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A single-center experience in radioembolization as salvage therapy of hepatic metastases of uveal melanoma

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Abstract

Background: Overall survival (OS) of patients with hepatic metastases of uveal melanoma is strongly linked with hepatic tumor control. Due to the lack of an effective systemic chemotherapy, locoregional therapies like radioembolization should play an increasingly important role.

Purpose: To report complications and response rates of radioembolization as salvage therapy for hepatic uveal melanoma metastases.

Material and Methods: Between October 2006 and January 2014, eight patients (age, 59.1 ± 15.3 years; 5 men) with histologically proven uveal melanoma and hepatic metastases received radioembolization with glass microspheres at a single center. All patients had been heavily pretreated with multiple systemic/locoregional therapies resulting in a long median interval between diagnosis of hepatic metastases and radioembolization (17.1 months; range, 6.4–23.2 months). Follow-up consisted of clinical assessment, laboratory tests and tri-phasic computed tomography (CT) before and 1, 3, 6, 9, and 12 months after radioembolization. Response to therapy was evaluated by CT using RECIST version 1.1 and by survival time. Safety (laboratory and clinical toxicity) was rated according to Common Terminology Criteria for Adverse Events 4.03. Using Kaplan-Meier analysis time to progression of hepatic metastases (hTTP) and OS were calculated.

Results: One month after radioembolization 50% of patients presented with stable and 50% with progressive disease. Median hTTP and OS after radioembolization were 4.3 weeks (range, 3.4–28.6 weeks) and 12.3 weeks (range, 3.7–62.6 weeks), respectively. Median OS after diagnosis of hepatic metastases was 19.9 months (range, 7.3–31.4 months). Radioembolization was tolerated well in all patients without toxicity higher than grade 2.

Conclusion: Radioembolization is a safe salvage therapy even in heavily pretreated hepatic metastases of uveal melanoma.

Keywords
Liver metastases, uveal melanoma, radioembolization

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Introduction

Uveal melanoma is the most common primary malignant intraocular tumor and has an annual incidence of 1200–1500 cases in the USA (1). Due to early hematogenous micrometastases, up to half of the patients develop distant metastases. The most common initial site of metastases is the liver, which is involved in over 90% of patients with metastases (1–3). Without therapy the median overall survival in patients with hepatic metastases is less than 6 months (in the range

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Table 1. Systemic and locoregional therapies prior and after radioembolization in eight patients suffering from hepatic uveal melanoma metastases.

Patient no.	Treatments prior radioembolization	Treatments after radioembolization
1	Sorafenib, Melphalan i.a.	Treosulfan i.v. and Gemcitabin i.v.
2	Dacarbazine i.v. (once), Sorafenib, Melphalan i.a.	–
3	Sorafenib, Melphalan i.a., Fotemustin i.a.	Ipilimumab i.v.
4	Sorafenib, Melphalan i.a.	Melphalan i.a.
5	Melphalan i.a., Fotemustin i.a., TACE	Dacarbazine i.v.
6	Sorafenib, Melphalan i.a.	–
7	Sorafenib, Melphalan i.a., Fotemustin i.a.	–
8	BI 1247.1, Melphalan i.a., Fotemustin i.a.	–

BI 1247.1, Aurora-Kinase inhibitor; i.a., intra arterial; i.v., intravenous; TACE, transarterial chemoembolization.

of 2–9 months) (3–6). Due to the strong link between overall survival and hepatic tumor control as well as the lack of an effective systemic chemotherapy (1,7), locoregional therapies should play an important role in tumor treatment in these patients. Currently, different locoregional therapies like surgical resection, chemoembolization with or without usage of drug-eluting beads, immunoembolization, radioembolization, Fotemustin infusion therapy, and hepatic perfusion therapy have shown promising results regarding prolongation of overall survival and are therefore propagated (2). Because of the excellent response rate of the primary intraocular tumor to radiation (8), radioembolization represents a promising therapy option for hepatic metastases. However, few studies report on radioembolization of hepatic uveal melanoma metastases with resin microspheres (2), but no study exists regarding radioembolization with glass microspheres. Furthermore, the overall reported number of patients is limited. Hence, the aim of this study was to report complications and response rates of radioembolization with glass microspheres as salvage therapy of hepatic uveal melanoma metastases in a single center.

Material and Methods

Patients

Retrospective analysis and use of patient data were approved by the local ethics committee. A database inquiry was performed searching for all patients who received radioembolization for hepatic metastases of histologically proven uveal melanoma between October 2006 and January 2014 at a single center. Inclusion criteria for radioembolization were: (i) not curatively treatable hepatic uveal melanoma metastases refractory to previous systemic/locoregional therapies; (ii) liver dominant tumor disease; and (iii) a total bilirubin of less than 2.0 mg/dl. Exclusion criteria were: (i) uncorrectable extrahepatic shunting to gastrointestinal structures; and (ii) a cumulative lung dosage of greater than 30 Gy (9). All patients provided written informed consent for the treatment.

Eight patients (3 women, 5 men) were identified. The mean age at initial diagnosis of uveal melanoma was 58.8 ± 13.9 years (age range, 33–70 years). All patients had been heavily pretreated with multiple systemic/locoregional therapies prior to radioembolization (Table 1), which was exclusively used as a salvage therapy. Hence, mean time intervals between initial diagnosis of uveal melanoma and radioembolization (42.0 ± 25.2 months; range, 19.4–97.1 months; median, 31.0 months) and between initial diagnosis of hepatic uveal melanoma metastases and radioembolization (14.5 ± 5.9 months; range, 6.4–23.2 months; median, 17.1 months) were extremely long. All patients suffered from bilobar hepatic metastases with a hepatic tumor burden of $\leq$25% in three patients (37.5%), of 26–50% in four patients (50%), and of $>$50% in one patient (12.5%). Only one patient presented with extrahepatic metastases (retroperitoneal) prior to radioembolization and no patient suffered from portal vein thrombosis. The alkaline phosphatase level prior to radioembolization was 228.8 ± 158.4 U/L (range, 75–474 U/L, being elevated in five patients) and the lactate dehydrogenase level was 657.6 ± 783.1 U/L (range, 227–2587 U/L, being elevated in seven patients).

Radioembolization

As previously described, a digital subtraction angiography including 99 m-technetium labeled human serum albumin microspheres administration was conducted for preparation of radioembolization (10). According to the subsequent anterior-posterior planar gamma camera imaging of the trunk the hepato-pulmonary shunt fraction was calculated (11) and an extrahepatic tracer accumulation in the gastrointestinal tract excluded. 90-yttrium glass microspheres (TheraSphere TM, BTG, Hertfordshire, UK) were used for

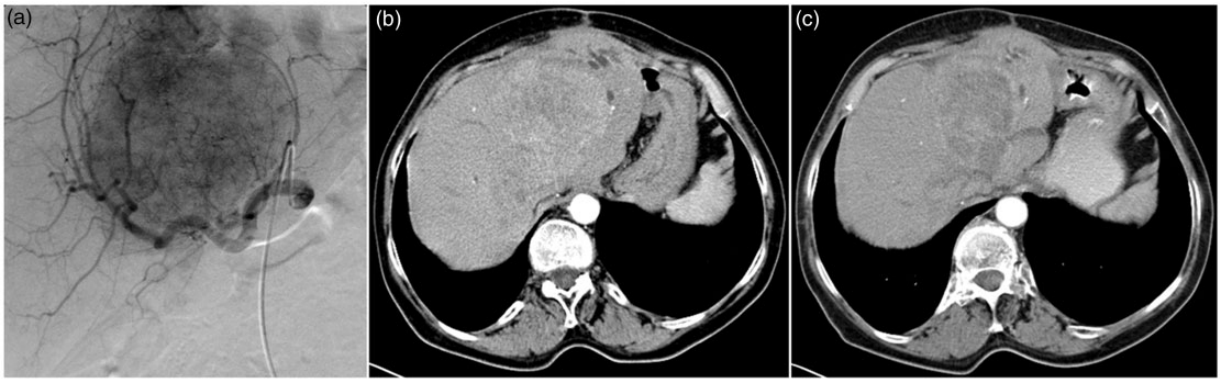

Fig. 1. A 78-year-old woman with bilobar hepatic metastases of uveal melanoma: prior to bilobar radioembolization in the digital subtraction angiography (a) and in the arterial CT images (b) a huge hypervascular tumor is visible, which presents 3 months after radioembolization (c: arterial CT image) with obviously decreased hypervascularity.

radioembolization. The radioembolization dose was calculated basing on the targeted liver volume, the used dose range was 110–130 Gy (12,13). Radioembolization was performed 5.6 ± 2.3 weeks (range, 3–9 weeks) after the pre-therapeutic digital subtraction angiography. The therapeutic procedures were done in the same way as the pre-therapeutic digital subtraction angiography using a lobar arterial approach.

Six patients received bilobar radioembolization on a single day (Fig. 1), one patient received a sequential radioembolization of both liver lobes with an in-between interval of 4 weeks, and one patient died after radioembolization of the right liver lobe before the intended left lobar radioembolization could be performed. The mean applied target dose was 122.3 ± 7.2 Gy (range, 110–130 Gy) in the right and 115.7 ± 5.3 Gy (range, 110–120 Gy) in the left liver lobe. The mean applied activity was 4.28 ± 3.36 GBq (range, 1.7–12.2 GBq) in the right and 1.51 ± 0.56 GBq (range, 1.0–2.6 GBq) in the left liver lobe. The median hepato-pulmonary shunt fraction was $3.3 \pm 1.0\%$ (range, 2.0–5.0%).

Assessment of complications and response rates

All patients received a clinical assessment, laboratory tests including bilirubin, glutamic oxaloacetic transaminase, glutamate pyruvate transaminase, gamma-glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, leukocytes, thrombocytes, quick, hemoglobin, creatinine, and S-100 beta (as tumor marker for metastatic uveal melanoma (14)), and a tri-phasic computed tomography (CT) of the upper abdomen before, 1 day after radioembolization (without S-100 beta and CT control), and 1, 3, 6, 9, and 12 months after radioembolization. All CT scans were acquired by a Somatom Definition scanner (Siemens Healthcare, Erlangen, Germany) at 120 kVp, using a collimation of 128×0.6 and a slice thickness of 5 mm. A total of 100 mL Ultravist 300 (Iopromid 300, Bayer HealthCare, Leverkusen, Germany) followed by 40 mL saline were administered at a rate of 3.0 mL/s. Therapy complications (clinical and laboratory toxicity) were rated according to Common Terminology Criteria for Adverse Events (CTCAE 4.03 (15)). To assess the response rate of the therapy all CTs were retrospectively reevaluated by an experienced radiologist (7 years of experience in abdominal imaging) focusing on the liver and using RECIST version 1.1 (16,17). Furthermore, dates of death were taken from the medical reports, respectively were gathered by telephone interview from the general practitioners.

Statistical analysis

Statistical analysis was performed using SPSS Statistics 19.0 (IBM Corp., Armonk, NY, USA). Means and standard deviations are given for normally distributed data and medians and ranges for other variables. Using Kaplan-Meier analysis, time to progression of hepatic metastases (hTTP) and overall survival (OS) were calculated. Because Stubbs et al. had reported currently that there was no significant difference in overall survival between patients presenting with stable disease (SD) and patients presenting with partial response (PR) after radioembolization for hepatic metastases of colorectal cancer (18), we rated complete response (CR), PR, and SD as local tumor control.

Results

Complications after radioembolization

Initially radioembolization was tolerated well by all patients and there was no peri-interventional toxicity higher than grade 2 (nausea which required antiemetic medication one day after radioembolization in one

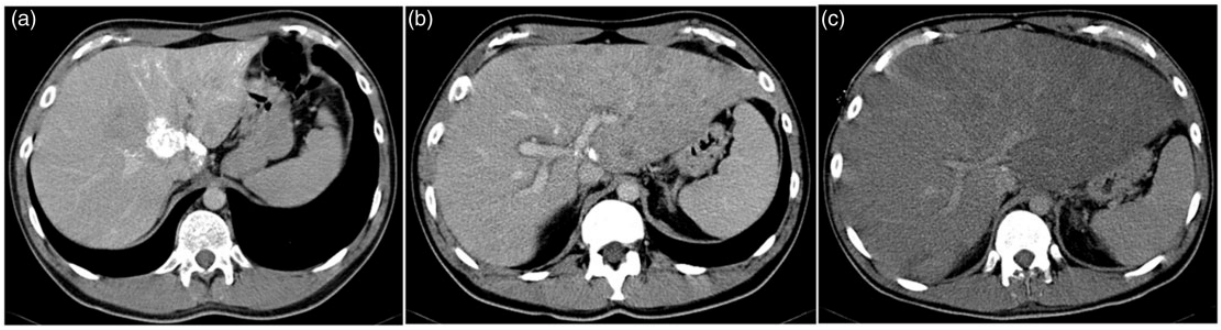

Fig. 2. A 35-year-old man with bilobar hepatic metastases of uveal melanoma (portal venous CT images): (a) prior to right-sided radioembolization, status after TACE, (b) 1 month after solely right-sided radioembolization: right-sided stable disease but progressive left-sided hepatic tumor, (c) 2 months after solely right-sided radioembolization and 7 days after Dacarbazine administration: extensive mainly left-sided diffuse liver edema and enlargement.

patient). In five of eight patients laboratory controls 1 month after radioembolization were available. This was due to intermittent death in one patient because of its progressive hepatic tumor disease and missing laboratory results in two other patients. In the five patients with available laboratory results these did not reveal any new relevant radioembolization induced laboratory toxicity (graded according to CTCAE 4.03).

One patient, in whom a sequential radioembolization was planned, showed good tumor response to radioembolization in the solely treated right liver lobe (SD), but had heavily progressive metastatic disease in the non-treated left liver lobe and extra-hepatically (Fig. 2a, b). Six weeks after radioembolization of the right liver lobe, on account of the left hepatic and extrahepatic tumor progression, this patient received Dacarbazine systemically. Subsequently a fulminant progressive liver failure developed, which presented as predominantly left-sided swollen liver on CT (Fig. 2c).

Response rates after radioembolization

One month after radioembolization four patients presented with SD (50%) and four patients with progressive disease (PD, 50%). Regarding CR, PR, and SD as local tumor control this was achieved in 50%. Within the patient group with SD three subjects had an initial tumor burden of $\leq$25% and just one subject of 26–50%. Within the patient group with PD one subject had an initial tumor burden of >50% and three subjects of 26–50%. The patient with the initial hepatic tumor burden of >50% died 26 days after radioembolization due to its progressive hepatic metastases. Three months after radioembolization, of the remaining seven patients three had SD (43%) and four PD (57%). Median hTTP after radioembolization was 4.3 weeks and mean hTTP after radioembolization 12.4 weeks (range, 3.4–28.6 weeks, Fig. 3). Median OS after radioembolization was 12.3 weeks and mean OS after radioembolization 25.1 weeks (range, 3.7–62.6 weeks, Fig. 3). Accordingly, median OS after the initial diagnosis of hepatic metastases was 19.9 months and mean OS after initial diagnosis of hepatic metastases 20.2 months (range, 7.3–31.4 months, Fig. 4). S-100 beta was available 1 month after radioembolization in three patients and had slightly decreased from $0.26 \pm 0.20\,\mu g/L$ prior to $0.15 \pm 0.05\,\mu g/L$ after radioembolization.

Discussion

The results of the current study suggest that radioembolization using glass microspheres is a safe locoregional salvage therapy in patients with hepatic metastases of uveal melanoma. Initially even in our heavily pretreated patients with a long interval between initial diagnosis of hepatic metastases and radioembolization SD was achieved in 50%.

Kennedy et al. reported on 11 patients from five different centers with bilobar hepatic metastases of uveal melanoma and radioembolization with resin microspheres (19). There was no relevant radioembolization related toxicity. Six weeks after radioembolization in nine patients, who underwent the follow-up examinations (CT or magnetic resonance imaging [MRI]), one patient was reported with CR, six with PR, one with SD, and one with PD. Three months after radioembolization, based on PET/CT, Kennedy et al. reported CR in one, PR in six, and SD in two patients. The survival rate at 1 year was 80%. In our cohort, considering CR, PR, and SD as local tumor control, 1 month after radioembolization, the local tumor control rate was only 50%. However, Kennedy's patients had a median time interval between initial diagnosis of uveal melanoma and radioembolization of only 25.5 months, in contrast to 31.0 months in our cohort. Unfortunately, Kennedy et al. did not specify the time interval between initial diagnosis of hepatic

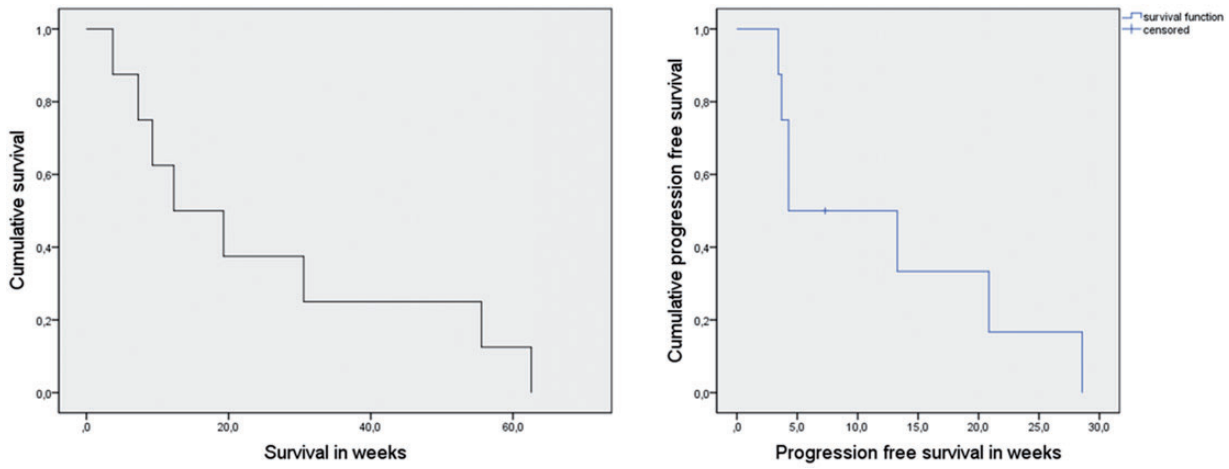

Fig. 3. Overall survival and time to progression of hepatic metastases (both starting at time of radioembolization) in eight patients with hepatic uveal melanoma metastases who received radioembolization (presented by Kaplan Meier curves).

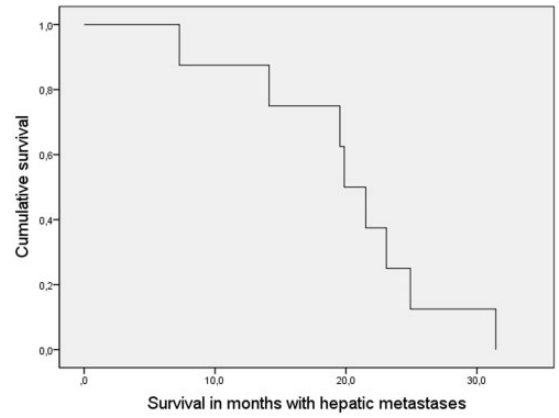

Fig. 4. Overall survival (starting at time of diagnosis of hepatic metastases) in eight patients with hepatic uveal melanoma metastases who received radioembolization (presented by Kaplan Meier curve).

metastases and radioembolization, nor did they report the initial hepatic tumor burden which is known to influence the clinical outcome after locoregional therapy of hepatic uveal melanoma metastases (20–22). Judged by the time difference between initial diagnosis of uveal melanoma and radioembolization between both patient cohorts, we assume a difference in initial tumor burden as well. This may present a possible explanation for the different rate of local tumor control in both cohorts after radioembolization.

Recently, Klingenstein et al. reported on 13 patients with hepatic uveal melanoma metastases treated by radioembolization with resin microspheres as a salvage therapy in a single center (23). No direct treatment related toxicity was seen, except for one partly treatment related hepatomegaly (rated as grade 4 toxicity). Two to three months after radioembolization Klingenstein et al. found PR in eight patients (62%), SD in two patients (15%), and PD in three patients (23%) applying RECIST version 1.0 criteria in MRI, corresponding to a local tumor control rate of 77%. Using PET/CT PR was found in three (23%), SD in three (23%), and PD in seven patients (54%). S-100 beta did not statistically decrease after radioembolization in their cohort. The median OS after radioembolization was 7 months, in contrary to only 2.8 months (mean OS after radioembolization, 5.8 months) in our cohort. In Klingelstein's cohort the median OS after diagnosis of hepatic metastases was 19 months, while it was 19.9 months in our cohort. This disparity between the shorter OS after radioembolization, but the longer OS after initial diagnosis of hepatic uveal melanoma metastases in our cohort may be explained by the heavy pretreatment and the longer median time interval between initial diagnosis of hepatic metastases and radioembolization in our study population (17.1 months, respectively, 5 months in Klingelstein's cohort). Klingelstein et al. found a 1-year survival rate of 38% and did not find a significant difference between RECIST and PET/CT criteria in predicting OS after radioembolization.

In 2014 Eldredge-Hindy et al. reported on 71 patients with radioembolization using resin microspheres for metastatic uveal melanoma ((24,25); the 32 patients initially reported by Gonsalves et al. seem to be included in the later reported 71 patients of Eldredge-Hindy et al.). Eldredge-Hindy et al. were the first to report on radioembolization as first-line therapy in hepatic uveal melanoma metastases (in 13 of their patients). No radioembolization related toxicity greater than grade 3 was observed. Three months after radioembolization cross sectional imaging (CT or MRI) in all 71 patients showed PR in 8%, SD in 52%, and PD in 39%

of the patients. Therefore, their local tumor control rate was 60%, while it was only 43% in our cohort. This difference of local tumor control rate again is most likely caused by the different time intervals between initial diagnosis of hepatic metastases and radioembolization (9.8 months in Eldredge-Hindy's cohort versus 17.1 months in our cohort), the extensive pretreatment and possibly a greater initial tumor burden in our cohort. Unfortunately Eldredge-Hindy did not report the initial tumor burden of all patients. They reported a median OS after radioembolization of 12.3 months, while it was only 2.8 months (mean OS, 5.8 months) in our cohort. Additionally, they reported a significantly longer OS in their first-line radioembolization group compared to their salvage therapy group, which may be caused by the different interval between initial diagnosis of hepatic metastases and radioembolization in both groups (2.1 versus 11.3 months) and by a possibly higher therapy resistance in the salvage therapy group. Because of this and other recent studies reporting a better clinical outcome after locoregional therapy of hepatic uveal melanoma metastases in patients with an initially low hepatic tumor burden (20–22), radioembolization should be embedded not too late in the therapeutic process in these patients. The median survival after diagnosis of hepatic metastases was 23.9 months in Eldredge-Hindy's cohort, while it was 19.9 months in our cohort.

In addition, Eldredge-Hindy et al. searched for prognostic factors for poor clinical outcome after radioembolization and identified male sex and high metabolic tumor volume (measured by PET/CT) as such (24). Comparing the gender distribution between our and Eldredge-Hindy's cohort, women were underrepresented in our group (37.5% versus 52%), which may as well partly explain our lower local tumor control rate. Eldredge-Hindy et al. did not find a significant difference in therapy response after radioembolization between the first-line therapy and the salvage therapy group, which may be caused by the small number of first-line radioembolizations (13 patients) in their study.

Because of the temporal sequence of events and the previously reported cases of liver necrosis and failure due to Dacarbazine administration, we interpreted the above described progressive liver failure in one patient as most likely Dacarbazine induced. As reported previously, there have been several cases of Dacarbazine induced liver failure with fatal outcome (26–29). In these patients a massive enlargement of the liver with signs of hepatic venous congestion has been reported, which was exactly the case in our patient. In all autopsied cases an occlusion of small- and medium-sized hepatic veins with an adjacent eosinophilic infiltration and a massive liver necrosis has been described, leading to the assumption that the underlying cause may be an allergic thrombophlebitis in the liver with secondary liver cell necrosis. Doering et al. therefore proposed to avoid Dacarbazine in patients with pre-existing liver disease (28). As radioembolization always leads up to a certain degree to radiation induced damage of the adjacent normal liver tissue, it has to be taken into account that the liver failure in our patient could be due to a reduced liver function after right lobar radioembolization and non target parenchyma irradiation. This may have led to an increased chemotoxicity of Dacarbacin and the subsequent liver failure. Therefore, Dacarbazine should be avoided after radioembolization to prevent this lethal drug complication.

Our study is not without limitations. First and foremost, this is a retrospective study of a small single-center patient cohort. However, due to the infrequence of uveal melanoma, only limited patient numbers of a few centers and no series using glass microspheres have been reported so far. For this reason it is important to gather further scientific data. Second, all patients had received different systemic and locoregional therapies for their hepatic uveal melanoma metastases before and partially after radioembolization, but this is a usual problem in observational studies.

In conclusion, radioembolization with glass microspheres is a safe and feasible salvage therapy even in heavily pretreated patients with hepatic metastases of uveal melanoma. Based upon recently published data, radioembolization is more efficient in limited initial hepatic tumor burden and should therefore be embedded not too late in the treatment regime of hepatic uveal melanoma metastases. Further investigation regarding radioembolization in hepatic uveal melanoma metastases in larger cohorts should be performed, especially focusing on radioembolization as first-line therapy.

Conflict of interest

None declared.

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