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ORIGINAL PAPER

Preliminary experience with transarterial chemoembolization (TACE) in liver metastases of uveal malignant melanoma: local tumor control and survival

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Abstract
Purpose To evaluate results in the palliative treatment of patients with liver metastases of uveal malignant melanoma using transarterial chemoembolization (TACE).
Materials and methods Superselective TACE was repeatedly performed in 12 patients with liver metastases of uveal malignant melanoma. Six patients presented with solitary liver metastases (6–12 cm in size) and six patients with oligonodular metastases ($n \leq 6$). The embolization suspension consisted of a maximum of 10 mg/m^2 Mitomycin C, 10 ml Lipiodol, and an injection of 200–450 mg resorbable microspheres for vascular occlusion. In the follow-up, magnetic resonance imaging was performed in 3-month intervals.
Results The TACE procedure was well tolerated in all patients without any relevant side effects. Three patients responded to TACE with a size reduction of more than 50% (partial response), five patients with stable disease, and four patients with progressive disease with an increase in volume of more than 25%. Mean survival following primary tumor treatment was 32.9 months, and after first embolization 19.5 months. Lower survival rates were recorded for the progressive group (16.5 months).
Conclusion Repeated TACE offers a palliative treatment option in patients with oligonodular liver metastases of uveal malignant melanoma.

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Introduction

The treatment of progressive growth and recurrent unresectable metastatic lesions of malignant melanoma confined to the liver is still a major clinical challenge. More than 80% of patients with ocular melanoma develop liver metastases as the first site of recurrent disease (Braun et al. 1998; Flaherty et al. 1998; Gragoudas et al. 2002). A vast majority of those patients are not suitable for surgical resection (Feldman et al. 2004). Death from progression of hepatic disease typically occurs a few months after diagnosis (Fan et al. 1998). Although ocular melanoma differs from cutaneous melanoma in terms of etiology, histopathological characteristics, and clinical entity, imaging characteristics and angiographic behavior are comparable.

From the anatomical and physiological points of view, the liver is the main organ that allows interventional local embolization and chemoperfusion to achieve necrosis of the cancer area by reducing or eliminating unnecessary systemic toxicity (Vogl et al. 1999, 2000). For this reason, transarterial chemoembolization (TACE) can be considered as a possible therapeutic method for liver-metastatic lesions of malignant melanoma in early diagnosed and selected patients (Feldman et al. 2004). By definition, the embolization components of TACE definitely interrupt the blood supply to the tumor and produce ischemic necrosis and shrinkage, thereby leading to controlled growth or even regression of the tumor (Vogl et al. 1999, 2000;

Livraghi 2001). Using TACE, a higher concentration of chemotherapeutic drugs might be delivered; in this respect, cisplatin and epirubicin are the most commonly used drugs (Wallace et al. 1990; Vogl et al. 2000).

The main purpose of this study is to evaluate the feasibility of selective TACE for controlling metastatic spread to the liver in a palliative approach. Additionally, prognostic factors like the degree of lipiodol enhancement are analyzed.

Materials and methods

From July 2000 to July 2004, TACE was performed in a prospective pilot study in a total of 12 patients (six males and six females). Six patients presented with solitary liver metastases (6–12 cm in size), six patients with oligonodular liver metastases (maximum number of metastases, six; 4–7 cm in size). The mean age was 53.4 years (SD ± 16.5 years). The mean tumor volume of the hepatic metastatic infiltration was 111.3 ml (SD ± 55.8 ml; range 12–204 ml) (Table 1). The mean number of treatment cycles was 4.6 (SD ± 1.9; range 3–7). The treatment was continued until no further size reduction was achieved or patients showed signs of progression after at least three repeated treatment cycles.

Patients were required to have a history of ocular melanoma and histologically proven liver metastases, verified by magnetic resonance imaging (MRI). Patients who met the inclusion criteria were consecutively recruited. Other inclusion criteria were as follows: age ≥18 years, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate hepatic (bilirubin <3× normal), hematological (white blood cell count >4,000/mm^3, platelet count >100,000/m^3), and renal (creatinine <2.0 mg%, creatinine clearance >50 ml/min) values. Any previous systemic antineoplastic therapy had to be completed at least 4 weeks prior to the study entry. Pregnancy was a contraindication to the treatment and all patients had to use an acceptable form of contraception while taking part in the study. The study was approved by the institutional review board, and written consent was obtained from all patients. All patients had been diagnosed as having no simultaneous involvement of other organs when they were referred to our center or initially evaluated.

The patients developed liver metastases 1 month to 3 years after first diagnosis of initial primary melanoma. Before undergoing TACE, the patients had received other treatments, which were surgical resection of liver tumors ($n = 4$), systemic chemotherapy ($n = 8$), and radiation therapy ($n = 3$).

TACE technique

After the introduction of a 4-5 French pigtail catheter through the femoral artery, an angiographic survey of the abdominal vessels was performed. Mesenteric arteriography was performed to check the presence of a right hepatic artery. Indirect portography was performed next to outline the portal circulation in the venous phase. A 4-5 French Cobra catheter (Terumo, Frankfurt/Main, Germany) was placed in the celiac trunk and advanced beyond the gastroduodenal artery. Depending on the size, location, and arterial supply of the tumor, the tip of the catheter was advanced further into the segmental arteries for superselective embolization using a Tracker catheter (Boston, Frankfurt, Germany). The embolization suspension consisted of a maximum of 10 mg/m^2 of Mitomycin C (Medac, Hamburg, Germany) as the chemotherapeutic agent and a maximum of 15 ml of iodized oil (Lipiodol; Guerbet,

Table 1 Patients, diagnosis, number of treatments, tumor volume, and clinical course

Patient number	Age	Sex	Total tumor volume (ml) per treatment	TACE cycles	Course	Survival (months) start with first TACE	Survival (months) onset of melanoma diagnosis
1	30	M	72	3	sd	18.3	30.2
2	30	M	70	8	pd	26	38
3	34	F	12	3	pr	21.7	39
4	39	F	145	5	sd	30	37
5	52	M	170	3	sd	15.7	27.9
6	60	F	145	7	pd	25 alive	45
7	60	M	47	3	pr	15 alive	24
8	60	F	204	3	sd	10 alive	33
9	61	M	148	4	pd	5.5	12.4
10	64	F	132	7	pr	21	36.5
11	72	F	80	6	sd	14.5	27.2
12	79	M	111	3	pd	8.3	27.9

sd Stable disease, pd Progressive disease, pr Partial response

Sulzbach, Germany), followed by an injection of 200–450 mg microspheres (Spherex, Pharmacia & Upjohn, Erlangen, Germany) for vascular occlusion. The embolization suspension was injected slowly under fluoroscopic control. After embolization, devascularization was confirmed by an additional angiographic study of the hepatic artery. The study was designed to perform three courses of repeated chemoembolization at 4-week intervals.

Pre-treatment and follow-up studies

The complete history and physical examination was performed prior to the study entry including pre-treatment laboratory values with complete blood count (CBC), including differential and platelet count, blood urea nitrogen (BUN), electrolytes, creatinine, glucose, calcium, phosphorus, magnesium, albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, direct bilirubin, prothrombin time (PT) and partial thromboplastin time (PTT), a pregnancy test for pre-menopausal women, urine analysis, carcinoembryonic antigen, and 24-h creatinine clearance. In the pre-study evaluation, all patients underwent chest X-ray and electrocardiogram. Baseline tumor evaluations were obtained by nonenhanced and enhanced MRI scans no longer than 6 weeks prior to the administration of the first treatment.

Tumor response was assessed via standard response criteria based on the MR evaluation. Complete response was defined as complete radiographic disappearance of evident hepatic disease for at least 4 weeks. A partial response was defined as a decrease of 50% or more in perpendicular diameter of all measurable hepatic lesions lasting at least 4 weeks, without an increase in size or the appearance of new lesions. Stable disease was defined as an increase of less than 25% in liver lesions or a decrease of less than 50% in all measurable lesions. Progressive disease was defined as an increase of more than 25% in liver lesions or the appearance of any new lesions within the liver or elsewhere.

Plain and contrast-enhanced CT and MRI for initial treatment planning were obtained in all patients. All CT studies were performed using a spiral technique with fourth-generation scanners (Somatom Plus or Somatom Plus 4, Siemens, Erlangen, Germany). Twenty-four hours after embolization, retention of Lipiodol in the tumor and liver parenchyma was verified by an unenhanced CT examination protocol (Siemens, VolumeZoom). The degree of lipiodol and embolization material uptake was visually graded as low, moderate, or high. Quantitative measurements were not possible due to partially inhomogeneous uptake of Lipiodol. Unenhanced and contrast-enhanced T1- and T2-weighted MRI studies (Siemens, Symphony, 1.5T) were performed in the post-treatment phase and plain MRI studies (T1-weighted spin-echo (SE), T1-weighted gradient echo (GRE) sequences) after every TACE cycle. The follow-up after TACE was based on the CT evaluation of lipiodol retention and MRI volumetric evaluation of the treated liver metastases. The tumor volume was measured using an automated software program, analyzing the area of the tumor per slice and adding those values for the tumor-containing slices.

The initial MRI studies were evaluated regarding the degree of vascularization of the metastases. Visually, the judgment was based on the degree of uptake. Similarly, the obtained angiograms were subjectively evaluated concerning the degree of vascularization. A hypovascular pattern was defined as a lower degree of contrast enhancement versus the surrounding normal liver parenchyma and a moderately hypervascular pattern as a stronger enhancement. A truly hypervascular morphology was judged as a constant-enhancing blush phenomenon versus the normal liver parenchyma.

The scheduled number of performed TACE examinations was based on the imaging findings during follow-up. The follow-up included a regular clinical follow-up and an MRI control of the liver in 3-month intervals in the first year after the first TACE session and in 4-month intervals in the following year. A minimum of three interventions with a 4-week interval was planned by performing further procedures until a stable disease was achieved or no further downsizing of the liver metastases was possible. The cumulative survival times were calculated beginning with the commencement of the first TACE treatment by using the Kaplan–Meier method. For statistical analysis, we used the X^2 and log-rank tests. $p = 0.5$ indicated a significant difference.

Results

Safety

All patients tolerated the repeated treatment well and no clinically relevant side effects or adverse events were observed. In the clinical observation period 8 h after treatment, one patient developed slight nausea without vomiting. Two patients developed transient headache 1 day after the procedure. Three patients had a temperature rise in the period from 2 to 4 days post-treatment

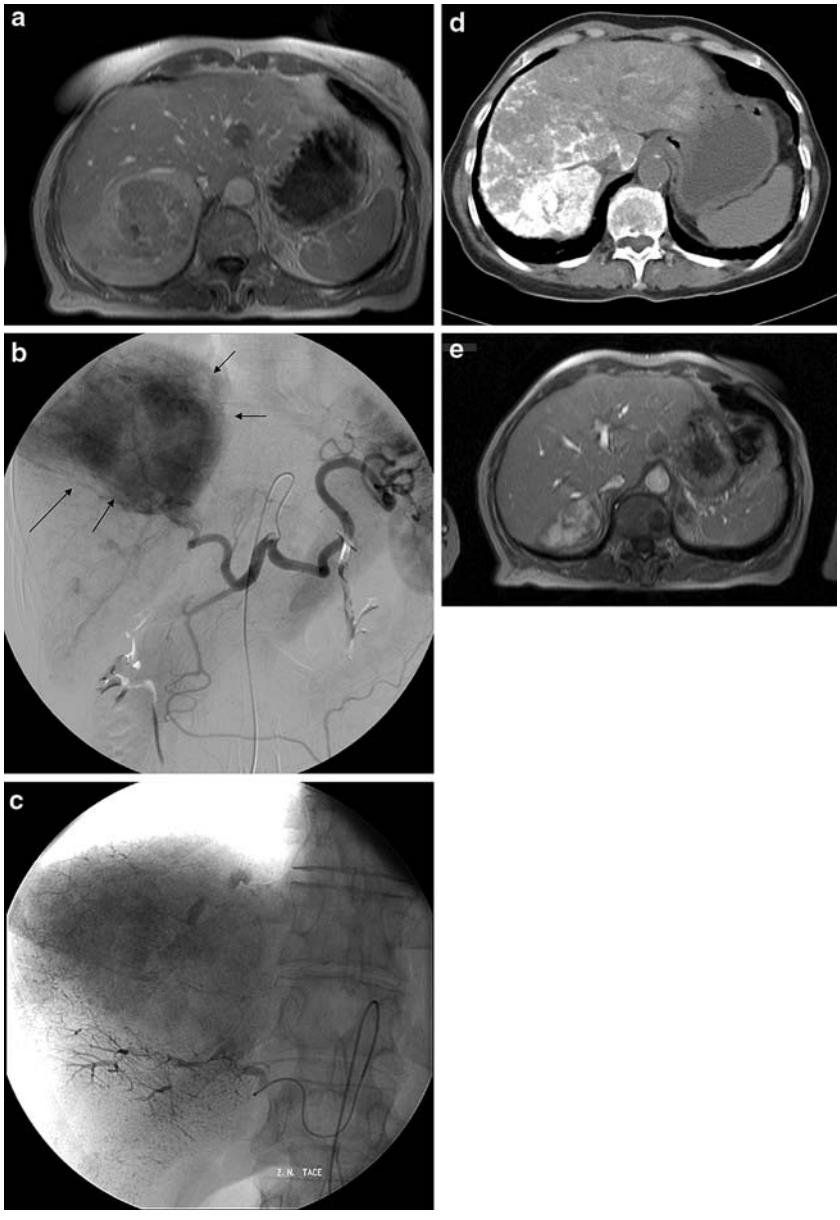

Fig. 1 A 64-year-old woman with a solitary liver metastasis of a malignant melanoma in segment 7. **a** Transverse T1-weighted (TR116/TE 5) contrast-enhanced image shows a moderately hypervascular metastasis of 80 × 68 mm in size in the right liver lobe pre-TACE. **b** Angiogram obtained during the first course of TACE reveals the hypervascularity of the target metastasis (*arrows*). **c** Angiography of the right hepatic artery with devascularization. The embolization suspension consisted of 10 mg/m^2 of Mitomycin C and 15 ml of lipiodol, followed by an injection of 200–450 mg microspheres for vascular occlusion. Note the hyperdensity of the treated metastases due to intratumoral lipiodol uptake during embolization. **d** Unenhanced transverse CT scan—after the first course of TACE—shows the tumoral lesion with hyperattenuation caused by retention of iodized oil. **e** Transverse contrast-enhanced T1-weighted MR image demonstrates a 50% volume reduction of the tumor post three cycles TACE

without the necessity for treatment. No treatment-related death or major complications such as abscess or bleeding were observed. The treatment protocol proved to be effective on an outpatient basis.

Imaging findings

The evaluation of pre-interventional MRI and selective hepatic angiography revealed a hypovascular pattern of the melanoma metastasis in one patient (8.3%), a moderately hypervascular pattern in five patients (41.7%), and a truly hypervascular morphology in six patients (50%).

The post-evaluation CT 24 h after embolization scanning revealed a post-TACE uptake pattern in accordance with the angiographic findings, with a low degree of intratumoral lipiodol uptake in the patient with hypovascular liver metastases, a moderate degree of uptake in six patients (50%), and a high degree of uptake in all patients with hypervascular morphology. In all patients, CT evaluation revealed a slight increase in the density of the normal liver parenchyma in the treated liver segments, due to the lipiodol uptake in the nontarget but neighboring liver parenchyma.

Local response and survival

The local response evaluation was based on the combined judgment of the size and volume of the lesions in plain MRI, the degree of uptake in unenhanced CT post embolization, and the angiographic evaluation of hypervascular intratumoral areas.

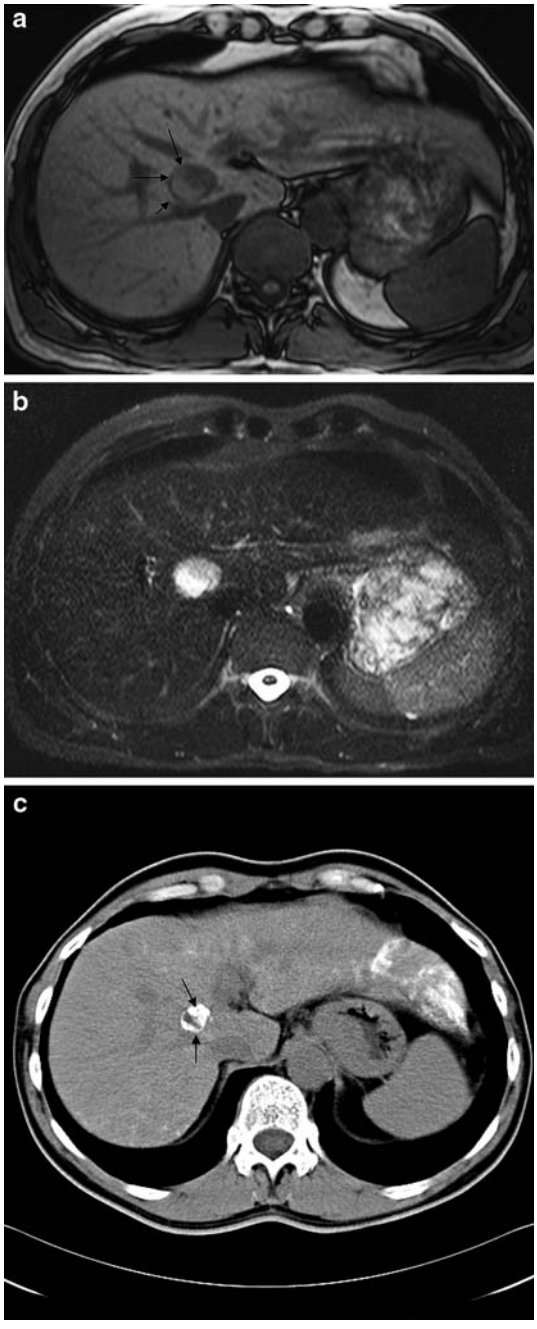

Fig. 2 A 60-year-old man with a liver metastasis of malignant melanoma undergoing three cycles of TACE (pre- and post-procedure) (partial response group). **a** Transverse T1-weighted (TR/TE/FA = 198 ms/2 ms/70°) MR scan showing a lesion of 25 × 20 mm in size in the right liver lobe pre-TACE. Note the hyperintense rim in the posterior part of the tumor (*arrows*). **b** Transverse T2-weighted (TR/TE/FA = 1,000 ms, 84 ms, 150°) MR scan demonstrates the metastases with an intratumoral rim of high signal intensity centrally in the liver pre-TACE. **c** Unenhanced transverse CT shows lipiodol retention (*arrows*) in the down-sized tumor post-chemoembolization in the 6-month follow-up after TACE

Three patients responded to TACE with a size reduction of more than 50% after the third course of TACE (Figs. 1, 2). The mean percentage of volume reduction was 56% in this group (Table 1). Five patients presented with stable disease and no significant change in the tumor volume before and after the third cycle of TACE. Four patients presented with progressive disease, with an increase of more than 30% in volume and total number of liver metastases after the third course of TACE. Interestingly, all patients with a hypervascular pattern of liver metastases (Fig. 3) showed either a partial response ($n = 3$) or stable disease ($n = 3$). Progressive disease was only found in patients with a lower degree of lipiodol enhancement.

Survival data

The analysis of the survival data is based on the calculated survival starting with the first TACE treatment. All patients underwent a minimum follow-up of 12 months. Although the data are limited, the overall survival rate is calculated as a mean survival rate of 19.5 months and a median survival rate of 21 months (Fig. 4). Evaluating the survival after the treatment of the primary tumor of the eye, the mean survival rate was 32.92 months, and the median survival rate was 36.50 months (Fig. 5).

For patients with stable disease after TACE, the mean survival rate was 19.63 months (median 15.7 months), and for for patients with partial response it was 21.35 months (median 21.0 months). Patients with progressive disease during TACE had a lower survival rate of 16.45 months (mean 8.3) ($p < 0.01$).

Discussion

Melanoma is the most common primary intraocular malignancy in adults, with an annual incidence of approximately seven per million in Europe and the United States (Flaherty et al. 1998; Gragoudas et al. 2002), differing according to the location, which is higher in the ciliary body. Up to 50% of patients eventually develop metastases, with a unique metastatic predilection regardless of the primary treatment. The 5-year survival estimates for primary ocular melanoma are 43–79% (Cantore et al. 1994; Flaherty et al. 1998). The presence of metastases is considered to be a poor prognostic marker for response to treatment and survival. After the development of liver metastases the 1-year survival estimates range from 2 to 9 months (Flaherty et al. 1998). At the time of initial diagnosis of choroid melanoma, most patients have no evidence of metastatic disease. However, within 2–5 years, metastases appear in about half of the patients. Unlike cutaneous melanoma, which metastasizes to various sites,

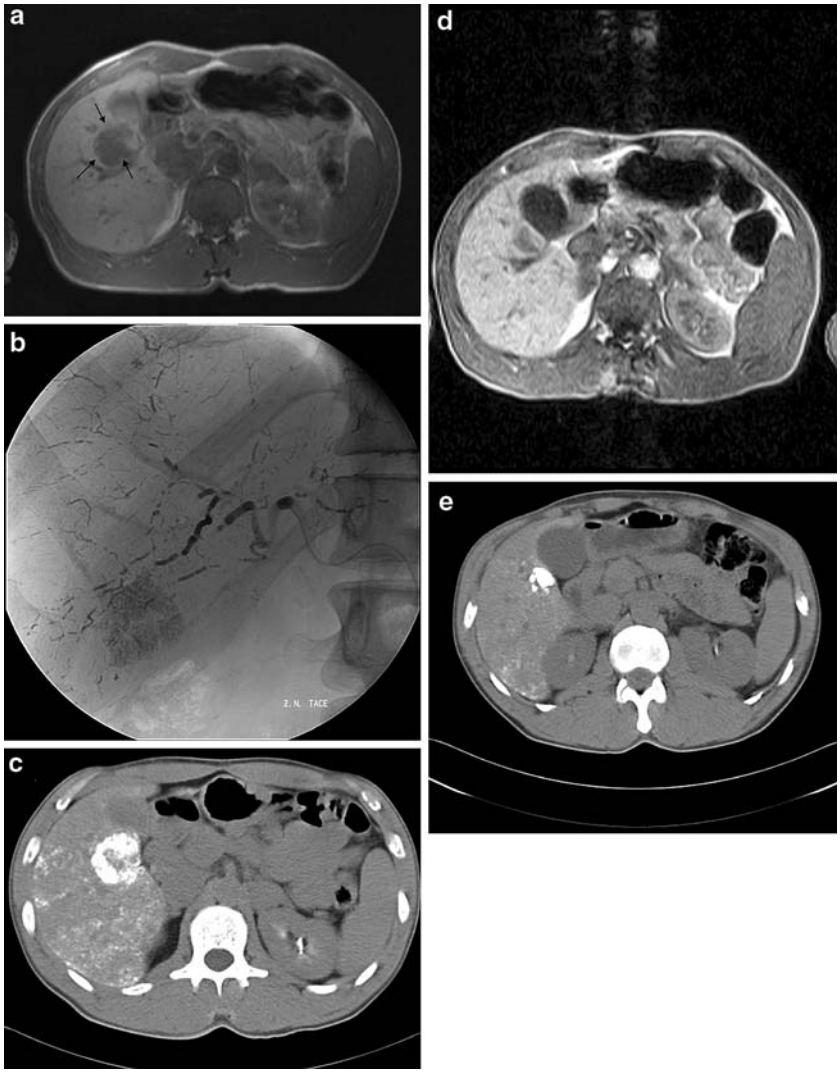

Fig. 3 A 61-year-old man with oligonodular liver metastases in segments 5 and 2 and partial response after TACE. **a** Transverse T1-weighted (TR 118/TE5) unenhanced image demonstrates a hypointense liver metastasis of 30 × 28 mm in size in liver segment 5 (*arrows*). **b** Angiographic image in the final phase of the embolization reveals an intratumoral uptake of lipiodol (*arrows*) with a central low-density area (**c**). In this phase the lipiodol suspension is still visualized in the right hepatic artery. **c** Unenhanced CT post-TACE 1 day post-intervention demonstrates a high degree of lipiodol uptake in the peripheral parts of the lesion with a central necrosis. **d** Transverse T1-weighted (TR 118/TE 5) unenhanced image 1 month post third TACE with verification of the enormous size reduction of the treated metastasis (*arrows*). **e** Unenhanced CT post-TACE demonstrated a further reduction in size with homogeneous lipiodol deposits

ophthalmic melanoma most commonly metastasizes to the liver. In fact, liver metastases develop in approximately two-thirds of patients with recurrent uveal melanoma (Flaherty et al. 1998). Despite conventional surgery for resectable segmental or lobar liver involvement, systemic chemotherapy, chemoimmunotherapy, or proton beam irradiation, the median survival of patients with liver metastases is less than 6 months (Feldman et al. 2004).

Response rates to systemic chemotherapy are reported to be ≤1% (Flaherty et al. 1998; Gragoudas et al. 2002; Schmittel et al. 2005). Regional chemotherapy concepts are mostly based on the use of implantable hepatic catheters in order to deliver intra-arterial chemotherapy directly to hepatic lesions. Thus, a higher concentration of chemotherapeutic agents can be locally delivered, with lower systemic toxicity. With this approach, response rates of 30–40% were reported in phase-II studies (Cantore et al. 1994; Leyvraz et al. 1997). In addition to intra-arterial embolization, chemoembolization provides theoretical advantages as secondary tumors of the liver derive ~80% of their blood supply from the hepatic artery (Feldman et al. 2004). Thus, embolization additionally leads to tumor ischemia, sparing normal tissue perfused through the portal vein. Drug concentrations during chemoembolization can reach 10–25 times of those obtained with intra-arterial infusion alone, allowing an increased dwell time of chemotherapeutic agents caused by stasis with minimization of systemic toxicity. The use of chemoembolization as a therapeutic modality for liver metastases of malignant melanoma was first published by Carrasco et al. (1986), who published two case reports describing the tumor regression with cisplatin and polyvinyl sponge (PVS). Following this, Mavligit et al. (1988) reported about 30 patients treated with chemoembolization and noted an overall response rate of 46% and a median survival of 11 months. A recent review of data from 201 patients with metastatic ocular melanoma from the MD Anderson Cancer Center

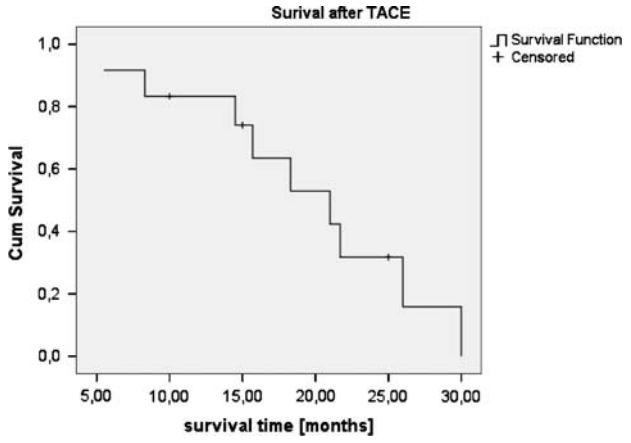

Fig. 4 Survival after first TACE cycle in patients with oligonodular metastases of uveal malignant melanoma (Kaplan–Meier)

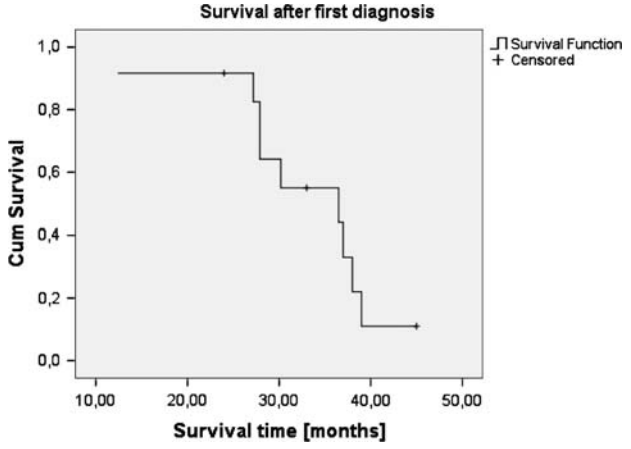

Fig. 5 Survival after ocular treatment of malignant melanoma (Kaplan–Meier)

revealed a 36% overall response rate for chemoembolization versus less than 1% for systemic chemotherapy and a median response duration of 14.5 months in responding patients. Argawala et al. (2004) performed a phase-I/II randomized trial of intrahepatic arterial infusion chemotherapy with cisplatin and chemoembolization with cisplatin and PVS in 19 patients with ocular melanoma metastatic to the liver. The cisplatin dose was escalated up to 125 mg/m^2 with a maximum tolerated dose of 125 mg/m^2 with or without PVS. In their paper, the authors showed that the overall response rate was 16%. The dose-limiting toxicity included renal, hepatic, and hematological effects. The authors summarize that this therapy produces a modest response rate in patients with ocular melanoma and liver metastases. In a phase II clinical trial, Patel et al. used a TACE technique with BCNU dissolved in ethiodized oil, combined with gelatine sponge as a transiently occlusive agent. The obtained response rate of 20.4% is lower in comparison to our patient material. While our survival rates in the nonresponder group was higher with 16.5 months versus 5.2 months, the survival rates were similar in the group with response with 19.5 months versus 21.9 months in the group of Patel et al. (2005).

A challenging technique might be the use of DC beads (Terumo) for chemoembolization where the chemotherapeutic agent is being absorbed via incubation (Weinreich and Alexander 2002). Via the docking of the chemotherapeutic agents to the particles, the locally applied concentration of chemotherapy is increased by a factor of 3.

Our data show that TACE using Mitomycin followed by embolization agents like Lipiodol and Spherex might produce a relevant response rate and that among our cases survival data are somewhat better than those reported in the literature (Pyrhonen 1998; Egerer et al. 2001; Rivoire et al. 2005). Our study is limited due to the nonrandomized design of the treatment protocol and the limited number of patients. However, even a palliative or symptomatic approach should be considered in patients with extremely poor prognosis (Wallace et al. 1990; Sasson and Sigurdson 2002; Weinreich and Alexander 2002). These data can be used as a basis for prospective trial studies (Wang et al. 1994; Hakansson et al. 1997; Song et al. 2001).

Conclusion

In summary, TACE can be considered to be a safe treatment for oligonodular liver metastases of uveal malignant melanoma offering a symptomatic or even palliative treatment option.

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