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Yttrium-90 Radioembolization for Hepatocellular Carcinoma: Virtual Tumor Absorbed Dose as a Predictor of Complete Response

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Abstract. *Background/Aim: To evaluate the impact of virtual tumor absorbed dose (vTAD) on tumor response in patients with hepatocellular carcinoma (HCC) treated with yttrium-90 radioembolization. Patients and Methods: The institutional review board approved this retrospective single center study, which comprised 100 patients with nodular HCC who underwent yttrium-90 radioembolization between November 2015 and December 2019. The vTAD was calculated assuming that all infused microspheres were distributed only in the tumor. The ability of mean absorbed dose (mAD) and vTAD in predicting complete response were evaluated by receiver operating characteristic (ROC) curve analyses. Results: The mAD was 263.9 Gy ± 125.8, and the mean vTAD was 2005.8 Gy ± 2348.9. In terms of tumor response, 63 patients had complete response, 25 partial response, and 12 stable disease. For predicting complete response, ROC curve analyses revealed that the area under the curve (AUC) value of the vTAD was significantly higher (p<0.001) than that of the mAD. Multivariate analysis revealed that Child–Pugh class A5, unilobar disease, and vTAD (>952 Gy) were significant factors in predicting complete response. Conclusion: High vTAD (>952 Gy) plays a significant role in complete response in patients with nodular HCC.*

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Key Words: Hepatocellular carcinoma, radioembolization, tumor absorbed dose.

Radioembolization with yttrium-90 microspheres is a potent intra-arterial therapy for hepatocellular carcinoma (HCC). Compared to chemoembolization, radioembolization provides longer time-to-progression and maintains higher quality of life (1, 2). Although it is more expensive than chemoembolization and it is minimally covered by health insurance in many Asian countries, radioembolization could be recommended to patients with a bulky tumor and/or portal vein invasion, based on the Asia-Pacific guidelines (3). Thus, radioembolization is recommended for patients with large tumors, in anticipation of a complete tumor response without severe postembolization syndrome.

The current dosimetry of glass microspheres recommended by the manufacturer is 80~150 Gy of the mean absorbed dose (mAD) to the target tissue, assuming that the radioactive microspheres are evenly distributed throughout the target tissue. In a study of selected patients (Child–Pugh class A, unilobar disease, sufficient hepatic reserve), however, boosted radioembolization (mAD to the target tissue >150 Gy) was well tolerated and had prolonged overall survival (4). In the case of radiation segmentectomy for small HCC, the mAD to the treated tissue is commonly more than 250~300 Gy (5, 6). Based on these clinical experiences, personalized dosimetry incorporated with macroaggregated albumin (MAA) single photon emission computed tomography/computed tomography (SPECT/CT) has been attempted with anticipation of a high tumor absorbed dose (TAD) (7, 8). A recent prospective study showed that the personalized dosimetry group had a better tumor response and longer survival than the standard dosimetry group (9).

Given the hypervascularity of HCC, the administered radioactive microspheres are preferentially delivered to the HCC, and TAD would be proportional to the radiation activity

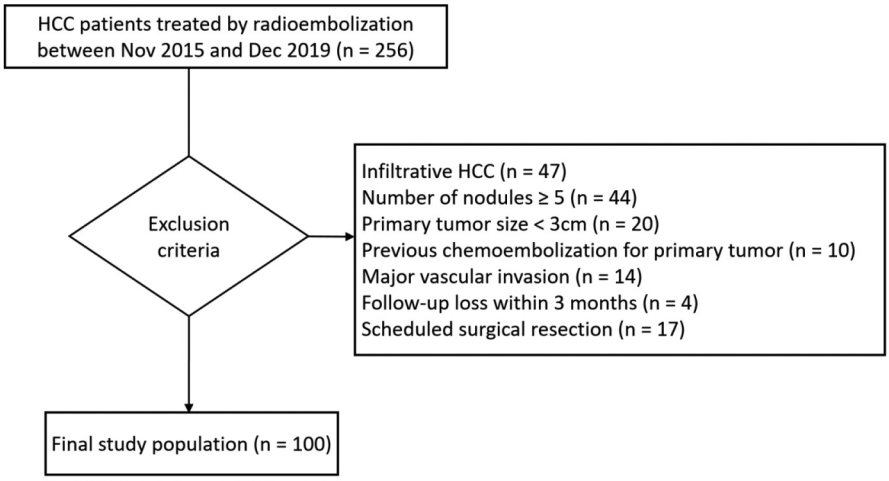

Figure 1. *Flow diagram of the study sample.*

administered. Thus, the present authors developed two hypotheses: first, virtual tumor absorbed dose (vTAD) can be simply calculated assuming that all infused radioactive microspheres are deposited in the tumor; second, high vTAD may be a good indicator of complete tumor response after radioembolization. Therefore, the purpose of this study was to evaluate the impact of vTAD on tumor response in patients with HCC treated with radioembolization.

Patients and Methods

Patients. This single center retrospective study was approved by the institutional review board, and informed consent was waived. From November 2015 to December 2019, 256 patients with HCC underwent yttrium-90 radioembolization using glass microspheres (TheraSphere; Boston Scientific, Marlborough, MA, USA). Inclusion criteria were: 1) nodular HCC, 2) four or fewer tumors, 3) 3 cm or larger in size, 4) no major vascular invasion, 5) no previous chemoembolization, ablation therapy, and systemic therapy (sorafenib) for primary target tumor, and 6) at least three-month imaging follow-up. Exclusion criteria were: 1) infiltrative HCC, 2) five or more tumors, 3) less than 3 cm in size, 4) major vascular invasion, 5) previous chemoembolization, ablation therapy, and systemic therapy (sorafenib) for primary target tumor, 6) scheduled surgical resection after radioembolization, and 7) follow-up loss within three months (Figure 1). Among the 256 patients, 100 met the inclusion and exclusion criteria. Twenty of the 100 patients have been previously reported (10). This prior article dealt with the feasibility of boosted radioembolization for HCC, whereas the present paper deals with the relationship between vTAD and tumor response after radioembolization for HCC.

One hundred patients [84 men and 16 women; mean age 64.6±12.2 years (range=33-89 years)] comprised this study population (Figure 1). The demographic characteristics of this study population are summarized in Table I. The mean primary tumor size was 7.7 cm ± 3.6. Sixty-eight patients had a single tumor and 32 patients had multiple tumors. The mean total radiation activity administered was 4.24 GBq ± 1.94 (median 4.04 GBq; range=0.62-10.35 GBq). The mean mAD was 263.9 Gy ± 125.8 (median 239.5 Gy; range=74.0-700.2 Gy). The mean vTAD was 2005.8 Gy ± 2348.9 (median 1311.1 Gy; range=105.2-12015.0 Gy).

Yttrium-90 radioembolization. Two interventional radiologists (H.C.K. with 14 years of experience in interventional oncology, M.L. with nine years of experience) performed all the procedures. In the early study period (November 2015-June 2016), radioembolization was performed with standard dosimetry (mAD of 100~150 Gy). In the late study period (July 2016-December 2019), boosted radioembolization (mAD >150 Gy) had been attempted as long as it was applicable. If at least two segments of normal liver could be saved from irradiation and estimated lung dose was less than 30 Gy, boosted radioembolization with selective catheterization was performed (mAD of 200~360 Gy). The detailed protocol was described in previous studies (10-12). Follow-up imaging studies (contrast-enhanced CT or magnetic resonance imaging) were commonly obtained one month after radioembolization and every two to three months thereafter.

Analysis. Two radiologists (H.C.K., J.W. Choi with four years of experience in interventional oncology) retrospectively reviewed the imaging studies independently, and disagreement was resolved by consensus. Tumor response was assessed by mRECIST (13). The primary target tumor was defined as all tumors present at the radioembolization (maximum tumor number was four). Complete response was defined as complete loss of tumoral enhancement of the primary target tumor in the arterial phase of any follow-up cross-sectional images (*i.e.*, best tumor response).

Total liver volume, treated liver volume, and total tumor volume were measured by volume analysis software (IntelliSpace Portal, version 7; Philips, Andover, MA, USA). The dose calculation was based on the Medical Internal Radiation Dose (MIRD) method recommended by the manufacturer of glass radioactive microspheres. Assuming that all infused microspheres were evenly

Table I. *Baseline characteristics of 100 patients with hepatocellular carcinoma.*

Gender	
Male	84
Female	16
Age, mean±SD (year)	64.6±12.2
Etiology	
HBV	74
HCV	9
HBV and HCV	3
Alcohol	2
Cryptogenic	12
Albumin, mean±SD (g/dl)	4.0±0.4
Total bilirubin, mean±SD (mg/dl)	0.6±0.3
Prothrombin time, mean±SD (INR)	1.03±0.09
Platelet, mean±SD (billion/l)	195.6±90.2
AST	45.9±33.3
ALT	39.5±29.0
BCLC stage‡	
A	62
B	29
C	9
ECOG	
0	91
1	9
Child-Pugh class	
A5	84
A6	15
B8	1
Tumor size	
mean±SD (cm)	7.7±3.6
Tumor number	
1	68
2	20
3	9
4	3
Tumor extent	
Unilobar	67
Bilobar	33
AFP	
≤20 (ng/ml)	52
>20 (ng/ml)	48
Radiation activity administered (GBq)	4.24±1.94
Target absorbed dose (Gy)	263.9±125.8
Virtual tumor dose (Gy)	2,005.8±2,348.9
Best target tumor response	
CR	63
PR	25
SD	12

HBV: Hepatitis B virus; HCV: hepatitis C virus; INR: international normalized ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BCLC: Barcelona Clinic Liver Cancer; ECOG: European Cooperative Oncology Group; AFP: alpha-fetoprotein; CR: complete response; PR: partial response; SD: stable disease.

distributed in the treated target tissue, mAD was calculated using the total infused radiation activity and total treated target volume. Assuming that all infused microspheres were distributed only in the tumor, vTAD was calculated using the total infused radiation activity and total tumor volume. The differences in mAD and vTAD values depending on the best tumor responses were evaluated by one-way analysis of variance (ANOVA) and the Student–Newman–Keuls *post-hoc* test. The performances of mAD and vTAD in predicting complete response were evaluated by receiver operating characteristic (ROC) curve analyses. Two ROC curves from mAD and vTAD were compared using the method by DeLong *et al*. (14).

Local progressive disease was defined as the regrowth of the primary target tumor, the appearance of a new lesion within the target tumor, or at least a 20% increase in the sum of diameters of the primary target tumor. If surgical resection or liver transplantation was performed, local progression-free survival was censored on the day of operation. If chemoembolization was performed for the primary target tumor without local progressive disease, local progression-free survival was censored on the day of chemoembolization, owing to the inability to conduct further assessment of local tumor response by radioembolization itself. Progressive disease was defined as local progressive disease, intrahepatic distant recurrence (the appearance of new lesions in the liver), or new extrahepatic metastasis.

Progression-free survival, local progression-free survival, and overall survival were defined as the time measured from the radioembolization. Fisher's exact test and multiple logistic regression analysis with a stepwise forward likelihood ratio were used to reveal the significant factor for achieving a complete response. Progression-free survival, local progression-free survival, and overall survival were obtained using the Kaplan–Meier method, and were compared by the log-rank test. To identify factors affecting progression-free survival and local progression-free survival, baseline characteristics and treatment factors were evaluated using the Cox proportional hazard model. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 25.0 software (SPSS, Inc., Chicago, IL, USA) and MedCalc version 18.11.3 software (MedCalc Software bv, Ostend, Belgium).

Results

Tumor response. Based on best tumor response, 63 patients had complete response (CR), 25 partial response (PR), and 12 stable disease (SD). The mAD (p=0.002) and vTAD (p<0.001) values were significantly different, depending on the best tumor responses: for both parameters, patients with CR had significantly higher values than the others, while there was no significant difference between PR and SD (Figure 2). In relation to predicting complete response, ROC curve analyses revealed that the area under the curve (AUC) value of the vTAD [0.875, 95% confidence interval (CI)=0.794-0.932] was significantly higher (p<0.001) than that of the mAD (0.697, 95%CI=0.597-0.785) (Figure 3). The sensitivity and specificity of mAD (>286 Gy) were 49.2% and 86.5%, respectively. The sensitivity and specificity of vTAD (>952 Gy) were 81.0% and 86.5%, respectively. Subgroup analysis of mAD and vTAD for prediction of complete response (according to tumor size and number) is summarized in Tables II and III, and Figure 4.

By univariate analysis, serum alanine aminotransferase (≤40

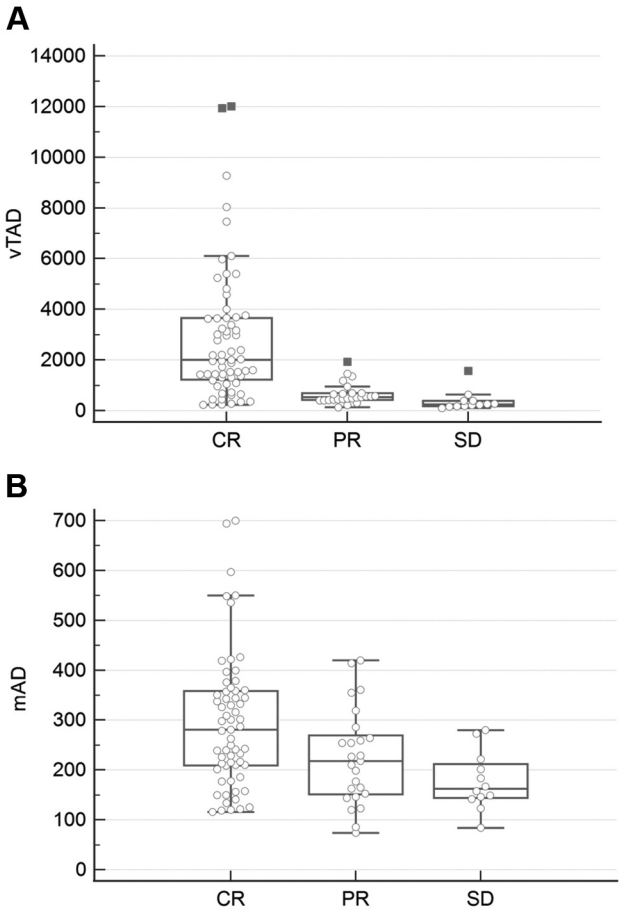

Figure 2. *The box-and-whisker plots of (A) mean absorbed dose (mAD) and (B) virtual tumor absorbed dose (vTAD) values, depending on the best tumor responses following yttrium-90 radioembolization in patients with hepatocellular carcinoma. Note: The central boxes represent the means and interquartile ranges. The vertical lines extend from the minimum to the maximum values, excluding outliers (circles and squares outside the vertical lines, outside and far-out values of Tukey, respectively). CR: Complete response; PR: partial response; SD: stable disease.*

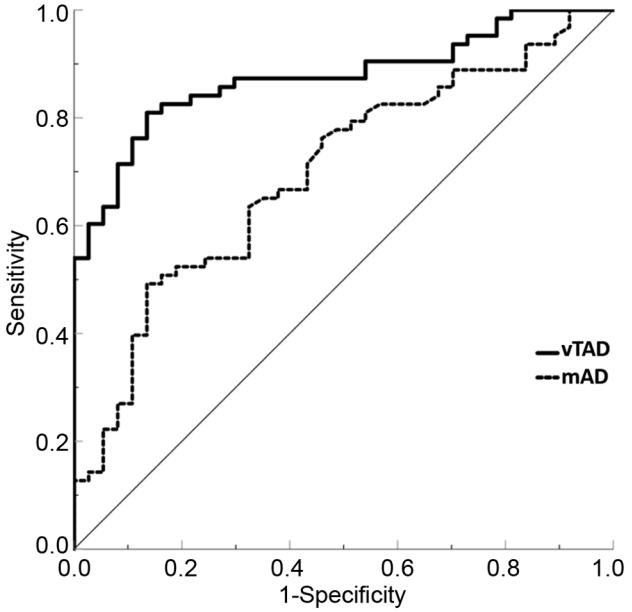

Figure 3. *The receiver operating characteristic curves of mean absorbed dose (mAD) and virtual tumor absorbed dose (vTAD) values in predicting complete response as the best response of yttrium-90 radioembolization in patients with hepatocellular carcinoma.*

Table II. *Performance of mean absorbed dose (mAD) and virtual tumor absorbed dose (vTAD) in predicting complete response in 100 patients with hepatocellular carcinoma.*

	AUC	95%CI	*p*-Value
All patients (n=100)			
vTAD	0.875	0.794-0.932	<0.001
mAD	0.697	0.597-0.785	
Subgroup			
Tumor <7 cm (n=51)			
vTAD	0.865	0.75-0.981	0.022
mAD	0.615	0.367-0.863	
Tumor ≥7 cm (n=49)			
vTAD	0.667	0.497-0.837	0.791
mAD	0.686	0.524-0.847	
Single tumor (n=68)			
vTAD	0.89	0.812-0.968	0.008
mAD	0.73	0.602-0.858	
Multiple tumor (n=32)			
vTAD	0.842	0.705-0.98	0.012
mAD	0.595	0.397-0.793	

IU/l *vs.* >40 IU/l), Child–Pugh class (A5 *vs.* A6/B), primary tumor size (<7 cm *vs.* ≥7 cm), tumor extent (unilobar *vs.* bilobar disease), mAD (>286 Gy *vs.* ≤286 Gy), and vTAD (>952 Gy *vs.* ≤952 Gy) were revealed as significant factors predicting complete response (Table IV). By multivariate analysis, Child–Pugh class A5, unilobar disease, and vTAD (>952 Gy) were revealed as significant factors predicting complete response (Table V).

Survival. Mean follow-up period was 23.8 months ± 13.6 (median 21.9 month; range=3.2-53.4 months). Local progression-free survival rates at one, two, and three years were 77.8%, 66.4%, and 62.3%, respectively (Figure 5A). Twenty patients had local progressive disease events: a new lesion within the primary target tumor of complete response (n=6), regrowth of the primary target tumor of partial response (n=12), and a 20% increase in the sum of diameters of the primary target tumor (n=2). In univariate analysis, Child–Pugh class A5, small tumor (<7 cm), complete

Table III. *Cut-off value of mean absorbed dose (mAD) and virtual tumor absorbed dose (vTAD) in predicting complete response in 100 patients with hepatocellular carcinoma.*

	Sensitivity	Specificity
All patients (n=100)		
vTAD >952 Gy	81.0%	86.5%
mAD >286 Gy	49.2%	86.5%
Subgroup		
Tumor <7 cm (n=51)		
vTAD >1927 Gy	73.9%	100%
mAD >280 Gy	56.5%	80%
Tumor ≥7 cm (n=49)		
vTAD >692 Gy	47.1%	93.8%
mAD >202 Gy	82.4%	59.4%
Single tumor (n=68)		
vTAD >692 Gy	86.4%	87.5%
mAD >286 Gy	54.5%	83.3%
Multiple tumor (n=32)		
vTAD >952 Gy	73.7%	84.6%
mAD >259 Gy	42.1%	92.3%

response, mAD >286 Gy, and vTAD >952 Gy were found to be significant factors for longer local progression-free survival (Table VI). In multivariate analysis, complete response was found to be the sole significant factor for longer local progression-free survival (p=0.028) (Table VII).

Median progression-free survival was 11.8 months (95%CI=7.5-16.1 months). Progression-free survival rates at one, two, and three years were 48.8%, 35.6%, and 25.4%, respectively (Figure 5B). Fifty-nine patients had progressive disease events: intrahepatic distant recurrence (n=34), local progressive disease (n=13), simultaneous intrahepatic distant recurrence and local progressive disease (n=2), and extrahepatic metastasis (n=10). Five patients had progressive disease (intrahepatic distant recurrence or extrahepatic metastasis) prior to the development of local progressive disease. In univariate analysis, small tumor (<7 cm), single tumor, complete response, and vTAD >952 Gy were found to be significant factors for longer progression-free survival (Table VIII). In multivariate analysis, single tumor was found to be the sole significant factor for longer progression-free survival (p=0.044) (Table IX).

Overall survival rates at one, two, and three years were 88.8%, 84.4%, and 76.5%, respectively (Figure 5C).

Complication. Clinical and biochemical toxicities are summarized in Table X. Sixteen events of grade 3 or more clinical toxicity occurred in 12 patients (eight patients of vTAD ≤952 Gy, four patients of vTAD >952 Gy). Grade 3 or more biochemical toxicity developed in 14 patients (five patients of vTAD ≤952 Gy, nine patients of vTAD >952 Gy).

Table IV. *Univariate analysis for predictors of complete response in 100 patients with hepatocellular carcinoma.*

Patient and tumor characteristics	Overall n=100	CR n=63	PR or SD n=37	p-Value
Gender				1.0
Men	84	53	31	
Women	16	10	6	
Age				0.214
<65	50	35	15	
≥65	50	28	22	
Hepatitis B virus				0.472
Positive	77	50	27	
Negative	23	13	10	
Serum albumin				0.097
≤4.0	53	29	24	
>4.0	47	34	13	
Serum total bilirubin				0.293
≤0.6	59	40	19	
>0.6	41	23	18	
Prothrombin time				0.834
≤1.0 INR	39	24	15	
>1.0 INR	61	39	22	
Serum AST level				0.048
≤40 (IU/l)	67	47	20	
>40 (IU/l)	33	16	17	
Serum ALT level				0.007
≤40 (IU/l)	69	50	19	
>40 (IU/l)	31	13	18	
Serum α-fetoprotein				1.0
≤20 (ng/ml)	52	33	19	
>20 (ng/ml)	48	30	18	
Platelet				0.149
≥170K	55	31	24	
<170K	45	32	13	
Child-Pugh Class				0.000
A5	84	60	24	
A6/B	16	3	13	
Tumor number				0.66
Single	68	44	24	
Multiple	32	19	13	
Primary tumor size				0.000
<7 cm	51	46	5	
≥7 cm	49	17	32	
Tumor extent				0.000
Unilobar	67	53	14	
Bilobar	33	10	23	
Target absorbed dose				0.000
≤286 Gy	64	32	32	
>286 Gy	36	31	5	
Virtual tumor dose				0.000
≤952 Gy	45	13	32	
>952 Gy	55	50	5	

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; CR: complete response; PR: partial response; SD: stable disease.

Discussion

The vTAD can be simply calculated using the total radiation activity administered and the total tumor volume by the MIRD method without involvement of MAA SPECT/CT.

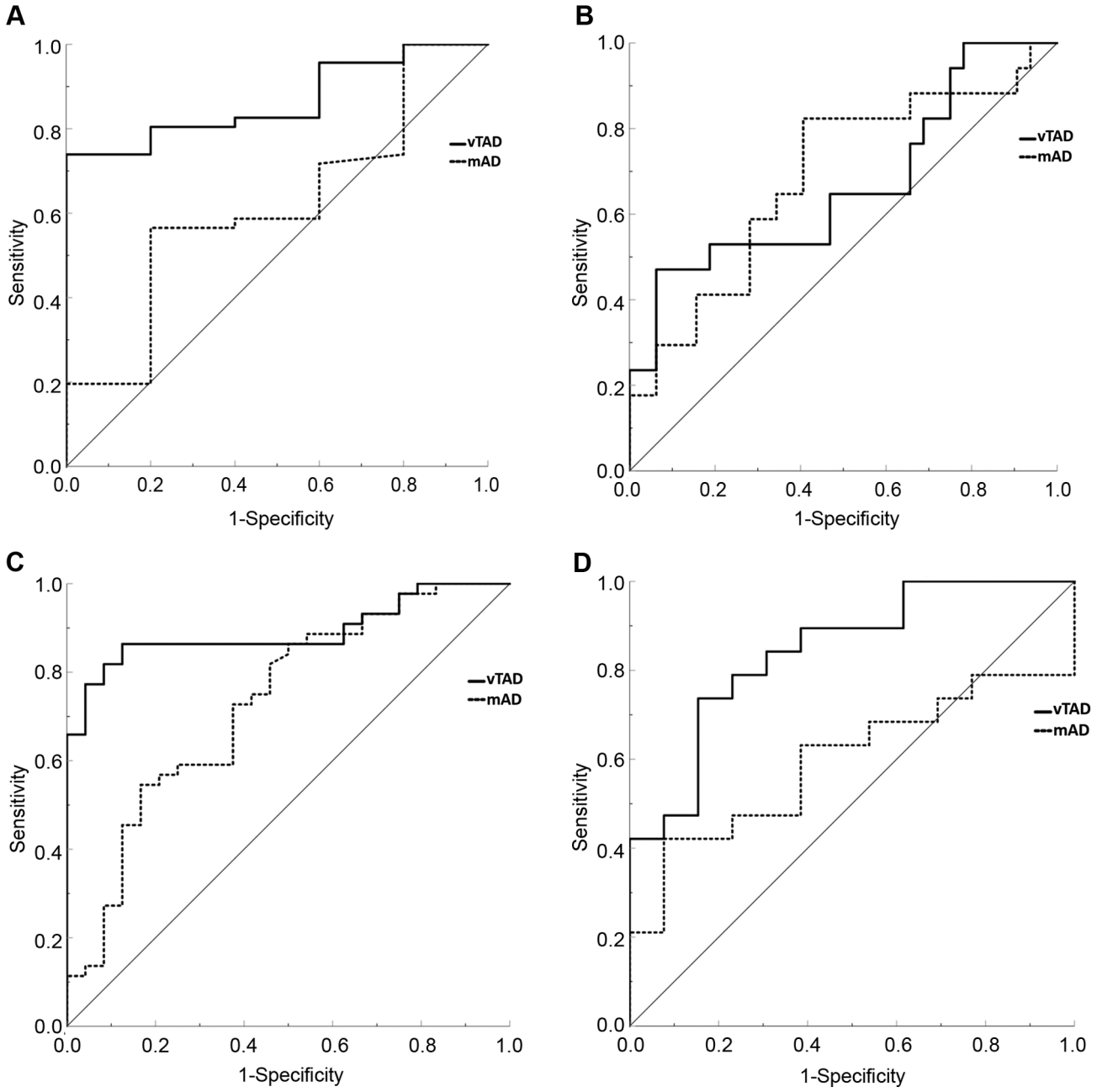

Figure 4. *The receiver operating characteristic curves of mean absorbed dose (mAD) and virtual tumor absorbed dose (vTAD) values in predicting complete response as the best response of yttrium-90 radioembolization in patients with hepatocellular carcinoma. (A) subgroup of tumor <7 cm, (B) subgroup of tumor ≥7 cm, (C) subgroup of single nodular tumor, (D) subgroup of multinodular tumors.*

Table V. *Multivariate analysis for predictors of complete response in 100 patients with hepatocellular carcinoma.*

Patient and tumor characteristics	Hazard ratio	95%CI	*p*-Value
Child-Pugh Class (A5 *vs.* A6/B)	5.721	1.175-27.862	0.031
Tumor extent (unilobar *vs.* bilobar)	6.4	1.93-21.221	0.002
Virtual tumor dose (>952 Gy *vs.* ≤952 Gy)	13.377	3.899-45.896	0.000

Table VI. *Univariate analysis for local progression-free survival in 100 patients with hepatocellular carcinoma.*

Patient and tumor characteristics	Overall n=100	Local progression-free survival (%)			*p*-Value
		6 months	1 year	2 year	
Gender					0.431
Men	84	96.9	80.2	67.2	
Women	16	78.0	66.9	66.9	
Age					0.220
<65	50	97.5	82.0	71.3	
≥65	50	90.3	74.8	62.5	
Hepatitis B virus					0.907
Positive	77	92.7	78.0	65.9	
Negative	23	95.2	77.2	67.6	
Serum Albumin					0.252
≤4.0	53	89.2	74.6	63.3	
>4.0	47	97.6	81.1	69.7	
Serum total bilirubin					0.466
≤0.6	59	93.6	80.2	61.8	
>0.6	41	92.9	73.5	73.5	
Prothrombin time					0.802
≤1.0 INR	39	93.0	75.9	63.2	
>1.0 INR	61	93.7	79.3	69.4	
Serum AST level					0.925
≤40 (IU/l)	67	92.1	76.6	64.7	
>40 (IU/l)	33	96.2	80.3	71.4	
Serum ALT level					0.649
≤40 (IU/l)	69	92.1	80.5	66.3	
>40 (IU/l)	31	96.4	68.8	68.8	
Serum α-fetoprotein					0.930
≤20 (ng/ml)	52	94.4	75.5	71.0	
>20 (ng/ml)	48	92.7	81.3	60.4	
Platelet					0.269
≥170K	55	98.0	73.3	55.9	
<170K	45	87.5	83.5	78.3	
Child-Pugh Class					0.025
A5	84	95.3	81.2	71.8	
A6/B	16	82.5	55.0	27.5	
Tumor number					0.876
Single	68	89.6	76.9	68.2	
Multiple	32	100	78.8	62.7	
Primary tumor size					0.002
<7 cm	51	97.3	89.9	84.2	
≥7 cm	49	89.6	65.2	45.7	
Tumor extent					0.782
Unilobar	67	92.3	79.4	69.9	
Bilobar	33	95.8	75.9	61.8	
Tumor response					0.001
Complete response	63	100	91.7	79.8	
Partial response/ Stable disease	37	81.3	50.1	40.1	
Target absorbed dose					0.002
≤286 Gy	64	89.7	67.7	51.9	
>286 Gy	36	100	95.5	95.5	
Virtual tumor dose					0.001
≤952 Gy	45	86.2	61.3	38.3	
>952 Gy	55	100	93.3	93.3	

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; CR: complete response; PR: partial response; SD: stable disease.

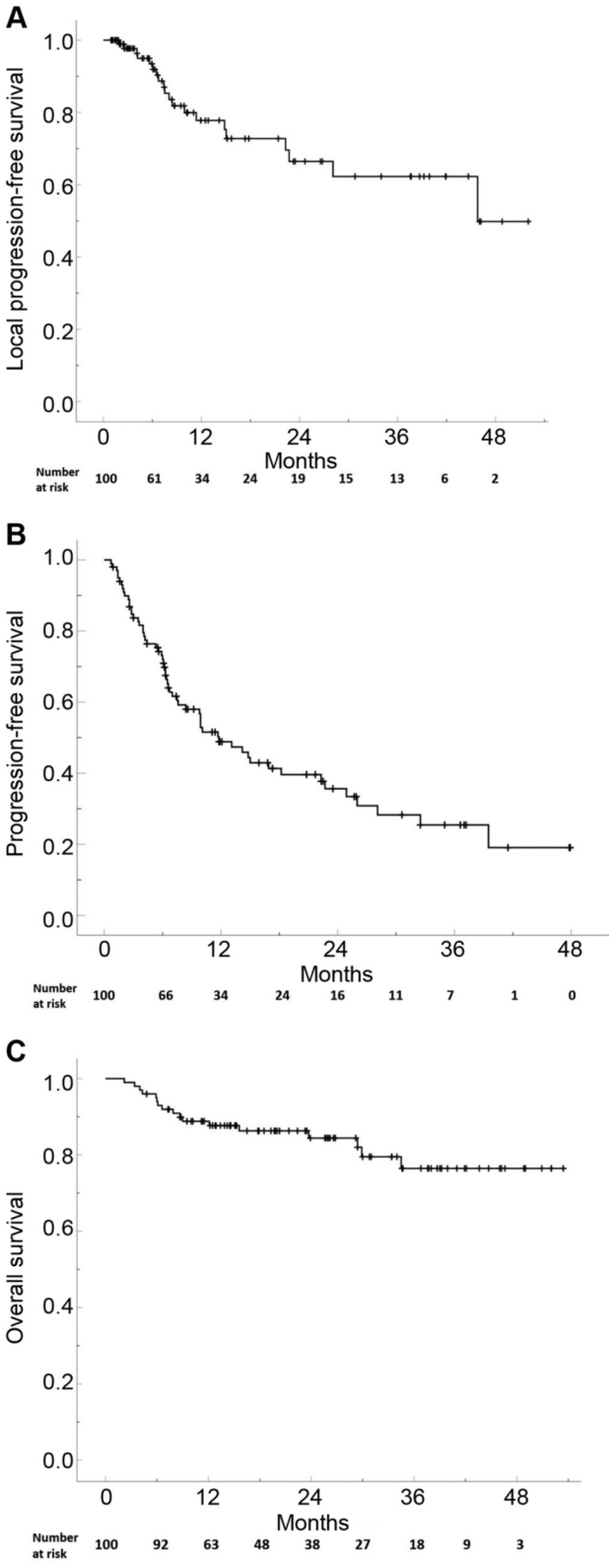

Figure 5. *Graphs illustrate local progression-free survival (A), progression-free survival (B), and overall survival (C) in patients with nodular hepatocellular carcinoma treated with yttrium-90 radioembolization.*

Table VII. *Multivariate analysis for local progression-free survival in 100 patients with hepatocellular carcinoma.*

Patient and tumor characteristics	Hazard ratio	95%CI	*p*-Value
Child-Pugh class (A5 *vs.* A6/B)	0.570	0.188-1.725	0.319
Tumor size (<7 cm *vs.* ≥7 cm)	0.893	0.212-3.755	0.877
Tumor response (CR *vs.* PR/SD)	0.264	0.081-0.867	0.028
Target absorbed dose (>286 Gy *vs.* ≤286 Gy)	0.219	0.025-1.945	0.173
Virtual tumor dose (>952 Gy *vs.* ≤952 Gy)	0.435	0.059-3.191	0.413

Because the basic assumption is that all radioactive microspheres are deposited in the tumor, the authors admit that the vTAD differs from the TAD. However, the vTAD can have a value similar to the TAD in hypervascular tumors, particularly in large HCCs. The present study demonstrated vTAD (>952 Gy) as a predictor of complete tumor response in nodular HCCs, and high vTAD has a better performance than high mAD in predicting complete tumor response. This finding means that the radiation activity prescribed should be proportional to the tumor volume rather than the target liver volume.

The standard dosimetry of MIRD estimates the mAD of the target tissue and cannot reflect the preferential delivery of radioactive microspheres in the hypervascular tumor. Thus, personalized dosimetry using MAA SPECT/CT has been tried in several studies, with promising results (7-9). However, personalized dosimetry using MAA SPECT/CT requires significant time and laborious work in the field of nuclear medicine. In addition, in terms of physical characteristics such as density and morphology, MAA differs from glass or resin microspheres and cannot follow the exact distribution of radioactive microspheres. Retrospective studies reported a weak correlation between the predicted and actual TAD (15-17) owing to the physical differences between MAA and radioactive microspheres, as well as different catheter tip position and injection speed, etc.

Post-treatment Y90 positron emission tomography/computed tomography (PET/CT) can provide highly accurate TAD (18), and a recent prospective trial demonstrated that responders had a higher median TAD than non-responders (225 Gy *vs.* 83 Gy) (19). However, post-treatment dosimetry using Y90 PET/CT cannot optimize the radioembolization procedure itself, but it can guide the subsequent adjuvant therapy if indicated. Thus, the concept of vTAD can serve as a simple guide for a tailored radioembolization procedure, although the optimal cut-off value of vTAD has not yet been determined.

Compared with the TAD calculated from the MAA SPECT/CT, the vTAD can be simply and accurately obtained from CT or magnetic resonance imaging (MRI). Because all infused Y90 microspheres are assumed to be delivered only in the tumor, the value of vTAD is always overestimated when compared with the TAD computed from MAA SPECT/CT or Y90 PET/CT. The TAD would be somewhere between the mAD and the vTAD. When the large hypervascular tumor is treated and the volume of treated normal liver is small, the vTAD is close to the TAD. If the target tumor is small and a large normal liver is included in the target tissue, the vTAD would be much higher than the TAD.

The vTAD of 952 Gy threshold used in this study is not to be considered as the absolute cut-off value for complete tumor response. In the prospective study, the TAD of 205 Gy using MAA SPECT/CT was adopted as a threshold (9). Thus, the vTAD of 952 Gy is much higher than that used in the current clinical practice. The optimal threshold of vTAD may be lower than 952 Gy in a patient with a large tumor and may be higher than 952 Gy in a patient with a small tumor. In subgroup analysis, the threshold of vTAD was 1927 Gy in tumors <7 cm, and 692 Gy in tumors ≥7 cm. In addition, the 952 Gy threshold was designed for complete tumor response. If a bridge to the liver transplantation is scheduled or combined systemic therapy is planned owing to extrahepatic metastasis, the threshold of vTAD could be lowered because the goal of radioembolization may be partial tumor response without serious complications. Further studies with a large study population are needed to determine the optimal threshold of vTAD in various situations.

A prospective multi-center study using Y90 glass microspheres demonstrated that the personalized dosimetry group (TAD >205 Gy) had a better objective response rate and overall survival than the standard dosimetry group (120±20 Gy of TAD) (9). The personalized dosimetry group had a 21% complete response rate and a 71% objective response rate, whereas the standard dosimetry group had an 11% complete response rate and a 36% objective response rate. Even though the present study was not involved with personalized dosimetry with MAA SPECT/CT, the tumor response (63% complete response rate and 88% objective response rate) was excellent compared with the above prospective study because most patients were treated with boosted radioembolization (263.9 Gy of mAD).

Table VIII. *Univariate analysis for progression-free survival in 100 patients with hepatocellular carcinoma.*

Patient and tumor characteristics	Overall n=100	Median PFS (95%CI) (months)	*p*-Value
Gender			0.104
Men	84	6.2 (0.5~11.9)	
Women	16	14.2 (7.2~21.2)	
Age			0.496
<65	50	11.7 (6.6~16.8)	
≥65	50	13.1 (4.8~21.4)	
Hepatitis B virus			0.963
Positive	77	11.7 (7.4~16.0)	
Negative	23	14.2 (1.8~26.6)	
Serum albumin			0.076
≤4.0	53	9.9 (7.6~12.2)	
>4.0	47	18.2 (4.4~32.0)	
Serum total bilirubin			0.293
≤0.6	59	14.8 (7.6~21.9)	
>0.6	41	7.0 (2.1~11.8)	
Prothrombin time			0.941
≤1.0 INR	39	10.1 (6.9~13.3)	
>1.0 INR	61	14.2 (3.9~24.4)	
Serum AST level			0.393
≤40 (IU/l)	67	13.1 (6.4~19.7)	
>40 (IU/l)	33	7.6 (3.6~11.6)	
Serum ALT level			0.492
≤40 (IU/l)	69	11.7 (7.4~15.9)	
>40 (IU/l)	31	24.9 (0.0~58.3)	
Serum α-fetoprotein			0.082
≤20 (ng/ml)	52	15.0 (6.6~23.4)	
>20 (ng/ml)	48	9.9 (6.1~13.7)	
Platelet			0.194
≥170K	55	9.9 (5.3~14.5)	
<170K	45	15.0 (1.3~28.7)	
Child-Pugh Class			0.083
A5	84	14.2 (8.6~19.8)	
A6/B	16	6.2 (0.3~12.1)	
Tumor number			0.016
Single	68	22.7 (8.1~37.3)	
Multiple	32	7.0 (5.3~8.6)	
Primary tumor size			0.01
<7 cm	51	22.3 (8.0~36.6)	
≥7 cm	49	6.7 (2.7~10.7)	
Tumor extent			0.293
Unilobar	67	14.2 (6.0~22.3)	
Bilobar	33	9.8 (4.5~15.1)	
Tumor response			0.001
Complete response	63	22.3 (11.6~33.0)	
Partial response/ Stable disease	37	6.4 (5.8~7.0)	
Target absorbed dose			0.127
≤286 Gy	64	9.9 (5.4~14.4)	
>286 Gy	36	18.2 (0.0~39.4)	
Virtual tumor dose			0.002
≤952 Gy	45	6.5 (3.4~9.6)	
>952 Gy	55	26.0 (5.5~46.5)	

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; CR: complete response; PR: partial response; SD: stable disease.

This study has several limitations. First, the TAD was not measured with Y90 PET/CT or MAA SPECT/CT. Because the vTAD was not directly compared with the TAD measured with Y90 PET/CT, it is unknown how much the vTAD overestimated the TAD. Further study is needed to reveal the relationship between the vTAD and TAD measured by Y90 PET/CT. Second, most of the study population was treated with boosted radioembolization (200~360 Gy of mAD) if possible. Thus, the ROC curve analysis suggested the vTAD of 952 Gy and the mAD of 286 Gy as a threshold for prediction of complete response. If more patients had been treated with standard dosimetry (80~150 Gy of mAD), the threshold would have been lower. Third, the high vTAD > 952 Gy was a significant factor for complete response, but was not a significant factor for longer progression-free survival. In addition, because of the relatively short follow-up period, overall survival was not analyzed. Fourth, the exact tumor volume cannot be measured on CT or MRI in patients with infiltrative HCC. Thus, the vTAD cannot be applied in such patients. Fifth, all patients were treated with glass microspheres in this study. If resin microspheres are used, the threshold of vTAD may be different.

In conclusion, when the vTAD is calculated assuming that all radioactive microspheres are deposited in the HCC, high vTAD (>952 Gy) plays a significant role in complete response in patients with nodular HCC. The vTAD has better ability than mAD in terms of prediction of complete response in patient with nodular HCC, which means that the radiation activity prescribed should be proportional to the tumor volume rather than the target liver volume.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

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

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Table IX. *Multivariate analysis for progression-free survival in 100 patients with hepatocellular carcinoma.*

Patient and tumor characteristics	Hazard ratio	95%CI	*p*-Value
Tumor size (<7 cm *vs.* ≥7 cm)	0.852	0.385-1.884	0.692
Tumor number (single *vs.* multiple)	0.584	0.345-0.987	0.044
Tumor response (CR *vs.* PR/SD)	0.583	0.278-1.223	0.153
Virtual tumor dose (>952 Gy *vs.* ≤952 Gy)	0.752	0.301-1.878	0.541

CR: Complete response; PR: partial response; SD: stable disease.

Table X. *Toxicity from radioembolization in 100 patients with hepatocellular carcinoma.*

	Total 100 patients						Virtual tumor dose ≤952 Gy (n=45)					Virtual tumor dose >952 Gy (n=55)				
		CTCAE grade														
	Number	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Clinical toxicity																
Pain	44		43	1				16					28	1		
Pain during procedure	22		22					6					16			
Pain after procedure	32		31	1				15					16	1		
Fever	11	8	1	2			3	0	2			5	1			
Abscess	1			1					1							
General weakness	1		1					1								
Benign biliary stricture	11	3		8					6			3		2		
Hepatic artery pseudoaneurysm	2			2										2		
Septic shock	1			1					1							
Ascites	2		2					1					1			
Radiation pneumonitis	1		1					1								
Pneumocystis carinii pneumonia	1					1					1					
Biochemical toxicity																
Increased AST	54	37	7	8	2		18	2	2	1		19	5	6	1	
Increased ALT	53	35	10	7	1		16	4	1	0		19	6	6	1	
Increased total bilirubin	41	31	5	4	1		15	2	2	0		16	3	2	1	

ALT: Alanine aminotransferase; AST: aspartate aminotransferase; CTCAE: Common terminology criteria for adverse events.

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