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Holmium-166 Radioembolization of Hepatic Metastases in Salvage Setting: Preliminary Findings from a Single Center Experience

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Abstract

Purpose The aim of this study is to report the early outcomes of holmium-166 (^{166}Ho) radioembolization in the treatment of liver metastases.

Methods Nine patients with liver metastases originating from different primary sites were treated with ^{166}Ho radioembolization between January 2019 and February 2020. The patients were assessed for pain using a visual analog scale (VAS) and quality of life (QoL) at various intervals during hospitalization and follow-up. Toxicity that may be attributable to radioembolization was graded according to CTCAE v5.0. The tumor dosimetry and tumor response were assessed with anatomic and metabolic imaging.

Results The mean tumor dose was 150 Gy, 95% confidence interval (CI) was 135.2 to 164.8, with a range of 100 to 200 Gy based on single-photon emission computed tomography (SPECT)/CT, and distribution verified with inline T2/R2* magnetic resonance imaging (MRI) maps. No early (30-day) mortality or grade greater than 2 toxicities were noted, but one patient had chylous ascites. QoL assessed with the European Quality of Life 5-Dimensions 3-Level version (EQ-5D-3L) revealed mean index scores of 0.748 (range: 0.5–1), 95% CI of 0.6 to 0.9, before the procedure, and 0.7 (range: 0.5–1) and 95% CI of 0.6 to 0.8, at 1 month. The mean VAS was 70.6, 95% CI was 65.5 to 75.6, immediately after the procedure, and decreased to the mean VAS of 65.7 and 95% CI of 55.9 to 75.5 after 1 month. Five patients showed a partial response, three showed a stable disease, and one showed progressive disease at the first 2- to 3-month imaging follow-up.

Conclusion Radioembolization with ^{166}Ho microspheres for liver metastases appears to be safe, tolerable, and effective during the short term in this small-scale study.

Keywords
- holmium-166 microspheres
- radioembolization
- liver metastases

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Introduction

The first description of the use of holmium-166 (^{166}Ho) for radioembolization of hepatic malignancies was described by Nijsen et al.[1] ^{166}Ho is a highly paramagnetic metal element that enables biodistribution and quantification on magnetic resonance imaging (MRI) with a good correlation with single-photon emission tomography (SPECT).[2,3] Besides β particles, ^{166}Ho emits gamma photons that can be visualized under SPECT facilitating treatment dosimetry.[4,5] After receiving the European CE mark recently, ^{166}Ho was introduced in a limited number of patients and centers.[6] We aimed to report our experience with ^{166}Ho radioembolization in the treatment of liver metastasis.

Materials and Methods

Between January 2019 and February 2020, nine patients (six females and three males; mean age ± standard deviation: 56.3 ± 11.9 years) with metastatic liver lesions of different primary origins were treated with ^{166}Ho microspheres. Patients with liver only disease or stable extrahepatic metastatic disease and liver predominant disease, who were chemoresistant and unsuitable for other types of locoregional therapy, were included in the study. A multidisciplinary institutional gastrointestinal tumor board proposed the treatment beforehand. The exclusion criteria were similar to ^{90}Y radioembolization.[7] This is a retrospective case cohort study, which was approved by the institutional ethical committee (protocol number 21–159), and all the procedures were performed in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all the participants.

Radioembolization with ^{166}Ho

Mapping angiography and treatment angiography were performed using a 2.7-Fr microcatheter or a 2.8-Fr temporary occlusion balloon catheter (Progreat or Occlusafe; Terumo, Tokyo, Japan), which was placed through a 5-Fr standard catheter. A scout dose of ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA; 50–150 MBq) depending on the perfused liver volume was administered and assessed using SPECT (Siemens e.cam Signature, Siemens Medical Solutions, Erlangen, Germany). Two weeks later, ^{166}Ho-loaded poly (L-lactic acid) microspheres (QuiremSpheres, Quirem Medical B.V., Deventer, the Netherlands) with a maximum whole-liver dose of 60 Gy were administered based on the Holmium Embolization Particles for Arterial Radiotherapy (HEPAR) trial.[8] The procedure was performed according to the guidelines of Cardiovascular and Interventional Radiological Society of Europe (CIRSE).[9]

Just before and after the procedure, T2* fl2D images with 16 echoes with a starting echo time (TE) value of 1.5 milliseconds, a repetition time (TR) of 175 milliseconds, and a flip angle of 35 degrees were obtained. The distribution of paramagnetic ^{166}Ho microspheres was inspected by signal loss under MRI (MAGNETOM Skyra 3T, Siemens, Erlangen, Germany) after the procedure.[10] Tumor dosimetry was performed using SPECT images taken 3 days after the treatment. Inline T2* and R2* maps derived from MRI were evaluated qualitatively and quantitatively in comparison with SPECT.

Postprocedural Evaluation

This study classified any acute or chronic hepatotoxicity attributable to radioembolization but not disease progression or any associated therapies using laboratory and clinical findings based on CTCAE v5. Radioembolization-induced liver disease (REILD) was evaluated with a clinical presentation of jaundice, ascites, and a bilirubin increase over 2.92 mg/dL besides further definitions such as sinusoidal obstruction and hepatic necrosis.[11,12]

Patients were assessed for pain using a visual analog scale (VAS) before the procedure and at 2- to 4-hour intervals after the procedure in the first 24 hours. The maximum VAS pain scores during hospitalization compared with the preprocedural VAS pain scores with an increase of at least one were considered procedure related. Patients did not receive any nonmandatory premedication, and postembolization syndrome findings were managed on a symptom basis approach. Quality of life (QoL) was assessed with the EuroQol 5-Dimensions (EQ-5D) questionnaire, which assessed mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[13] A single index score and VAS were calculated at baseline and at 1 month.

The procedure was performed by an interventional radiologist and a nuclear medicine physician with 8 years of experience in performing radioembolization; they also evaluated the follow-up images. To evaluate the tumor response after radioembolization, in addition to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) with MRI, the metabolic response with a reduction in glycolysis on fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT was also considered in proper patients.[14,15]

Results

Nine patients who received radioembolization with ^{166}Ho microspheres had intrahepatic metastases originating from different primary sites (►**Table 1**). All patients had multiple metastases (>5), except for one who had two metastases. The mean size of the index lesions was 33 mm (smallest 10 mm and largest 123 mm). Patients had preserved liver function based on laboratory tests and sufficient performance status before treatment.

All but one patient had a bilobar disease; however, none of the patients received whole-lobar ^{166}Ho radioembolization during the single-session treatments. One patient had ^{90}Y radioembolization, four of the patients had radiofrequency ablation (RFA), and three had transarterial chemoembolization (TACE) separately before or after a time ranging from 3 weeks to 6 months. They all had previously received first-line chemotherapy regimens according to their primary disease. Six patients received unilobar treatment, and three patients received bilobar multisegmental treatment with split doses. In three patients, the standard dose of 60 Gy could not be administered due to the embolization effect creating a sluggish flow. The mean absorbed liver dose was

Table 1 Patient and treatment characteristics

Primary site	Age/ gender	Adjunct treatments	*t* number/size[a]	^{166}Ho TARE approach and dose[b]	Response[c]
Ovary ca	61/F	Paclitaxel + carboplatin, Caelyx + carboplatin, + bevacizumab TACE to LL (post-)	Multiple >5/15–12–11 mm	RL 40 Gy (150–175 Gy)	Stable
Colon ca	37/F	Metastasectomy RL FOLFOX + cetuximab, FOLFIRI + cetuximab, RFA to LL FOLFIRI + bevacizumab, irinotecan + bevacizumab Folinat-FU-cisplatin + VEctibix, LOnsurf	2/65 and 35 mm	LL 60 Gy (170–180 Gy)	Partial
Gastric ca	70/F	Herceptin + paclitaxel TACE to LL (post-)	Multiple >5/123–63–67 mm	RL 60 Gy (170–200 Gy)	Stable
Pancreas ca	58/M	FOLFIRINOX, capecitabine RFA and TACE to RL (post-)	Multiple >5/31–24–23 mm	RL 45 Gy (100–170 Gy)	Partial
Uveal melanoma	60/F	Paclitaxel + carboplatin ^{90}Y to RL	Multiple >5/13–10–10 mm	LL segments 2–3 and 4 60 Gy	Partial
Breast ca	61/F	Tamoxifen, Ibrance + Arimidex, docetaxel + Herceptin + Perjeta, capecitabine + vinorelbine	Multiple >5/45–27–25 mm	RL and segment 4 60 Gy (110–190 Gy)	Partial
Colangio ca	33/F	GEMOX mFOLFIRI	Multiple >5/29–23–17 mm	RL 40 Gy (110–130 Gy)	Stable
Colon ca	66/M	FOLFOX + bevacizumab RFA Capecitabin, FOLIRI-aflibercept, regorafenib	Multiple >5/39–17–13 mm	RL segments 5 and 6, 55 Gy (150–170 Gy) LL 55 Gy (135–170 Gy)	Partial
Pancreas ca	61/F	FOLFORINOX, GEMOX, FOLFIRI, docetaxel + gemcitabine RFA to LL (post-)	Multiple >5/48–42–28 mm	RL and segment 4 60 Gy (100–120 Gy)	Progression

Abbreviations: ca, cancer; F, female; LL, left lobe; M, male; t, tumor; RL, right lobe; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.
[a]Three index lesions if multiple.
[b]Absorbed liver doses versus tumoral doses in () according to posttreatment dosimetry.
[c]Respond assessed with RECIST 1.1 criteria and mRECIST where appropriate.

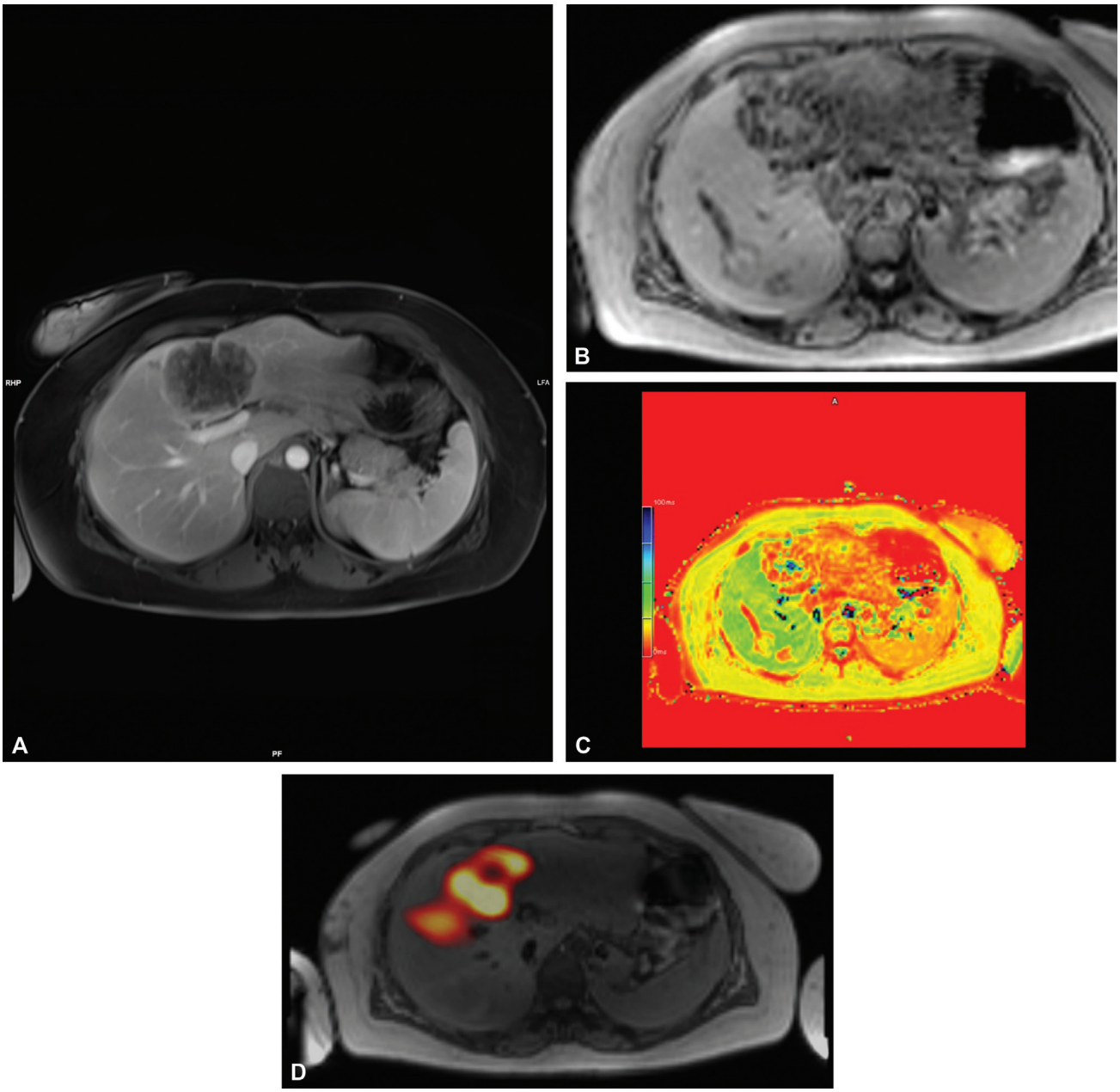

Fig. 1 A 37-year-old man with colorectal liver metastases. (**A**) Contrast-enhanced T1-weighted image showing a mass in the left lobe. (**B**) $T2^*$ and corresponding (**C**) $T2^*$ map (ms) showing increased paramagnetism in the left lobe and the tumor after ^{166}Ho radioembolization. (**D**) Corresponding posttreatment single-photon emission computed tomography (SPECT) fused on magnetic resonance imaging (MRI).

54.1 Gy, 95% confidence interval (CI) of 49.2 to 59, in 11 doses, including two split doses. The mean tumor dose was 150 Gy, 95% CI (135.2–164.8), with a minimum of 100 Gy and a maximum of 200 Gy. In one patient with uveal melanoma, tumor dosimetry SPECT could not be performed, as she was lost to follow-up after treatment. In all patients including the former one, the distribution of microspheres was confirmed with MRI using $T2^*$ and $R2^*$ maps (►**Fig. 1**). The mean follow-up period after ^{166}Ho radioembolization was 10.4 ± 3.17 months. One patient died 9 months after the procedure due to disease progression. One patient was lost to follow-up during the pandemic 6 months after the procedure. Five patients showed a partial response, three had stable disease, and one had progressive disease at the first follow-up.

Clinical and laboratory results during a 3-month follow-up were reviewed to assess treatment-related adverse events. Two cases of grade 3 pain, two cases of grade 3 nausea (in the same two patients), and no cases of early (30-day) mortality were identified. No grade greater than 2 toxicities was observed after the early period (►**Table 2**). In one patient, grade 3 delayed hepatobiliary toxicity with bilirubin levels greater than 3 mg/dL and intractable chylous ascites occurred within 6 weeks.

Immediately after the procedure, four patients had a pain VAS score of 9 to 10, which was relieved by patient-controlled morphine analgesia. The mean VAS in the first 24 hours was 5.8, 95% CI (3.2–8.3). Only two patients required extra analgesics or extended hospitalization because

Table 2 Follow-up according to CTCAE v5 and QOL besides VAS pain

	Pre-op	First 24 h	1 d post-op	1 mo post-op	3 mo post-op
Mean index score VAS (EQ-5D-3L)	0.748 70.555	–	–	0.717 65.666	–
Pain VAS (*n*)	–	9–10 (4), 6 (2), 3 (1), 0 (2)	3 (2), 4 (1), 0 (3), Grade 3 (2)	3 (1), 2(1)	–
Fever (*n*)	–	(2)	–	–	–
Nausea (*n*)	–	(4)	Grade 3(2)	–	–
Fatigue (*n*)	–	(9)	8	2	
Ascites (*n*)	–	–	–	Grade 3 (1)	Grade 3 (1)
Hyperbilirubinemia (*n*)	–	–	–	Grade 1	Grade 2
Hypoalbuminemia (*n*)	–	–	–	–	–
REILD (*n*)	–	–	–	–	–

Abbreviations: EQ-5D-3L, European Quality of Life 5-Dimensions 3-Level version; QOL, quality of life; REILD, radioembolization-induced liver disease; VAS, visual analog scale.

of pain after the procedure; these two patients were treated with split doses toward larger volumes of liver parenchyma.

QoL was assessed with EQ-5D-3L, which revealed mean index scores of 0.748 (range: 0.507–1), 95% CI (0.6–0.9), before the procedure and 0.7 (range 0.5–1), 95% CI (0.6–0.8), at 1 month. The mean VAS score was 70.6, 95% CI (65.5–75.6), immediately after the procedure and decreased to 65.7, 95% CI (55.9–75.5), 1 month after the procedure. Better index scores and VAS scores before radioembolization corresponded to better scores after the procedure.

Discussion

Although patients with liver metastases were successfully treated with ^{166}Ho radioembolization during the phase 1 and 2 studies of the HEPAR trials, multicenter experiences are still lacking related to real-world patients.[8,16] In this study, we investigated the feasibility of ^{166}Ho radioembolization for hepatic metastases in salvage settings. The patients had liver tumor involvement due to different primary cancers; accordingly, they also received various treatments, such as surgical ablation and embolization, in addition to systemic chemotherapy. ^{166}Ho radioembolization was associated with limited toxicity during the early period except for one case. Five patients showed a partial response, three showed stable disease, and one showed progressive disease at the first 2- to 3-month imaging follow-up. After the procedure, the patients were successfully treated for pain and postembolization syndrome during the first 24 hours. Compared with the preoperative QoL, the postoperative QoL was not obviously different during the clinical follow-up.

In their single-center study with ^{166}Ho radioembolization, Radosa et al reported no grade greater than 3 postembolization syndrome in three of nine patients with bilobar involvement of hepatocellular carcinoma (HCC) and corresponding bilobar treatment.[6] The results in their small cohort were comparable to those in ^{90}Y radioembolization studies performed with glass microspheres and resin microspheres.[17,18] When the latter two studies with two different microspheres were compared for radioembolization of HCC, the rate of postembolization syndrome was as high as 53% with resin microspheres and in similar ranges (2.5–5.9% at maximum) within 3 months in both studies. According to CTCAE v5, our study had two grade 3 cases of pain and two grade 3 cases of nausea, leading to prolongation of two patients' hospitalization. Given the heterogeneity of the patients, the multiplicity of the tumors and possible prior systemic chemotherapy side effects may also have contributed to the severity of the postembolization syndrome in our study. Prince et al reported grade 3 or 4 adverse events, with abdominal pain (18%) and nausea (8%) being the most common among a total of 37 metastatic liver patients after ^{166}Ho radioembolization procedures.[8] These findings are also comparable to those of Benson et al, who performed ^{90}Y radioembolization in 151 liver patients with liver metastases of several origins.[19]

No grade greater than 2 toxicities were observed after the early period, and no early (30-day) mortality was noted. One patient had a grade 3 delayed hepatobiliary toxicity, which may have been attributable to disease progression in the setting of progressive metastatic disease in the untreated segments of the liver.

Despite recent advances in tumor-directed therapies, such treatments are not without toxicities, and up to 95% of cancer patients consider the possible side effects of treatment to be as significant as survival.[20] van Roekel et al reported that the QoL did not change significantly in patients with liver metastases treated with ^{166}Ho radioembolization during the HEPAR trials.[21] They also reviewed the effect of Y^{90}-RE on the QoL in 14 studies with different liver malignancies and found similar results. In only two studies, including one on HCC and another on colorectal metastases, the QoL deteriorated after Y^{90} radioembolization.[22,23] We analyzed the QoL at 1 month, as the QoL was affected in the first weeks posttreatment due to postembolization syndrome.[20] Similarly, in our study, a better index

score and VAS score before radioembolization resulted in better scores after the procedure. Our data were not sufficiently large to produce statistically significant results. However, many factors should also be considered in metastatic liver patients, such as age, sex, cancer type, performance status symptoms, and extrahepatic disease, as they can affect the QoL.[16,24,25]

We performed ^{166}Ho radioembolization in 11 doses with the intent of achieving the maximum allowed liver absorbed dose of 60 Gy. Local control of the tumor was achieved in all but one patient during the follow-up. The major limitation of this study was the small sample size and heterogeneous cohort of liver metastases to determine the efficacy and feasibility. Yet, there are only a few reports published with ^{166}Ho radioembolization including HEPAR studies and a study focusing on nine cases of HCC. The novelty of the treatment might justify the need for small single-center studies before larger-scale multicenter prospective studies are designed.

After calculation with SPECT, the tumor dose was found to be between 100 and 200 Gy, while the liver dose was maintained below 60 Gy in our patients. As they were approved at later stages of this study, neither the Q-Suite software platform enabling evaluation of MRI signal loss due to T2* relaxation time shortening based on gradient echo sequences acquired with multiple echo times nor QuiremScout consisting of identical low-energy ^{166}Ho microspheres was used. This was another limitation of our study. Although performing ^{166}Ho radioembolization using ^{99m}Tc-MAA for the scout dose, SPECT, and MRI for dosimetry is feasible, the aforementioned CE-marked techniques may increase the consistency and quality of treatment. Inline R2* maps derived from MRI were used to calculate doses manually in our patients, and simplistic dosimetry calculations were performed comparable to SPECT dosimetry results. However, further discussion of these results is beyond the scope of this study since our method is not validated. Due to high energy caused by gamma emissions along with β particles that are considered suitable for internal radionuclide therapy, patients generally undergo SPECT on days 3 to 5 after ^{166}Ho radioembolization to prevent image degradation and noise. The distribution of the microspheres in relatively small volumes or with cystic necrotic components could be confirmed with qualitative assessment of MR images. This distribution was visualized under MRI up to several months after radioembolization, as it is independent of activity (►**Fig. 2**).

In three patients who had tumors with relatively small volumes, cystic necrotic components, and relatively hypovascular characteristics, the standard dose could not be administered due to the embolization effect creating a sluggish flow. Early stasis during radioembolization with

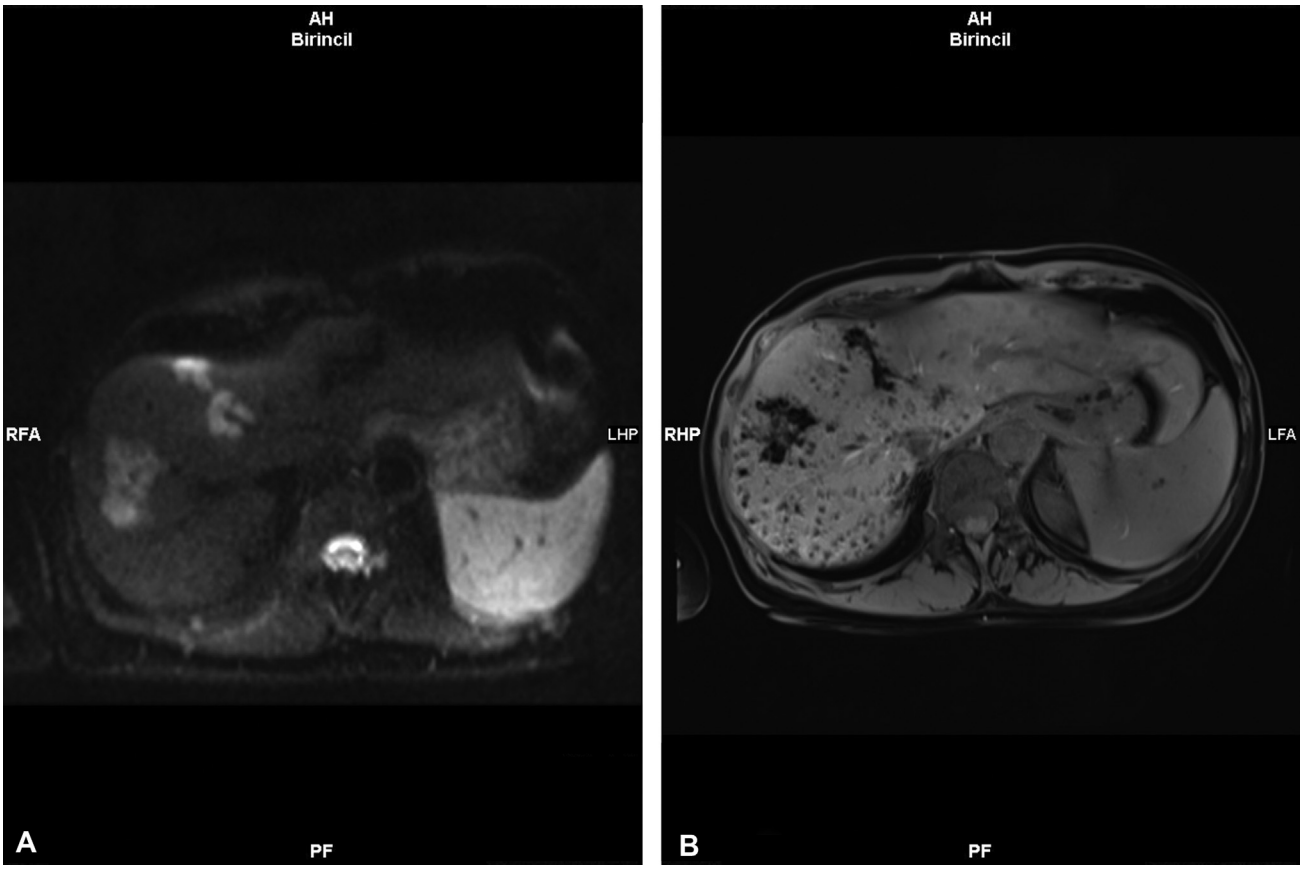

Fig. 2 A 61-year-old woman with breast cancer liver metastases. (**A**) Diffusion weighted image magnetic resonance (MR) showing hyperintense lesions. (**B**) T1-weighted multigradient echo image showing paramagnetic ^{166}Ho microspheres in the liver persisting 3 months after radioembolization with some shrinkage of the tumors.

resin microspheres has been reported in 20% of patients and even more frequently (38%) in patients receiving multiple prior lines of chemotherapy, such as those with colorectal cancer liver metastases.[26,27] ^{166}Ho microspheres have more particles and may have a more significant embolic effect than glass microspheres, similar to resin microspheres, which might also be true when managing relatively hypovascular and necrotic liver tumors such as metastases.[28] On the other hand, more particles, resulting in a more uniform particle distribution in a tumor, may be beneficial for larger tumor volumes or more hypervascular tumors and for multiple tumors.[29]

Conclusion

^{166}Ho microspheres in radioembolization for liver metastases with diverse origins in patients with a history of resection, ablation, chemoembolization, and ongoing chemotherapy appear to be safe, tolerable, and effective.

Ethical Approval

This is a retrospective case cohort study, which was approved by the institutional ethical committee (protocol number 21–159). Written informed consent was obtained from all the participants.

Conflict of Interest

None declared.

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