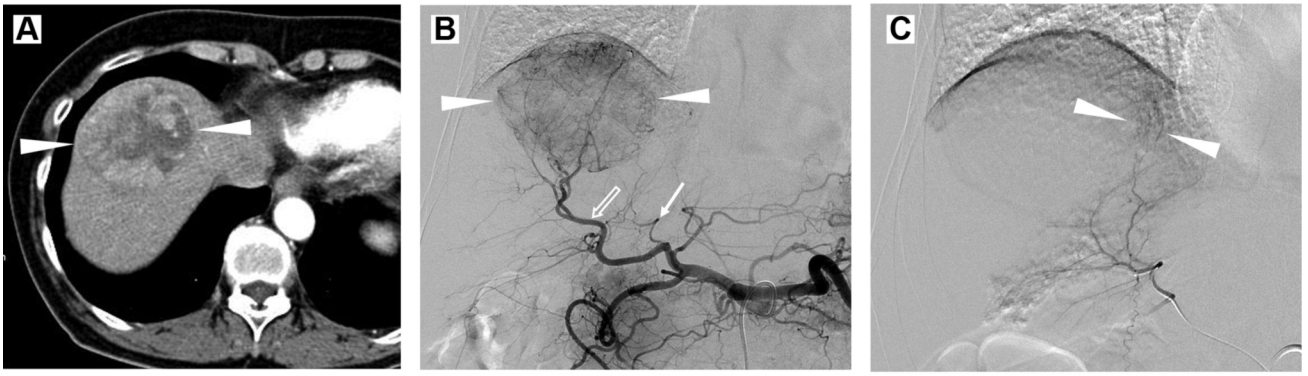

Figure 2. *A 66-year-old woman with hepatocellular carcinoma. (A) Axial CT image of the arterial phase shows a 6.1 cm sized hypervascular tumor (arrowheads). (B) Celiac angiogram shows a hypervascular tumor (arrowheads) which is supplied by the right anterior hepatic artery (open arrow) and middle hepatic artery (arrow). A total of 8 GBq of 1st week dosing was administered at the right anterior hepatic artery. (C) Middle hepatic angiogram shows a small tumor blush (arrowheads). A total of 4 GBq of 2nd week dosing was administered at the distal middle hepatic artery.*

disagreements were resolved in consensus. The injection level of radioactive microspheres was classified into lobar, segmental, and subsegmental. If microspheres were infused into extrahepatic collateral arteries, such as the right inferior phrenic artery (RIPA), the injection level was recorded as subsegmental.

Tumor response was determined by the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (10). Toxicity was graded using the Common Terminology Criteria for Adverse Events version 4.03 (11). For biochemical toxicities, adverse events of grade 3 or more severe were recorded. Clinical and biochemical toxicities were recorded for 90 days after radioembolization. Benign biliary stricture was recorded until the last follow-up. The Fischer's exact test and *t*-test were used to compare the categorical and continuous variables between the two groups. Local progression-free survival for the primary index tumor was evaluated by Kaplan-Meier curves. If patients received surgical resection of the primary target tumor, local progression-free survival was censored at the day of operation.

Results

Radioembolization procedure. Among 53 patients, 32 patients underwent radioembolization with glass microspheres of single calibration date (single-dosing group), and 21 patients were treated with combined 1st and 2nd week dosing of glass microspheres (combined-dosing group). The combined-dosing group had larger tumors and higher administered radiation activity than the single-dosing group (Table I). Extrahepatic collateral arteries supplied the tumor in 18 (34%) patients, including RIPA (n=14), left inferior phrenic artery (n=2), inferior adrenal artery (n=1), and RIPA, adrenal artery and renal capsular artery (n=1).

Mean total liver volume was 1,612±547 ml (median=1,517 ml; range=913-3,600 ml). Mean treated liver volume was 1,014±525 ml (median=909 ml; range=300-2,800 ml). Mean total infused radiation activity was 4.71±2.1 GBq (median=4.25 GBq; range=1.35-10.39 GBq). Lastly, the mean target perfused tissue dose was 236.8±104.6 Gy (median=222.6 Gy; range=83.5-694.7 Gy).

Table II. *Toxicity from radioembolization in 53 patients with hepatocellular carcinoma.*

	Total patients (n=53)	Single dosing group (n=32)	Combined dosing group (n=21)	CTCAE grade				
				1	2	3	4	5
Clinical toxicity								
Pain	21 (40%)	16	5		21			
Fever	3 (6%)	2	1	2	1			
Abscess	1 (2%)	1	0			1		
General weakness	1 (2%)	1	0		1			
Benign biliary stricture	8 (15%)	6	2	4		4		
Ascites	1 (2%)	1	0			1		
Pneumocystis pneumonia	1 (2%)	1	0					1
Biochemical toxicity								
Increased AST	11 (21%)	8	3			8	3	
Increased ALT	6 (11%)	5	1			4	2	
Increased total bilirubin	2 (4%)	2				2		

Mean number of vials used per treatment was 3.36±1.4 (median=3; range=1-6). One vial (n=5), 2 vials (n=12), 3 vials (n=12), 4 vials (n=11), 5 vials (n=9), and 6 vials (n=4) were infused in 53 patients. A total of 178 vials were injected at the lobar artery (n=33, 18.6%), segmental artery (n=114, 64.0%), and subsegmental artery (n=31, 17.4%).

Toxicity and tumor response. Clinical and biochemical toxicities are summarized in Table II. Twenty one (40%) patients complained of abdominal/chest pain requiring

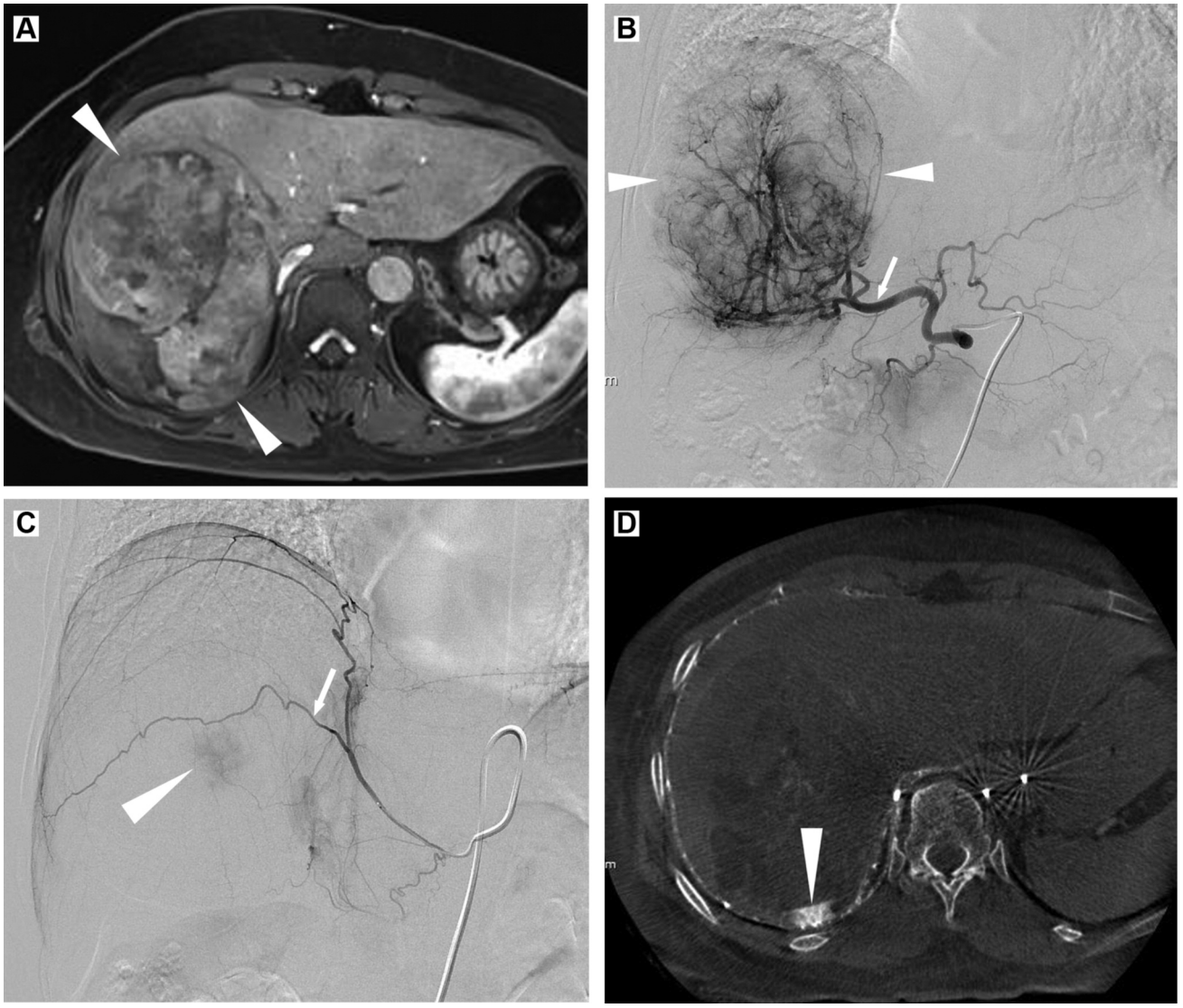

Figure 3. *A 64-year-old woman with hepatocellular carcinoma. (A) Axial MR image shows an 11.3 cm sized hypervascular tumor (arrowheads). (B) Common hepatic angiogram shows a large tumor blush (arrowheads). A total of 15 GBq of 1st week dosing was administered at the right hepatic artery (arrow). (C) Right inferior phrenic angiogram shows a small tumor blush (arrowhead). A total of 3 GBq of 2nd week dosing was administered at the posterior branch (arrow) of right inferior phrenic artery. (D) Axial image of cone-beam CT obtained at the right inferior phrenic artery confirms the presence of tumor part (arrowhead) supplied by the right inferior phrenic artery.*

analgesics during and/or after the procedure (CTCAE grade 2). The combined-dosing group tended to have a lower frequency of pain requiring analgesics without statistical significance (p=0.085). Eight (15%) patients had intrahepatic bile duct dilation, which was noted on CT scans 3~6 months after radioembolization. One patient died of pneumocystitic carinii pneumonia 9 weeks after radioembolization.

Tumor response is summarized in Table III. The complete response rate was 11.3% (6 out of 53) at 1 month and 32% (17 out of 53) at 3 months. The objective response rate at 3 months in single-dosing group and combined-dosing group was 46.9% (15 out of 32) and 66.7% (14 out of 21), respectively. A total of 17 patients underwent surgical resection (n=14) or chemoembolization (n=3) without tumor progression within 3 months.

Discussion

Glass microspheres (TheraSphere®) have a wide range of dosing from 3-20 GBq at calibration with 0.5 GBq increment. Thus, standard glass microsphere radioembolization at the lobar hepatic artery can be performed with a single calibration

Table III. *Tumor response by mRECIST in 53 patients with hepatocellular carcinoma.*

Tumor response	1-month response			3-month response		
	Total patients (n=53)	Single dosing group (n=32)	Combined dosing group (n=21)	Total patients (n=53)	Single dosing group (n=32)	Combined dosing group (n=21)
CR	6 (11.3%)	6 (18.8%)	0	17 (32.0%)	11 (34.4%)	6 (28.6%)
PR	28 (52.8%)	18 (56.3%)	10 (47.6%)	12 (22.6%)	4 (12.5%)	8 (38.1%)
SD	18 (34.0%)	7 (21.9%)	11 (52.4%)	4 (7.5%)	1 (3.1%)	3 (14.3%)
PD	0	0	0	1 (1.9%)	1 (3.1%)	
Not applicable	1 (1.9%)	1 (3.1%)	0	19 (35.8%)	15 (46.9%)	4 (19.0%)
No follow-up image	1 (1.9%)	1 (3.1%)	0	1 (1.9%)	1 (3.1%)	
Other treatment*				17 (32.0%)	13 (40.6%)	4 (19.0%)
Expired				1 (1.9%)	1 (3.1%)	

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease. *Not applicable due to surgical resection (n=14) or chemoembolization without tumor progression (n=3) within 3 months.

date and by adjusting treatment schedules of either late 1st week or early 2nd week dosing (12, 13). Since a 20GBq vial has 6.7-times stronger activity than a 3 GBq vial, it was possible to treat both the lobar and segmental artery at the same time (14).

When treatment through both a small tumor-feeding artery and a lobar hepatic artery is needed, there are two treatment plans with single calibration dosing. First, 3 GBq vial of late 2nd week dosing is infused into a small tumor-feeding artery, and multiple large vials of late 2nd week dosing are infused into a lobar hepatic artery. In this situation, a higher number of glass microspheres may be administered into a lobar artery, which might result in arterial flow stasis, gastrointestinal ulcers or abdominal pain due to the embolic effect. Second, a single large vial of late 1st week or early 2nd week dosing is infused into a lobar artery, and a 3 GBq vial of late 1st week or early 2nd week dosing is infused into a small tumor-feeding artery. In this option, a 3 GBq vial may generate excessive radiation activity in a small treated volume, which might cause focal hepatic radiation necrosis (15). To overcome these potential issues, combined usage of 1st week and 2nd week dosing may be useful in these situations. Late 1st week dosing into the lobar artery can have enough radiation activity without embolic complication, and late 2nd week dosing into a small tumor-feeding artery can prevent potential hepatic radiation necrosis.

The expected benefit of combining 1st and 2nd week dosing is to broaden the radiation activity spectrum of the glass microspheres, which allows treatment of a wide range of target tissue volume with a single vial at each target vessel in one session. Thus, in superselective radioembolization for large tumors supplied by both large and small vessels, the number of vials required can be reduced, and complications such as non-target treatment and hepatic radiation necrosis can be prevented. Its potential disadvantages include i) limitation of treatment schedule to late week day, and ii) small number of microspheres for main tumor-feeding vessels because 2nd week dosing cannot be used for main tumor-feeding vessels.

This study population showed feasibility of combined 1st and 2nd week dosing of glass microspheres with an acceptable toxicity profile. In terms of tumor response, 14 (66.7%) out of 21 patients of combined-dosing group showed complete response or partial response on 3-month imaging by mRECIST, which is thought to be a favorable outcome considering the large tumor size involved (mean=11.1cm).

There are several limitations to this study. First, because baseline characteristics such as the tumor size were different between the two groups and the patient population was relatively small, comparison of complication rates and tumor response between the two groups was not evaluated. Combined-dosing may be applied only when radioembolization through a small tumor-feeding artery is needed, thus comparison between two groups may not be needed. Second, the indication of combined-dosing was not defined objectively. The authors had tried to perform superselective radioembolization in most cases, thus, combined-dosing treatment might have been overused in this study population. Third, the mean target perfused tissue dose was 236.8 Gy in this study, which means that radiation segmentectomy or boosted radioembolization was performed in most cases. Thus, combined-dosing treatment might be needed less frequently for the treatment of multifocal disease by a standard dose (120 Gy).

In conclusion, the combined 1st and 2nd week dosing of glass microspheres demonstrated acceptable toxicity and tumor response when both a lobar hepatic artery and a small tumor-feeding artery need to be treated in one session.

Conflicts of Interest

The Authors have no conflicts of interest with regard to the present study.

Authors' Contributions

Guarantor of integrity of the entire study: Hyo-Cheol Kim, Jin Wook Chung. Study concept and design: Hyo-Cheol Kim. Literature search: Hyo-Cheol Kim, Jeong-Hoon Lee, Jin Chul Paeng. Clinical studies: Hyo-Cheol Kim, Myungsu Lee, Jeong-Hoon Lee, Yoon Jun Kim, Jin Chul Paeng, Jin Wook Chung. Data analysis: Hyo-Cheol Kim, Jeong-Hoon Lee, Jin Chul Paeng. Stastitical analysis: Hyo-Cheol Kim, Myungsu Lee, Yoon Jun Kim. Manuscript preparation: Hyo-Cheol Kim. Manuscript editing: Myungsu Lee, Jeong-Hoon Lee, Yoon Jun Kim, Jin Chul Paeng, Jin Wook Chung.

References

1 Padia SA, Lewandowski RJ, Johnson GE, Sze DY, Ward TJ, Gaba RC, Baerlocher MO, Gates VL, Riaz A, Brown DB, Siddiqi NH, Walker TG, Silberzweig JE, Mitchell JW, Nikolic B, Salem R and Society of Interventional Radiology Standards of Practice Committee: Radioembolization of hepatic malignancies: background, quality improvement guidelines, and future directions. J Vasc Interv Radiol *28(1)*: 1-15, 2017. PMID: 27836405. DOI: 10.1016/j.jvir.2016.09.024

2 Salem R and Thurston KG: Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: Technical and methodologic considerations. J Vasc Interv Radiol *17(8)*: 1251-1278, 2006. PMID: 16923973. DOI: 10.1097/01.RVI.0000233785.75257.9A.

3 Padia SA, Johnson GE, Horton KJ, Ingraham CR, Kogut MJ, Kwan S, Vaidya S, Monsky WL, Park JO, Bhattacharya R, Hippe DS and Harris WP: Segmental yttrium-90 radioembolization *versus* segmental chemoembolization for localized hepatocellular carcinoma: results of a single-center, retrospective, propensity score-matched study. J Vasc Interv Radiol *28(6)*: 777-785, 2017. PMID: 28365172. DOI: 10.1016/j.jvir.2017.02.018

4 Biederman DM, Titano JJ, Korff RA, Fischman AM, Patel RS, Nowakowski FS, Lookstein RA and Kim E: Radiation segmentectomy *versus* selective chemoembolization in the treatment of early-stage hepatocellular carcinoma. J Vasc Interv Radiol *29(1)*: 30-37, 2018. PMID: 29169782. DOI: 10.1016/j.jvir.2017.08.026

5 Kim HC, Kim YJ, Lee JH, Suh KS and Chung JW: Feasibility of boosted radioembolization for hepatocellular carcinoma larger than 5 cm. J Vasc Interv Radiol *30(1)*: 1-8, 2019. PMID: 30293734. DOI: 10.1016/j.jvir.2018.07.002

6 Kim HC, Chung JW, Lee W, Jae HJ and Park JH: Recognizing extrahepatic collateral vessels that supply hepatocellular carcinoma to avoid complications of transcatheter arterial chemoembolization. Radiographics *25(Suppl)1*: S25-39, 2005. PMID: 16227494. DOI: 10.1148/rg.25si055508

7 Chung JW, Kim HC, Yoon JH, Lee HS, Jae HJ, Lee W and Park JH: Transcatheter arterial chemoembolization of hepatocellular carcinoma: prevalence and causative factors of extrahepatic collateral arteries in 479 patients. Korean J Radiol *7(4)*: 257-266, 2006. PMID: 17143029. DOI: 10.3348/kjr.2006.7.4.257

8 Choi JW, Yoo MY, Kim HC, Paeng JC, Kim YJ and Chung JW: Prophylactic temporary occlusion of the cystic artery using a fibered detachable coil during 90Y radioembolization. Cardiovasc Intervent Radiol *40(10)*: 1624-1630, 2017. PMID: 28500460. DOI: 10.1007/s00270-017-1688-z

9 Kim HC, Kim YJ, Paeng JC and Chung JW: Yttrium-90 radioembolization of the right inferior phrenic artery in 20 patients with hepatocellular carcinoma. J Vasc Interv Radiol *29(4)*: 556-563, 2018. PMID: 29373246. DOI: 10.1016/j.jvir.2017.10.010

10 Lencioni R and Llovet JM: Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis *30(1)*: 52-60, 2010. PMID: 20175033. DOI: 10.1055/s-0030-1247132

11 National Cancer Institute. Common Terminology Criteria for Adverse Events. Version 4.03. 2010. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm [Last accessed November 14, 2016]

12 Salem R, Padia SA, Lam M, Bell J, Chiesa C, Fowers K, Hamilton B, Herman J, Kappadath SC, Leung T, Portelance L, Sze D and Garin E: Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. Eur J Nucl Med Mol Imaging *46(8)*: 1695-1704, 2019. PMID: 31098749. DOI: 10.1007/s00259-019-04340-5

13 Lewandowski RJ, Minocha J, Memon K, Riaz A, Gates VL, Ryu RK, Sato KT, Omary R and Salem R: Sustained safety and efficacy of extended-shelf-life (90)Y glass microspheres: long-term follow-up in a 134-patient cohort. Eur J Nucl Med Mol Imaging *41(3)*: 486-493, 2014. PMID: 24114004. DOI: 10.1007/s00259-013-2575-8

14 Arslan B, Padela MT, Madassery S, Masrani A, Tasse J, Supanich M and Ahmed O: Combination ipsilateral lobar and segmental radioembolization using glass yttrium-90 microspheres for treatment of multifocal hepatic malignancies. J Vasc Interv Radiol *29(8)*: 1110-1116, 2018. PMID: 30055781. DOI: 10.1016/j.jvir.2018.04.005

15 Joo I, Kim HC, Kim GM and Paeng JC: Imaging evaluation following 90Y radioembolization of liver tumors: What radiologists should know. Korean J Radiol *19(2)*: 209-222, 2018. PMID: 29520178. DOI: 10.3348/kjr.2018.19.2.209

Received May 27, 2020
Revised June 15, 2020
Accepted June 16, 2020