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Radioembolization-induced Tumor Calcifications as a Surrogate Marker of Tumor Response in Patients With Hepatocellular Carcinoma

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Abstract. *Background/Aim: Tumoral calcification after chemotherapy or radiation therapy has been reported in various cancer patients, but not after radioembolization. The purpose of this study was to evaluate the prognostic value of radioembolization-induced tumor calcification of hepatocellular carcinoma (HCC) treated by radioembolization. Patients and Methods: This retrospective study comprised patients with single nodular HCC who underwent yttrium-90 radioembolization between November 2015 and April 2019. The presence of tumoral calcification was visually assessed on a follow-up computed tomography (CT) scan. Results: Fifty-five patients (64.8±11.8 years, 43 men) were evaluated. Tumoral calcification was present in 21 (38.2%) of 55 patients in the one-month CT scan (calcification group). The complete response rate for the primary index tumor was 72.7% (40 of 55) in the total study population, and 100% (21 of 21) in the calcification group, respectively. The calcification group had a longer local progression-free survival rate than the non-calcification group (p=0.017). Conclusion: Radioembolization-induced tumoral calcification is relatively common and can be used as an early surrogate marker of complete response.*

Radioembolization with yttrium-90 microspheres is increasingly used for hepatocellular carcinoma (HCC) patients with similar overall survival, longer time-to-progression, and higher quality of life compared to chemoembolization (1, 2). To assess tumor response after locoregional therapy, European Association for the Study of the Liver and modified response evaluation criteria in solid tumors (mRECIST) guidelines are commonly adopted (3, 4), considering the enhancing portion of the tumor in the arterial phase. Whereas chemoembolization is generally associated with an immediate tumoricidal effect related to ischemic necrosis, radioembolization has slower effects of radiation on tumor necrosis, resulting in persistent tumoral enhancement in the early period (5, 6). Therefore, differentiation of a non-responding viable tumor from the well-responding tumor is often challenging on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) in HCC patients treated with radioembolization. To overcome this problem and predict tumor response at an early follow-up period, the role of diffusion-weighted MRI and ^{18}F-fluoroethylcholine positron emission tomography was investigated (7, 8).

Irradiated tumors or normal tissues have been reported to have delayed calcification (9). Tumoral calcification after chemotherapy has also been reported in patients with glioblastoma, colorectal liver metastases, and ovarian cancer (10-14). It has been reported that tumoral calcification occurs in up to 28% of hepatic colorectal metastases after chemotherapy and implies better prognosis (13, 14). To our knowledge, however, tumoral calcification after radioembolization for HCC has not been reported. Therefore, the purpose of this study was to evaluate the incidence and prognostic value of tumoral calcification in HCC patients treated with radioembolization.

Patients and Methods

Patients. The institutional review board approved this retrospective study and permitted the waiving of informed consent. From November 2015 to April 2019, 210 patients with HCC underwent yttrium-90 radioembolization using glass microspheres (TheraSphere; BTG,

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London, UK). Inclusion criteria were: i) single nodular HCC and ii) an available follow-up CT scan within two months after radioembolization. Exclusion criteria were: i) multinodular or infiltrative HCC, ii) previous conventional chemoembolization, iii) surgical resection or conventional chemoembolization of the primary target tumor within six months, and iv) follow-up loss within six months. Among the 210 patients, 55 met the inclusion and exclusion criteria. Thirteen of the 55 patients have been previously reported (15). This prior article dealt with the feasibility of boosted radioembolization for HCC, whereas in this manuscript we report on the prognostic value of tumoral calcification after radioembolization for HCC.

Yttrium-90 radioembolization. All 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). Radioembolization was performed with yttrium-90 glass microspheres, and the detailed protocol was described in the previous studies (15-17). Follow-up imaging (contrast-enhanced CT or magnetic resonance imaging) took place one month after radioembolization, and every 2-3 months thereafter. CT scans were obtained using various CT scanners and included precontrast, hepatic arterial phase, portal venous phase, and equilibrium phase images (18).

Analysis. Two radiologists (H.C.K., and I.J. with 10 years of experience in liver imaging) retrospectively reviewed the CT scans independently, and disagreement was resolved by consensus. Preprocedural and postprocedural CT images were retrospectively reviewed with an emphasis on tumoral calcification and tumor response.

The presence of tumoral calcification was visually assessed and was recorded as "present" when parts within the tumor showed higher attenuation than normal liver on precontrast CT images. When tumoral parts that had higher attenuation than normal liver showed lower attenuation than normal liver on further follow-up CT scan, it was considered an intratumoral hemorrhage rather than calcification. The shape of tumoral calcification was classified as spotty, rim-like, or diffuse. The extent of tumoral calcification was divided into less than 50% and more than 50% of tumors. The presence of tumor calcification was recorded on one-month CT scans (first follow-up CT scan) and CT scans around six months after radioembolization. According to the presence or absence of tumoral calcification on one-month CT scans, patients were classified into calcification and non-calcification groups.

Baseline characteristics between the calcification group and non-calcification group were compared using the Chi-square test or the independent *t*-test. Tumor response was assessed by mRECIST (4). The Kaplan-Meier method and log-rank test were used to compare local progression-free survival for the primary index tumor depending on the presence of tumoral calcification. To identify factors affecting local progression-free survival, baseline characteristics and treatment factors were evaluated using the Cox proportional hazard model. A *p*-value less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with SPSS version 25.0 software (SPSS Inc. Chicago, IL, USA).

Results

Patient demographics. Fifty-five patients [43 men and 12 women; mean age=64.8±11.8 years (range=33-89 years)] comprised our study population (Figure 1). The demographic characteristics of our study population are summarized in Table I. The mean tumor size was 6.5±4.0 cm. The mean total radiation activity infused was 3.25±2.1 GBq (median=3.53 GBq; range=0.2-9.15 GBq). The mean target perfused tissue dose was 264.8±110.6 Gy (median=248.0 Gy; range=80.8-536.2 Gy).

Table I. *Baseline characteristics of 55 patients with hepatocellular carcinoma*.

	All patients (n=55)	Calcification on 1-month CT		*p*-Value
		Present (n=21)	Absent (n=34)	
Gender				0.75
Male	43	17	26	
Female	12	4	8	
Age, mean±SD (years)	64.8±11.8	61.2±9.8	67.0±12.6	0.08
Etiology				0.09
HBV	31	11	20	
HCV	6	4	2	
HBV & HCV	2	2	0	
Non-viral	16	4	12	
Albumin, mean±SD (g/dl)	4.1±0.5	4.2±0.4	4.0±0.5	0.09
Total bilirubin, mean±SD (mg/dl)	0.7±0.3	0.7±0.3	0.7±0.3	0.85
Prothrombin time INR, mean±SD	1.04±0.09	1.03±0.09	1.04±0.10	0.89
Platelet, mean±SD (billion/l)	191.8±101.5	173.7±128.3	203.0±80.9	<0.01
Child-Pugh class				0.61
A5	47	19	28	
A6	7	2	5	
B7	1	0	1	
Tumor size				
Mean±SD (cm)	6.5±4.0	4.5±3.3	7.7±4.0	0.003
≤5 cm	23	13	10	
>5 cm	32	8	24	
Tumor extent				0.104
Unilobar	43	19	24	
Bilobar	12	2	10	
AFP				0.029
≤200 ng/ml	40	19	21	
>200 ng/ml	15	2	13	
Radiation activity administered (GBq)	3.25±2.1	2.50±2.0	3.71±2.5	0.039
Target perfused tissue dose (Gy)	264.8±110.6	277.2±95.4	257.2±119.8	0.52

AFP: Alpha-fetoprotein; CT: computed tomography.

Tumoral calcification. The mean time interval between radioembolization and first follow-up CT scan (one-month CT scan) was 26.9±7.8 days (median=24 days; range=14-47 days). Tumoral calcification was present in 21 (38.2%) of 55 patients on one-month CT scans (calcification group). The shape of tumoral calcification was spotty (n=11) (Figure 2B),

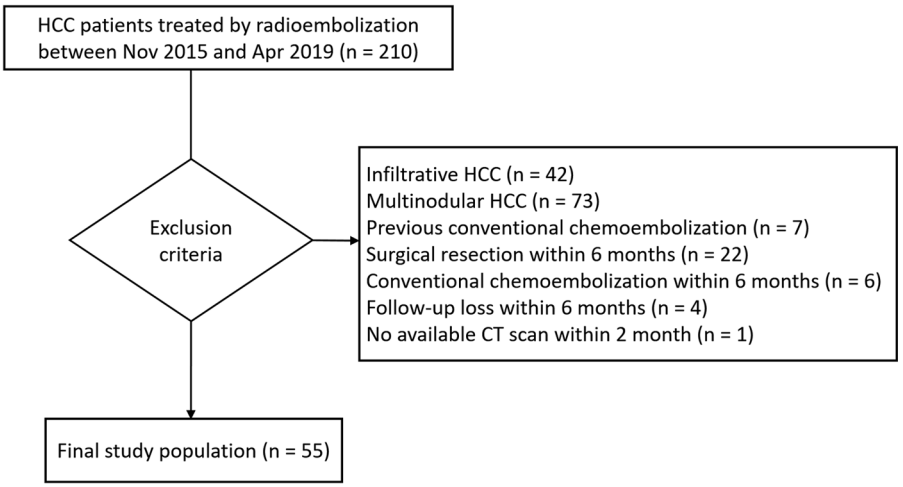

Figure 1. *Flow diagram of the study.*

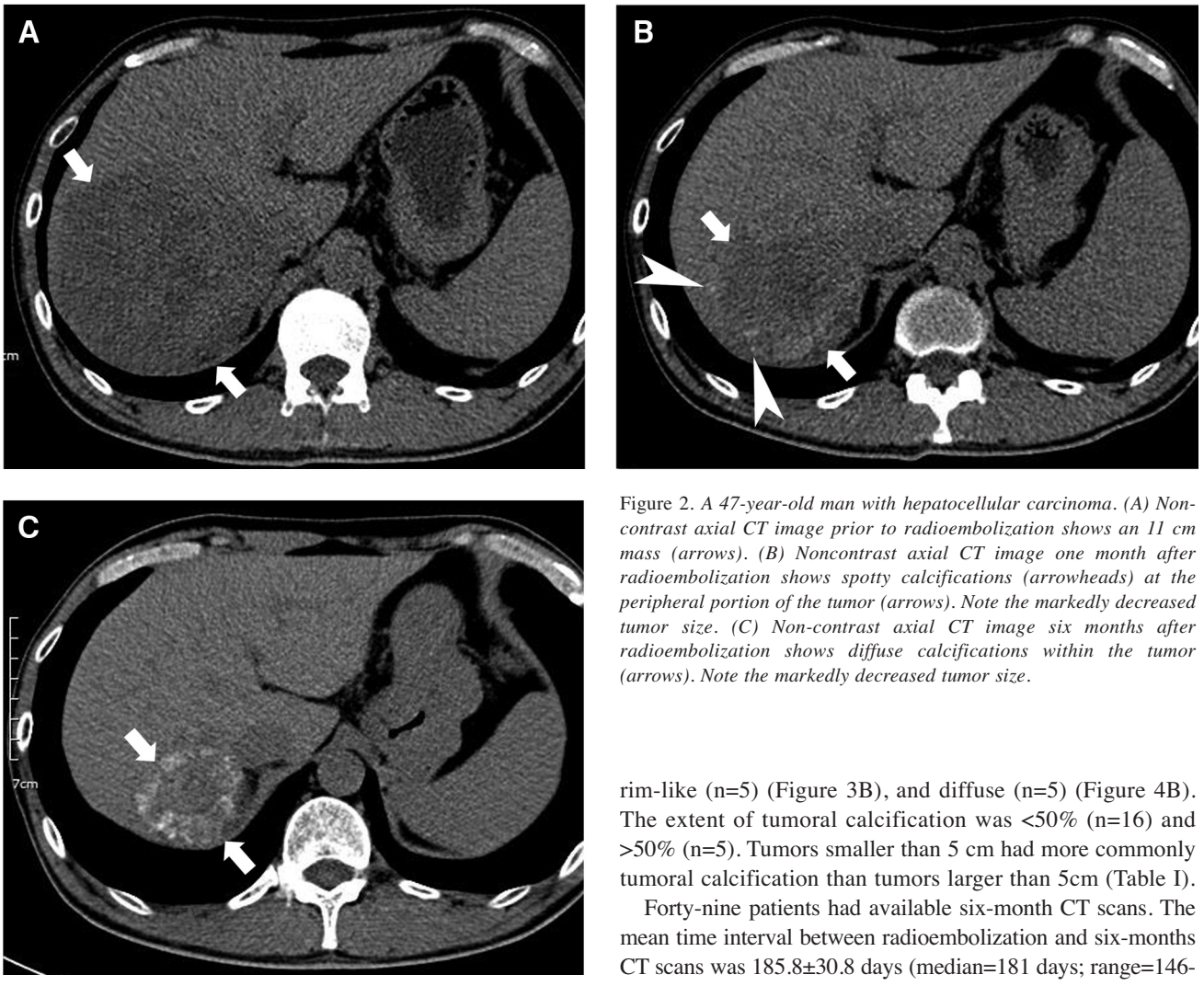

Figure 2. *A 47-year-old man with hepatocellular carcinoma. (A) Non-contrast axial CT image prior to radioembolization shows an 11 cm mass (arrows). (B) Noncontrast axial CT image one month after radioembolization shows spotty calcifications (arrowheads) at the peripheral portion of the tumor (arrows). Note the markedly decreased tumor size. (C) Non-contrast axial CT image six months after radioembolization shows diffuse calcifications within the tumor (arrows). Note the markedly decreased tumor size.*

rim-like (n=5) (Figure 3B), and diffuse (n=5) (Figure 4B). The extent of tumoral calcification was <50% (n=16) and >50% (n=5). Tumors smaller than 5 cm had more commonly tumoral calcification than tumors larger than 5cm (Table I).

Forty-nine patients had available six-month CT scans. The mean time interval between radioembolization and six-months CT scans was 185.8±30.8 days (median=181 days; range=146-

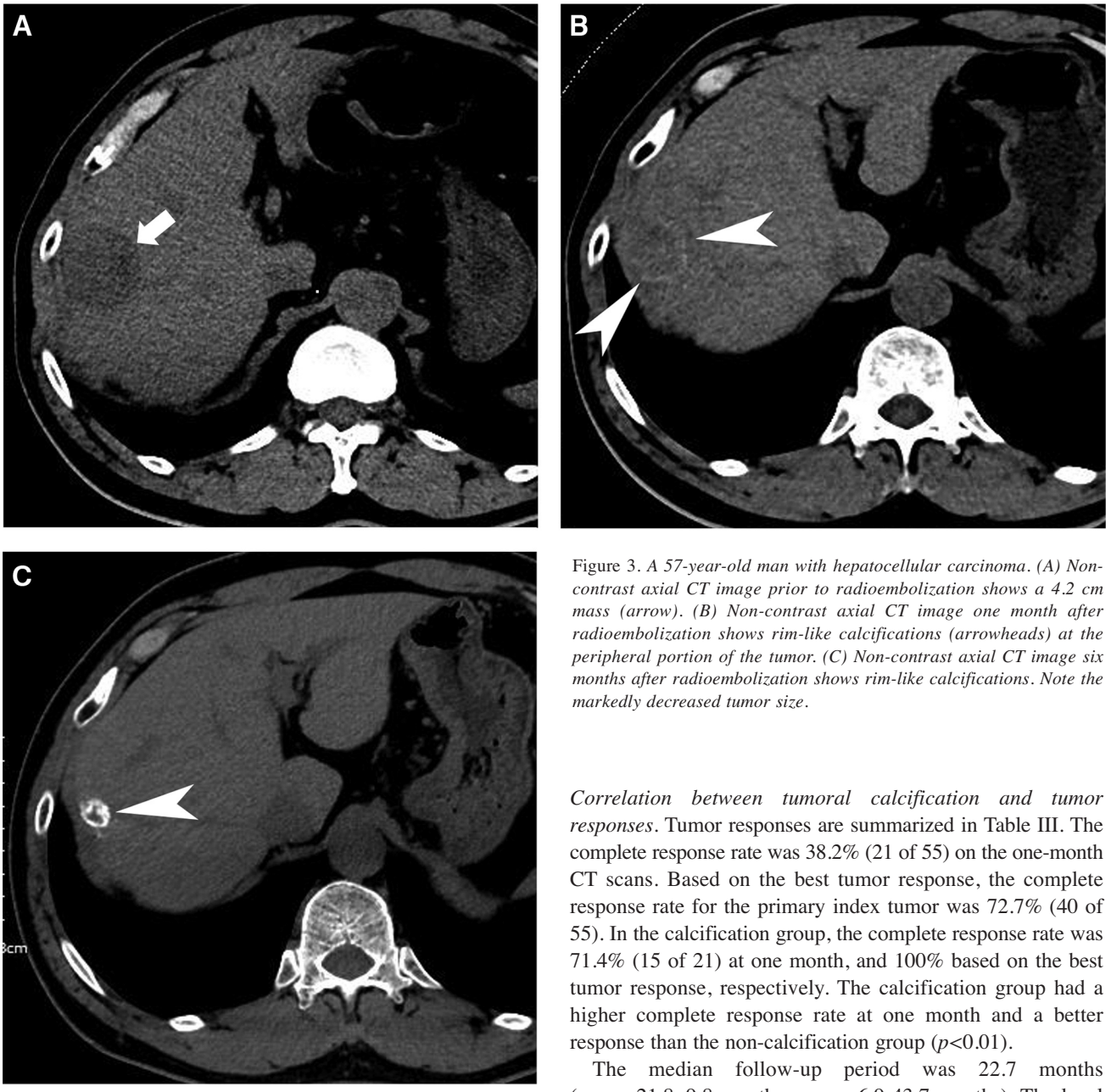

Figure 3. *A 57-year-old man with hepatocellular carcinoma. (A) Non-contrast axial CT image prior to radioembolization shows a 4.2 cm mass (arrow). (B) Non-contrast axial CT image one month after radioembolization shows rim-like calcifications (arrowheads) at the peripheral portion of the tumor. (C) Non-contrast axial CT image six months after radioembolization shows rim-like calcifications. Note the markedly decreased tumor size.*

268 days). Tumoral calcification was present in 35 (71.4%) of 49 patients on six-month follow-up CT scans. Tumoral calcification tends to increase over time; In 14 out of 35 patients, tumoral calcification was absent on 1-month CT scan, and spotty (n=5) or rim-like (n=4) calcification on 1-month CT scan changed as diffuse calcification on 6-month CT scan (Figure 3C). The shape of tumoral calcification was spotty (n=7), rim-like (n=7), and diffuse (n=21). The extent of tumoral calcification was <50% (n=16) and >50% (n=19) (Table II).

Correlation between tumoral calcification and tumor responses. Tumor responses are summarized in Table III. The complete response rate was 38.2% (21 of 55) on the one-month CT scans. Based on the best tumor response, the complete response rate for the primary index tumor was 72.7% (40 of 55). In the calcification group, the complete response rate was 71.4% (15 of 21) at one month, and 100% based on the best tumor response, respectively. The calcification group had a higher complete response rate at one month and a better response than the non-calcification group ($p<0.01$).

The median follow-up period was 22.7 months (mean=21.8±9.8 months; range=6.9-43.7 months). The local progression-free survival rates of the study population were 79.6% at one year and 70.3% at two years. The local progression-free survival rates were 68.9% at one year and 58.3% at two years in the non-calcification group and 94.7% at one year and 86.1% at two years in the calcification group, respectively. The calcification group had a longer local progression-free survival rate than the non-calcification group ($p=0.017$) (Figure 5A). In univariate analysis, a small tumor size, the calcification group, and a complete response on one-month CT scans are significant factor for longer progression-free survival. In multivariate analysis, a small tumor size was a sole significant factor for longer progression-free survival

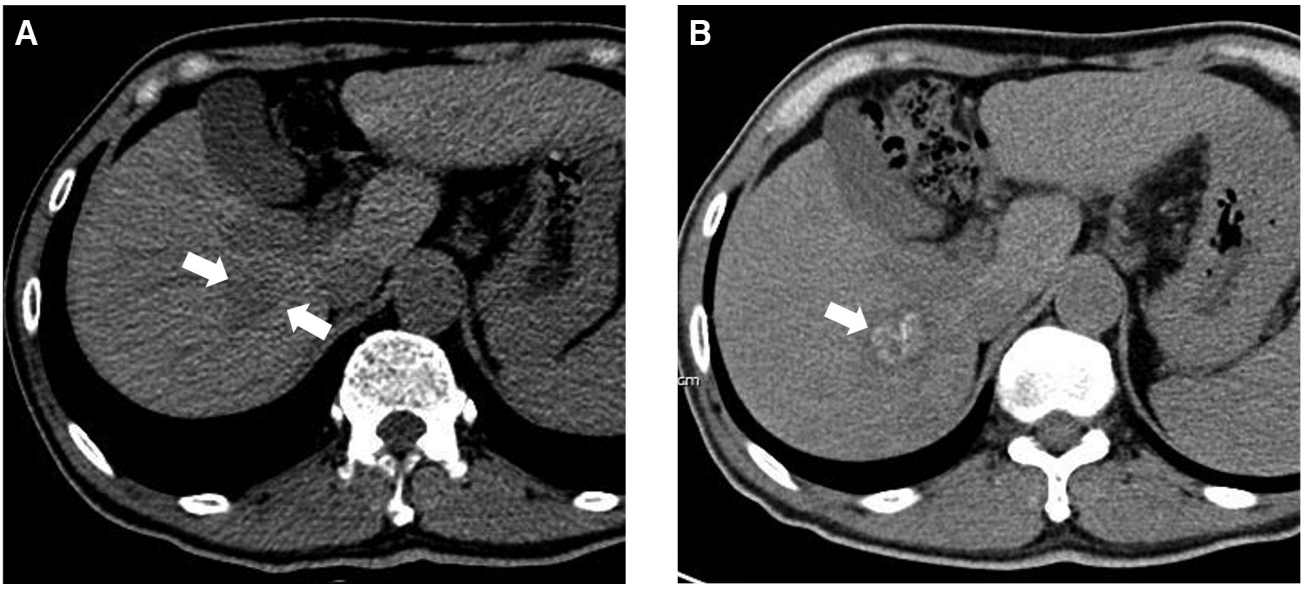

Figure 4. *A 58-year-old man with hepatocellular carcinoma. (A) Non-contrast axial CT image prior to radioembolization shows a 3 cm mass (arrows). (B) Non-contrast axial CT image one month after radioembolization shows diffuse calcifications (arrow) within the tumor.*

Table II. *Tumoral calcification.*

	1-month CT (n=55)	6-month CT scan (n=49)
Calcification		
Present	21 (38.2%)	35 (71.4%)
Absent	34 (61.8%)	14 (28.6%)
Shape of calcification		
Spotty	11	7
Rim-like	5	7
Diffuse	5	21
Extent of calcification		
<50%	16	16
>50%	5	19

CT: Computed tomography.

(p=0.035) (Table IV). The local progression-free survival rate between the calcification and non-calcification groups was not statistically different in the subgroup of tumor size ≤5 cm (p=0.202) (Figure 5B) and in the subgroup of tumor size >5 cm (p=0.167) (Figure 5C), respectively.

Discussion

Calcification associated with atherosclerosis, granulomatous infection, inflammation, fat necrosis and degenerating tumors are also common examples of dystrophic calcification. In the living tissue, most necrotic cells and their debris disappear by enzymatic digestion and phagocytosis of leukocytes. In dead tissue, this clearance process may be limited. Thus, necrotic

Table III. *Tumor response by modified response evaluation criteria in solid tumors (mRECIST) in 55 patients with hepatocellular carcinoma.*

55 patients			Tumoral calcification on 1-month CT			
			Present (n=21)		Absent (n=34)	
Tumor response	1-month response	Best response	1-month response	Best response	1-month response	Best response
CR	21 (38.2%)	40 (72.7%)	15 (71.4%)	21 (100%)	6 (17.6%)	19 (55.9%)
PR	20 (36.4%)	10 (18.2%)	5 (23.8%)	0	15 (44.1%)	10 (29.4%)
SD	14 (25.5%)	5 (9.1%)	1 (4.8%)	0	13 (38.2%)	5 (14.7%)

CT: Computed tomography; CR: complete response: PR: partial response; SD: stable disease.

cells and debris tend to attract calcium salt and other minerals, and become calcified. Although the pathophysiological mechanism of tumoral calcification after radioembolization is unclear, tumoral calcification might be a dystrophic calcification secondary to necrosis after radioembolization. Radiation can induce tumor cell necrosis or apoptosis, and dystrophic calcification occurs as a reaction to tissue damage.

In this study, small tumors had a strong tendency of having tumoral calcification induced by radioembolization. Although the target perfused tissue dose did not statistically differ between the calcification and non-calcification groups, the mean tumor dose of the calcification group would likely be higher than that of the non-calcification group. Since a single compartment model based on the Medical Internal Radiation Dose (MIRD) scheme was used in this study, small hypervascular tumors would receive a much higher dose than large tumors. A high tumor dose would result in a better tumor response, and tumoral calcification may be the surrogate of a high tumor dose.

None of the previous studies evaluating post-radioembolization imaging findings have described the presence of tumoral calcification. In this study, the incidence of tumoral calcification was 38.2% on one-month CT scans and 71.4% on six-month CT scans, respectively. This is relatively higher than that of colorectal metastasis after chemotherapy (13, 14). However, the study population includes only single tumors, and many patients were treated with boosted radioembolization, such as radiation segmentectomy. Thus, the incidence of tumoral calcification in patients with multinodular tumors would be lower than that of this study.

Whereas spotty calcification was the most common pattern on one-month CT scans, diffuse calcification was the most common on six-month CT scans. As time goes on, the extent of tumoral calcification has increased, resulting in a diffuse pattern. Thus, a diffuse pattern of tumoral calcification might indicate an excellent tumor response. Interestingly, regardless of the calcification pattern, all 21 patients in the calcification group, who had tumoral calcification on one-month CT scans, showed a complete response as the best tumor response. Thus, tumoral calcification on one-month CT scans can be used as an early surrogate marker of tumor response.

There are several limitations to this study. First, this was a retrospective study with variable imaging times after radioembolization. The pattern and incidence of tumoral calcification may depend on the timing of the CT scan. Second, the factors affecting calcification formation were not analyzed. The tumor dose, which is thought to be the most probable factor, was not measured in this study. Third, only single nodular tumors were included in this study because of the convenience of evaluating tumor response. In multinodular tumors or infiltrative tumors, tumoral calcification should be evaluated as a prognostic factor in future research. Fourth, because of the small study population, an independent validation group is lacking. Fifth, in multivariate analysis, tumoral calcification did not have any statistical significance. However, if tumor calcification is seen on 1 month CT scan, low chance of local tumor recurrence can be expected in daily

Table IV. *Univariate and multivariate analysis in 55 patients.*

	No of patients	Univariate analysis	Multivariate analysis	
			Hazard ratio	*p*-Value
Age		0.16		
<65	29			
≥65	26			
Gender		0.76		
Male	43			
Female	12			
Hepatitis virus		0.12		
Viral	39			
Non-viral	16			
Albumin		0.19		
<4.0	18			
≥4.0	37			
Total bilirubin		0.77		
<1.0	45			
≥1.0	10			
Prothrombin time (INR)		0.42		
<1.0	21			
≥1.0	34			
Platelet		0.19		
<120	11			
≥120	44			
Alpha-fetoprotein		0.24		
<200	40			
≥200	15			
Tumor extent		0.59		
Unilobar	43			
Bilobar	12			
Tumor size		0.001		0.041
≤5 cm	23		0.099 (0.011, 0.913)	
>5 cm	32			
Total activity administered		0.37		
≤3.0 GBq	22			
>3.0 GBq	33			
Mean target perfused tissue dose		0.13		
≤200 Gy	15			
>200 Gy	40			
Calcification on 1-month CT		0.017		0.124
Present	21		0.293 (0.062, 1.400)	
Absent	34			
Tumor response on 1-month CT		0.018		0.938
CR	21		0.935 (0.174, 5.027)	
PR or SD	34			

CT: Computed tomography; CR: complete response: PR: partial response; SD: stable disease.

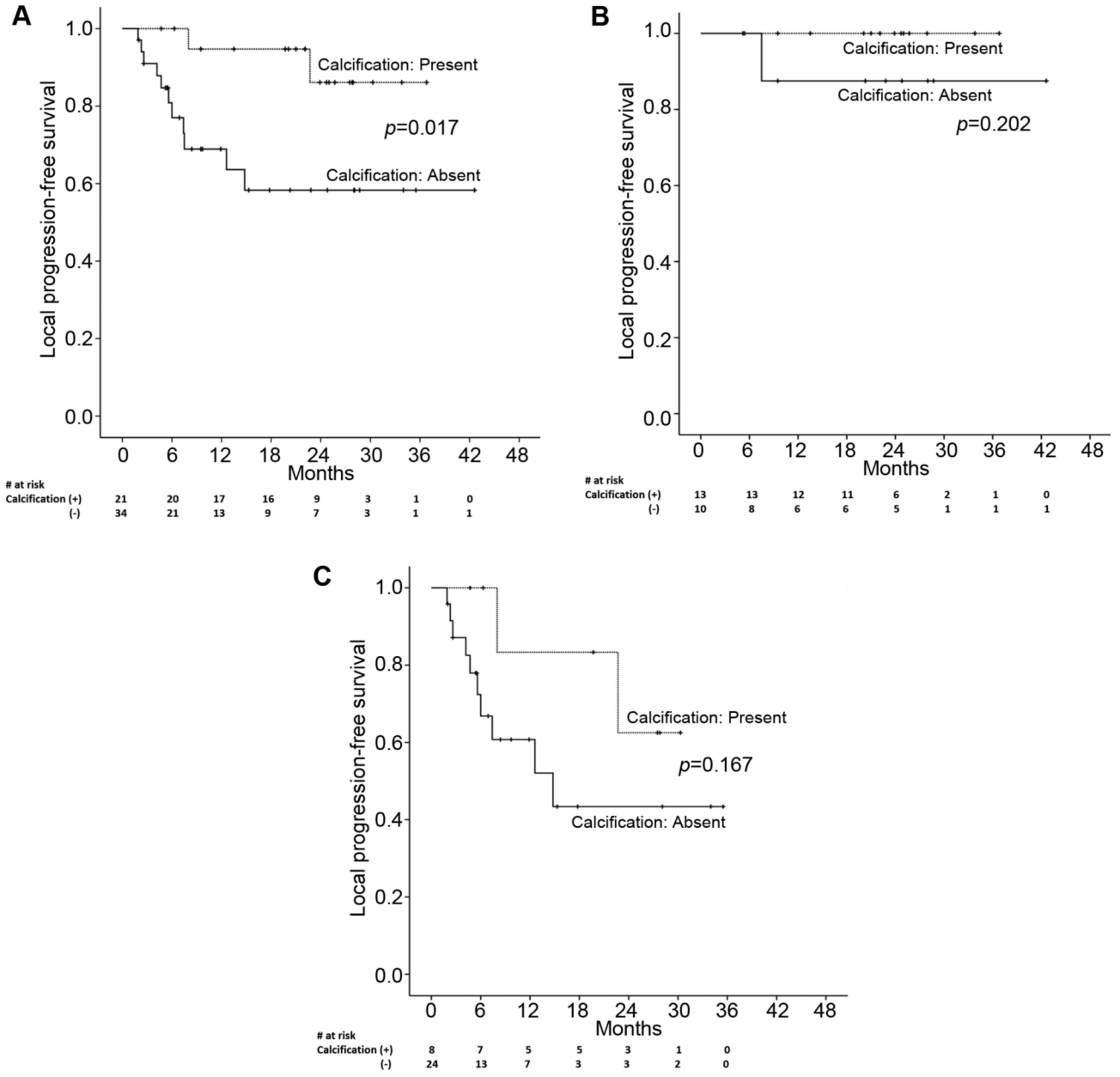

Figure 5. *Local progression-free survival. (A) Entire study population. (B) Subgroup of tumor size ≤5 cm. (C) Subgroup of tumor size >5 cm.*

clinical practice. Sixth, MRI imaging is commonly employed as a follow-up tool in many institute. Calcification may not be defined in most MRI imaging, thus this study may have limited clinical applicability.

In conclusion, yttrium-90 radioembolization can induce tumoral calcification in approximately one third of single nodular HCC patients on one-month CT scans. Tumors with calcification had a high probability of a complete response at one-month or the follow-up imaging study.

Conflicts of Interest

Nothing to disclose.

Authors' Contributions

Guarantor of integrity of the entire study: Hyo-Cheol Kim, Jin Wook Chung. Study concepts and design: Hyo-Cheol Kim, Ijin Joo. Literature research: Hyo-Cheol Kim, Ijin Joo, Jin Chul Paeng. Clinical studies:

Hyo-Cheol Kim, Ijin Joo, Myungsu Lee, Yoon Jun Kim, Jin Chul Paeng, Jin Wook Chung. Data analysis: Hyo-Cheol Kim, Ijin Joo, Jin Chul Paeng. Stastitical analysis: Hyo-Cheol Kim, Myungsu Lee, Yoon Jun Kim. Manuscript preparation: Hyo-Cheol Kim, Ijin Joo. Manuscript editing: Myungsu Lee, Yoon Jun Kim, Jin Chul Paeng, Jin Wook Chung.

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