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

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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.

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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).

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 from a single calibration date (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

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

|                        | Total (n=53) | 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 (mg/dl)   | 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                     | 11.4±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   | 1,457±359                   | 1,850±693                     | 0.024   |
| Treated liver volume (ml)| 1,014±525   | 890±379                     | 1,204±657                     | 0.031   |
| Administered activity (GBq)| 4.7±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.

Figure 1. Flowchart of the study population.

HCC patients treated by radioembolization between Nov 2015 and Sept 2019 (n = 242)

- Single Nodular HCC
  - Infiltrative HCC (n = 45)
  - Multinodular HCC (n = 81)
  - Yes (n = 116)
  - No

- Tumor size > 5 cm (n = 40)
  - Yes (n = 76)
  - No

- BCLC A
  - Yes (n = 60)
  - No

- Treatment-naive
  - Yes (n = 53)
  - No

- Previous treatment (n = 7)
  - Yes

In Table I, B. C. C. is described as stage C or D, and previous treatment for HCC is included in the exclusion criteria. The median tumor diameter was 9.2 cm (mean=9.6 cm; range=5.1-18.4 cm).
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).

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

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

| CTCAE grade | Total patients (n=53) | Single dosing group (n=32) | Combined dosing group (n=21) |
|-------------|-----------------------|-----------------------------|-----------------------------|
| 1 | 2 | 3 | 4 | 5 |
| Clinical toxicity | | | | | |
| Pain | 21 (40%) | 16 | 5 | 21 |
| Fever | 3 (6%) | 2 | 1 | 2 |
| 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 | | | |
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.
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 3 GBq vial of late 1st week or early 2nd week dosing is infused into a lobar hepatic artery. This in 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 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.

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

| Tumor response | 1-month response | 3-month response |
|----------------|------------------|------------------|
|                | Total patients   | Single dosing group | Combined dosing group | Total patients   | Single dosing group | Combined dosing group |
|                | (n=53)           | (n=32)            | (n=21)            | (n=53)           | (n=32)            | (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.
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. Statistical 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.

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