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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Short-term changes of angiogenesis factors after transarterial radioembolization in hepatocellular carcinoma patients

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PURPOSE
To analyze changes in angiogenesis factors after transarterial radioembolization (TARE) with Yttrium-90-loaded resin microspheres in hepatocellular carcinoma (HCC) patients.

METHODS
Interleukin-6, interleukin-8, hepatocyte growth factor, platelet-derived growth factor, fibroblast growth factor, vascular endothelial growth factor-A (VEGF-A), and angiopoietin-2 levels in 26 patients were measured before TARE and on day 1, 7, 14, and 30 after TARE and evaluated regarding radiological response.

RESULTS
In the sixth month of follow-up, 11 (42.30%) patients had a complete or partial response to treatment, while progressive disease was found in 15 (57.69%) patients. The percentage changes in VEGF-A in the non-responders on day 30 ($P = 0.034$) after TARE were significantly more obvious. Peak formation rates of VEGF-A were higher in non-responders ($P = 0.036$).

CONCLUSION
Short-term changes in angiogenesis factors in HCC patients after TARE with Yttrium-90-loaded resin microspheres fluctuate with different amplitudes at different times. The upregulation of growth factors has a prognostic capacity. Changes in VEGF-A after TARE may be helpful for the early recognition of non-responders.

KEYWORDS
Angiogenesis, Hepatocellular carcinoma, Resin microspheres, transarterial Radioembolization, Y-90

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver; its prevalence increases annually, causing over 600,000 deaths per year.[1] Resection, liver transplantation, and ablations are potential curative treatment options in the very early and early stages, according to the Barcelona Clinic Liver Cancer (BCLC) staging system.[2,3] However, most HCC patients are beyond these stages at the time of diagnosis,[3] and transarterial chemoembolization (TACE) is the standard of care in a palliative manner in the BCLC intermediate stage. For patients with unresectable HCC, who are not appropriate candidates for TACE due to advanced liver disease, multifocal disease, vascular invasion, and portal venous thrombosis, transarterial radioembolization (TARE) with Yttrium-90-loaded microspheres appears to be a safe alternative treatment to TACE with a comparable complication profile and survival rates.[4] United States[5] and Asia-Pacific guidelines[6] endorse TARE as a treatment choice for hepatobiliary malignancies. With transcatheter intra-arterial embolization treatments, the hepatic artery's tumor-feeding branch is selectively targeted; therefore, high-dose therapy can be applied to the index tumor by protecting the tumor-free parenchyma of the liver.[7,8] However, despite technically successful treatment, rapid progression can be detected in some

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patients. The cause of this undesirable development in HCC patients depends on many factors, and hypoxia caused by tissue embolization may trigger angiogenesis. It is known that angiogenesis is directly related to tumor progression and metastasis development in hypervascular tumors such as HCC.[9,10] In randomized controlled cohort studies, it was determined that the release of angiogenesis factors after TACE increased, and this escalation was associated with survival duration.[11,12] Since the microspheres used in TARE are smaller (glass or resin microspheres; 20–30 vs. 20–60 microns, respectively) compared with those used in TACE (40–500 microns), TARE is a micro-embolic therapy that maintains hepatic artery patency. Therefore, theoretically, there should be less hypoxia. Thus, triggering the angiogenesis cascade due to hypoxia was not expected in patients undergoing TARE. However, pilot studies reported that the angiogenesis changes are activated after TARE in HCC patients.[13,14] In line with these findings, understanding the short-term serial changes of angiogenesis factors after TARE is important for developing different treatment strategies (for example, TARE combined with systemic anti-angiogenic therapies) to prevent possible rapid progression after TARE.

The aim of this study was to analyze the short-term changes in angiogenesis factors after TARE with Yttrium-90-loaded resin microspheres and their relationship with the radiological response.

Methods

Study design

This study was conducted as a single-center prospective observational investigation in accordance with the 1964 Helsinki Declaration principles and approved by the Institutional Clinical Research Ethical Committee (decision 8-95/2019). Written consent was obtained from all patients before diagnostic and treatment procedures. The study included all consecutive patients with HCC admitted to the hospital between March 2017 and March 2019 and scheduled for TARE in the interventional radiology unit. The multidisciplinary tumor board decided on TARE due to the patients' ineligibility to other treatment modalities for different reasons. The indication for TARE was unresectable HCC for various reasons and a life expectancy of at least three months.[2]

Main points

- The angiogenesis response after transarterial radioembolization (TARE) with Yttrium-90 occurs among hepatocellular carcinoma patients.
- Short-term changes in angiogenesis factor levels fluctuate with different amplitudes at different times.
- The changes in vascular endothelial growth factor-A after TARE may help with the early identification of non-responders to the treatment.

The inclusion criteria for this study were a diagnosis of HCC proven by biopsy or typical imaging findings[15] and meeting the eligibility criteria for TARE.[16] Previously performed liver-targeted thermal ablations or embolization procedures, failure to evaluate radiological response during planned follow-up periods, systemic treatment administered within the first six months after TARE, and extrahepatic metastases detected before radioembolization were the exclusion criteria. TARE with Yttrium-90-loaded resin microspheres was applied to 34 consecutive patients during the study period. During the same period, TARE with Yttrium-90-loaded glass microspheres was applied to five consecutive patients. These five patients were excluded from the study to form a homogeneous group. During the follow-up period, eight patients were excluded from the study (five due to the administration of systemic therapy within the first six months after TARE, two because of their deaths related to non-oncological reasons, and one because of the detection of newly developed extrahepatic metastasis just before treatment). Therefore, 26 patients with HCC were included in the study after applying the inclusion and exclusion criteria.

Radioembolization procedure

Cone-beam computed tomography-guided splanchnic angiographies were performed 7 to 10 days prior to TARE in accordance with reported recommendations.[7] All patients underwent 99m-Technetium-labeled macroaggregated albumin injection into the artery feeding the tumor to determine arteriovenous lung shunt fraction and appropriate dose adjustment. The lung shunt fraction for every patient was calculated with the implementation of a single-photon emission computed tomography γ-camera in the nuclear medicine department. Desired dose calculation was performed using partition model dosimetry.[17] During TARE, standard trans-femoral access was performed for the placement of a 4F or 5F catheter to select the origin of the coeliac axis. A microcatheter was then inserted and selectively advanced to a segmental or sub-segmental tumor-feeding hepatic artery branch. Infusion of the previously calculated dose of the Yttrium-90-loaded resin microspheres was done selectively or super-selectively under fluoroscopic guidance.

Evaluation of the radiological response to radioembolization

All investigated patients were evaluated by dynamic contrast-enhanced magnetic resonance imaging before and after the treatment in the first and third months and then at three-month intervals. The radiological response assessment of the treated tumors was conducted by the modified Response Evaluation Criteria in Solid Tumors.[18]

Regarding the imaging findings obtained at the six-month follow-up visit, the patients were divided into responders (i.e., patients with complete or partial response) and non-responders (i.e., stable disease or progressive disease patients).

Evaluation of the short-terms changes in angiogenesis factors after radioembolization

Blood samples of all patients were taken at baseline (one day before treatment) and on days 1, 7, 14, and 30 after the TARE procedure. The serum levels of commercially available interleukin-6 (IL-6), IL-8, hepatocyte growth factor, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor-A (VEGF-A), and angiopoietin-2 (Ang-2) were measured with a commercially available enzyme-linked immunosorbent assay test. Compared with the baseline levels, the percentage changes of the angiogenesis factors on days 1, 7, 14, and 30 after TARE were calculated. An increase of angiogenesis factor levels at any time more than 50% compared with the relevant baseline values was accepted as a significant peak formation according to Carpizo et al.[13] Rates of significant peak formation and percentage changes regarding baseline values of every angiogenesis factor were registered.

Statistical analysis

Categorical variables were expressed as numbers and percentages, whereas continuous variables were given as means, standard

deviations, medians, and minimum-maximum values where appropriate. The chi-square test was used to compare categorical variables between the response groups. The normality of distribution for continuous variables was confirmed with the Shapiro-Wilk test. The Mann–Whitney U test was used to compare continuous variables between two sets. The statistical level of significance for all tests was considered to be 0.050. All data were analyzed using IBM Statistical Package for the Social Sciences Statistics software (version 20; IBM Corp, NY, US) and the TURCOSA software package (TURCOSA Analytical Ltd, Turkey).

Results

Table 1 shows the patients' demographic and clinical characteristics. In the sixth month of follow-up, eight (30.76%) patients were consistent with a complete response to treatment, while the status of three (11.53%) patients was interpreted as a partial response. During this period, progressive disease was found in 15 (57.69%) patients, which was due to local tumor progression in 12 (46.15%) patients and extrahepatic lung metastasis in 3 (11.53%) patients. Therefore, at 6 months, 11 (42.30%) patients were evaluated as responders, while the remaining 15 patients (n = 15.00; 57.69%) were interpreted as non-responders. The median duration of the entire follow-up period after treatment was 18 (range 6–38) months. During the follow-up period, 12 (46.15%) patients died.

The evaluation of the dynamics of angiogenesis factors after TARE showed that their levels fluctuated from the baseline values at different times (Table 2). Responders had significantly higher initial VEGF-A than non-responders (P = 0.021). No significant difference was found between the baseline values of other angiogenesis factors for the two groups (P > 0.050). The percentage change in VEGF-A values at day 30 in non-responders was significantly more pronounced during

Table 1. Demographic and clinical characteristics of the study population, n = 26

Characteristics	Values Non-Rp (n = 15) vs. Rp (n = 11)	*P*
Age, years; median (min-max)	66.50 (52.00–86.00) vs. 67 (56.00–86.00)	0.867
Gender, n (%) Male Female	 13.00 (86.66) vs. 10 (90.90) 2.00 (13.33) vs. 1.00 (9.10)	0.738
Etiology, n (%) HBV HCV	 10.00 (66.66) vs. 8.00 (72.72) 5.00 (33.33) vs. 3.00 (27.27)	0.931
Child–Pugh score, n (%) A B	 13.00 (86.66) vs. 11.00 (100.00) 2.00 (13.33) vs. 0.00 (0.00)	0.425
BCLC stage, n (%) B C	 9.00 (60.00) vs. 11.00 (100.00) 6 (40.00) vs. 0 (0.00)	0.017
Tumor size, cm; median (min-max)	8.00 (3.00–12.00) vs. 4.50 (2.00–7.20)	0.132
Tumor distribution, n (%) Unilobar Bilobar	 10.00 (66.66) vs. 8.00 (72.72) 5.00 (33.33) vs. 3.00 (27.27)	0.741
Radiation activity, GBq; median (min-max)	1.75 (0.37-2.75) vs. 1.20 (0.45-3.03)	0.652

The chi-square test, Fisher's exact test, and Mann-Whitney U test were used. HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer staging system; GBq, Gigabecquerel; min-max, minimum-maximum.

Table 2. Short-term dynamics and comparison of angiogenesis factor levels in the study population after TARE with baseline values, n = 26

Angiogenesis factor*	Baseline	1st day *P*	7th day *P*	14th day *P*	30th day *P*
IL-6	39.80 (12.20–2560.00)	31.30 (7–3020.10) 0.570	39.40 (5.403050.10) 0.949	36.50 (0.10–3000.00) 0.942	35.90 (12.20–3100.20) 0.942
IL-8	41.20 13.20–538.50)	43.70 (4.40–515.80) 0.596	49.20 (14.70–528.90) 0.464	48.20 (6.60–1194.00) 0.701	42.20 (4.40–485.7) 0.687
HGF	19.30 (6.20–1980.10)	21.20 (0.40–772.70) 0.749	21.20 (2.10–803.50) 0.176	19.10 (0.70–820.90) 0.770	18.50 (0.10–566.40) 0.492
VEGF-A	93.60 (0.20–498.90)	72.30 (0.40–474.10) 0.634	47.3 (1.20–449.60) 0.570	30.90 (0.70–480.20) 0.534	52.10 (0.60–486.60) 0.956
FGF	12.20 (2.30–387.20)	13.70 (2.60–267.50) 0.647	16.50 (3.50–299.40) 0.784	15.20 (3.70–258.40) 0.985	18.50 (3.40–203.00) 0.756
Ang-2	59.00 (42.90–191.80)	52.50 (31.50–176.50) 0.421	53.90 (31.70–174.80) 0.297	59.10 (37.00–186.20) 0.621	58.40 (40.70–121.20) 0.898
PDGF	1208.80 (59.30–3665.70)	1662.60 (66.60–3838.50) 0.220	1230.2 (14.90–4322.10) 0.390	1161.50 (14.90–4198.70) 0.942	1184.70 (28–2825.40) 0.701

*pg/mL, median (minimum-maximum), P > 0.050 for all parameters, the Mann–Whitney U test.TARE, transarterial embolization; IL-6, interleukin-6; IL-8, interleukin-8; HGF, hepatocyte growth factor; VEGF-A, vascular endothelial growth factor; FGF, fibroblast growth factor; Ang-2, angiopoietin-2; PDGF, platelet-derived growth factor.

Table 3. Relationship between the percentage changes in angiogenesis factors compared to baseline values with radiological response in the sixth month of follow-up after TARE, n = 26

Angiogenesis factor*	1st day percentage change Non-Rp vs. Rp	*P*	7th day percentage change Non-Rp vs. Rp	*P*	14th day percentage change Non-Rp vs. Rp	*P*	30th day percentage change Non-Rp vs. Rp	*P*
IL-6	−14.72 (−53.60–6.73) vs. 6.10 (−82.80–106.72)	0.897	−113.71 (86.65–1,154.01) vs. 0.00 (−76.60–587.90)	0.815	−30.74 (−99.71–442.24) vs. −4.51 (−85.82–433.04)	0.586	2.44 (−86.53–164.43) vs. 6.41 (−86.31–166.12)	0.897
IL-8	−4.20 (−85.42–208.01) vs. −6.00 (−74.33–95.47)	0.775	11.72 (−51.30–491.31) vs. 8.61 (−25.49–142.52)	0.697	−7.84 (−74.92–1,254.41) vs. 10.71 (35.91–271.04)	0.364	−10.79 (−84.01–451.04) vs. −1.10 (−49.15–120.91)	0.204
HGF	−39.50 (−96.22–508.03) vs. −5.70 (84.80–1,819.02)	0.402	13.92 (−98.95–778.01) vs. 10.51 (−70.79–436.03)	0.921	−10.03 (94.32–3,381.31) vs. 10.12 (−99.21–1169.72)	0.805	−32.90 (−96.01–716.24) vs. 10.41 (−99.91–225.92)	0.657
PDGF	31.00 (−60.73–742.34) vs. 30.20 (−50.40–883.65)	0.856	17.69 (−84.63–552.31) vs. 5.82 (−93.59–897.01)	0.484	−8.51 (−94.74–422.71) vs. −31.02 (−78.93–384.22)	0.204	−22.93 (−92.25–753.39) vs. −22.21 (−73.12–364.24)	0.736
FGF	−10.10 (−78.84–66.69) vs. −20.60 (−69.03–405.01)	0.775	13.53 (−61.49–307.11) vs. 0.71 (−45.25–61.52)	0.186	−6.59 (−68.71–732.32) vs. −11.14 (−53.49–96.42)	0.622	−4.29 (−79.21–584.11) vs. −20.22 (−75.84–108.23)	0.364
VEGF-A	−29.73 (−65.14–3,007.02) vs. −10.21 (−83.01–473.57)	0.659	−15.34 (−83.83–944.01) vs. −36.61 (−76.19–13.49)	0.092	−7.83 (−58.84–44.91) vs. −45.81 (−89.59–15.34)	0.204	2.80 (−43.21–12788.03) vs. −16.11 (−77.92–16.01)	0.034
Ang-2	−9.91 (−58.54–51.92) vs. −6.42 (−19.65–26.61)	0.169	−6.64 (−58.62–74.79) vs. −16.31 (−30.29–7.72)	0.392	1.72 (−58.81–44.91) vs. −16.22 (−49.45–76.09)	0.154	3.31 (−57.72–83.12) vs. −7.61 (−50.24–105.85)	0.169

*Median (minimum-maximum), the Mann–Whitney U test. TARE, transarterial embolization; Non-Rp, non-responders; Rp, responders; IL-6, interleukin-6; IL-8, interleukin-8; HGF, hepatocyte growth factor; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; VEGF-A, vascular endothelial growth factor; Ang-2, angiopoietin-2.

the 6-month radiological response assessment compared to responders (P = 0.034) (Table 3). However, no significant difference was found between the percentage changes of other angiogenesis factors compared with the baseline values (Table 3).

At the six-month follow-up evaluation, the rates of peak formation of the VEGF-A values of the non-responders were significantly higher than in responders. The rates of the peak formation of the VEGF-A levels in non-responders and responders were 53.33% and 9.00%, respectively (P = 0.036). However, no significant difference was found between the groups for the peak detection rates of other angiogenesis factors according to radiological response findings (Table 4).

Discussion

Angiogenesis is an important factor in the early recurrence and metastasis of vascular tumors such as HCC. Studies have found that angiogenesis activity increases in line with the carcinogenesis steps of liver tumors.[19] In addition, embolization of the hepatic artery with intra-arterial therapies triggers the angiogenesis cascade regardless of the tumor's nature.[20] Suzuki et al.[21] reported that angiogenesis factors increased after bland transarterial embolization of the liver tumors, and the angiogenesis cascade was initiated. Later studies determined a relationship between hypoxia and the tumor parenchyma caused by embolization after TACE. The authors demonstrated the relationship between the strength of angiogenesis launched by hypoxia, the tumor response to the treatment, and the survival time of the patients.[22,23] During TARE, hypoxia occurring in the tumor parenchyma is theoretically more limited compared to other intra-arterial embolization procedures because smaller particles are used for TARE. However, few studies on the existence of the angiogenesis response after TARE have been published.[13,14,24]

Only two studies investigate the angiogenesis response after TARE in patients with HCC. Carpizo et al.[13] applied TARE with Yttrium-90-loaded on resin microspheres to 22 patients with primary and secondary liver tumors (7 HCC and 15 colorectal carcinoma metastases). After the treatment, it was determined that classical (VEGF-A, Ang-2, FGF, and PDGF) and non-classical (IL-8, leptin, and follistatin) angiogenesis factor levels peaked in more than half of the patients compared to the baseline values. Later, Lewandowski et al.[14] applied TARE with Yttrium-90-loaded glass microspheres to 13 patients with HCC and found that all angiogenesis factor levels increased after treatment. However, when compared with baseline values, no significant increase was found in the post-treatment values. When the results of the two aforementioned studies and this study are evaluated together, the hypothesis that TARE triggers the angiogenesis cascade can be considered proven. However, the angiogenesis response after TARE may not be the only factor to consider; external radiotherapy alone also triggers the angiogenesis response in tumors.[25] Therefore, randomized controlled trials with more patients are needed to make a definitive conclusion.

The relationship between the response to TARE and the baseline levels of angiogenesis factors was previously investigated. Carpizo et al.[13] found that the baseline IL-8 and Ang-2 values of patients with shorter overall survival were significantly higher. The authors surmised that baseline levels of angiogenesis factors might have a predictive significance for overall survival durations. However, in the prospective cohort study of Rosenbaum et al.[24] on circulating angiogenesis factors and treatment response after TARE for colorectal cancer and liver metastases, it was determined that baseline angiogenesis values of patients who did not respond to treatment did not differ compared to responders. The authors emphasized that the comparison between patients may be misleading since the baseline levels of angiogenesis factors show wide variations between patients, and there are no standard lower and upper limit levels.

The presented study results showed that levels of angiogenesis factors varied at different times with fluctuating amplitudes within the first month after TARE. In more than half

Table 4. Relationship between the peak formation of angiogenesis factors compared to baseline levels with radiological response after TARE in the study population, n = 26

Angiogenesis factor	Peak formation, n (%) in Rp (n = 11)	Peak formation, n (%) in Non-Rp (n = 15)	*P*
IL-6	5 (45.45)	8 (53.33)	0.691
IL-8	4 (36.36)	6 (40.00)	1.000
HGF	8 (72.72)	12 (80.00)	1.000
PDGF	6 (54.54)	9 (60.00)	1.000
FGF	3 (27.27)	6 (40.00)	0.683
VEGF-A	1 (9.090)	8 (53.33)	0.036
Ang-2	4 (36.36)	1 (13.33)	0.128

*The chi-square test and Fisher's exact test. TARE, transarterial embolization; Non-Rp, non-responders; Rp, responders; IL-6, interleukin-6; IL-8, interleukin-8; HGF, hepatocyte growth factor; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; VEGF-A, vascular endothelial growth factor; Ang-2, angiopoietin-2.

of the study population, some angiogenesis factors significantly peaked at different times after treatment. In comparison, the same significant increase at various times of some angiogenesis factors was detected in less than half of the patients. The short-term changes of angiogenesis factors after TARE over time show that angiogenesis is a very complex event in HCC patients. The baseline levels of angiogenesis factors show wide variations between patients, and there are no standard lower and upper limit levels.[24] The percentage change of VEGF-A values at day 30 of the non-responders during the 6-month follow-up was significantly greater compared with the responders. The increased angiogenesis factor was VEGF-A in the present study. However, in the literature, VEGF-A and other angiogenesis factors, such as IL-6 and IL-8, were identified as factors that increased after TARE.[13,14,24] The reason for this difference may be the studies' small sample size and the patients' heterogeneity. However, according to the data obtained in the studies in the literature so far, including this one, VEGF-A is an angiogenesis factor that shows an increase after TARE. More data is needed to decide on other factors.

Based on these results, it can be assumed that percentage changes in VEGF-A values may help predict non-responders and shorter overall survival after TARE in HCC patients. This study's results show that the percentage changes of the angiogenesis factors at different times after TARE may help with early recognition of the non-responders to TARE. Thus, TARE can be combined with systemic treatments (anti-VEGF-A) for non-responding HCC patients. More than 50% of HCC patients with disease progression after TARE were ineligible to receive sorafenib due to poor liver function.[26] Therefore, it may be reasonable to begin the therapeutic regimen with a combined approach aimed at effectively treating patients while preserving liver function. Although the SORAMIC trial found no superiority of the TARE plus sorafenib combined treatment over the sorafenib regimen alone, the subgroup analysis indicated a survival benefit in patients aged <65 years, patients without cirrhosis, and patients with cirrhosis of non-alcoholic etiology.[27]

The angiogenesis cascade is regulated by the mechanism of balance in blood levels of angiogenesis and anti-angiogenesis factors.[28] Studies have shown that instantaneous increases in angiogenesis factor levels in the blood are more conducive than chronically high angiogenesis factor levels to recurrence and metastasis development.[29-31] Therefore, determining temporary changes in angiogenesis factor levels may be important for angiogenesis response analysis in patients undergoing TARE. Supporting this hypothesis, the levels of angiogenesis factors in the samples taken from the patients included in this study showed instantaneous increases in non-responders and a continuous decrease in responders. However, the large number of angiogenesis factors and the fact that increasing factors differ from patient to patient make it difficult to determine the accuracy of this hypothesis.

There are a number of limitations to this study. First, it was a single-center (although prospective) observational study, thus reducing its precision. Second, only a relatively small number of patients were included in the study. However, the number of patients was comparable with previously reported studies and the follow-up periods were long enough. Larger multicenter studies should be performed to better assess the changes in angiogenesis factors after TARE in HCC patients. Third, the only anti-angiogenesis factor levels evaluated were Ang-2. Since the cascade is a balance mechanism, angiogenesis and anti-angiogenesis factors should be analyzed together to evaluate the angiogenesis response. Fourth, patients with tumor thrombus were included in this study, whereas Lewandowski et al.[14] stated that the angiogenesis response due to chronic hypoxia might be affected in patients with tumor thrombus. However, in the presented study, changes in the angiogenesis factor levels and not absolute angiogenesis factor levels were emphasized. Therefore, the chronic hypoxia effect due to tumor thrombus can be ignored. Fifth, as all patients received segmental treatment, it was not possible to compare the effects of the lobar and segmental approaches. Segmental therapies would cause more embolic impact and higher radiation doses. In theory, then, growth factor upregulation would be higher in those patients. Last, only resin microspheres were used, characterized by higher particle volume, larger particle size, and lower specific activity. Comparative studies of resin vs. glass microspheres are therefore needed.

In conclusion, the angiogenesis response after TARE with Yttrium-90 occurs among HCC patients. Short-term changes in angiogenesis factor levels fluctuate with different amplitudes at different times. Assessing the changes of VEGF-A after TARE may help with the early identification of non-responders to the treatment. Gradual changes in the angiogenesis factor values, rather than instantaneous changes, are more valuable for evaluating the angiogenesis response after TARE.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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