Percutaneous hepatic perfusion in unresectable liver metastases: focus on ocular melanoma

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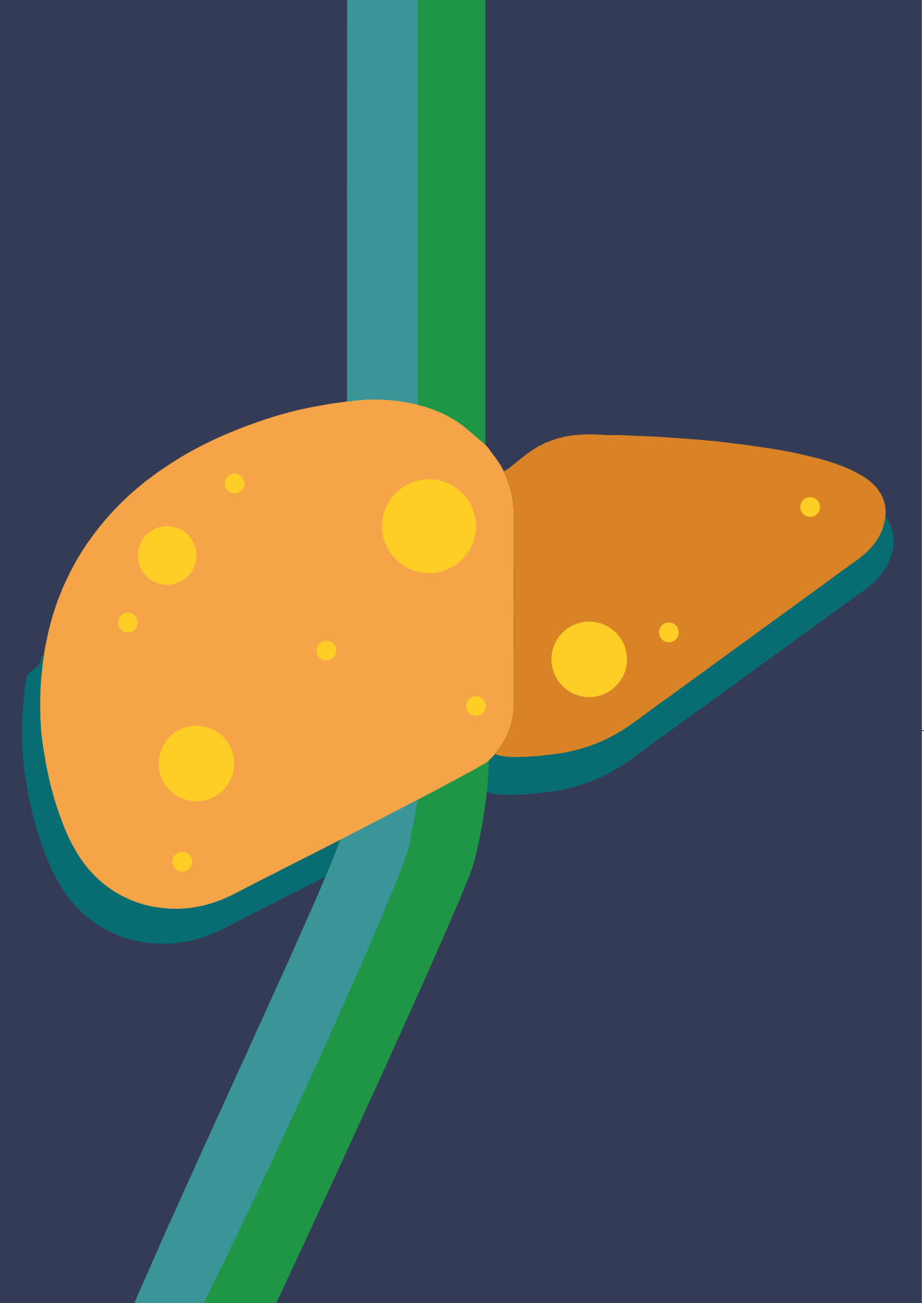

CHAPTER 2

Regional therapies for hepatic melanoma metastases

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ABSTRACT

Melanoma arises through malignant transformation of melanocytes. The most common primary location of melanoma is the skin (~90%), followed by the uveal tract of the eye (~5%). Cutaneous and uveal melanoma differ substantially in terms of metastatic pattern and mutation status. While metastatic disease from uveal melanoma is mostly liver-dominant, this is rarely the case in metastatic cutaneous melanoma. This, together with the lack of effective systemic therapies in metastatic uveal melanoma explains why regional therapies for hepatic metastases, or liver-directed therapies, play a key role in metastatic disease from uveal melanoma.

Liver-directed therapies in the treatment of hepatic melanoma metastases include several arterial therapies, surgical resection and thermal ablation. Although considered the only curative treatments, most patients are not eligible for resection or thermal ablation as first-line treatment. All arterial therapies share the common advantage of being an intensified treatment to both radiologically visible and occult tumors (micrometastases), while systemic toxicity is limited. The main arterial therapies that are performed in the treatment of hepatic melanoma metastases are hepatic arterial infusion (HAI), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and percutaneous hepatic perfusion with melphalan (M-PHP). There is no current consensus on what liver-directed therapy would be best practice for patients with hepatic melanoma metastases, but M-PHP seems one of the most attractive treatment options with promising effects on survival and an acceptable safety profile.

INTRODUCTION

Worldwide, each year 1.7% of all newly diagnosed primary malignancies (excluding non-melanoma skin cancer) and 0.7% of all cancer deaths are accounted for by cutaneous melanoma.[1] Although the vast majority of melanomas (~90%) arise through malignant transformation of melanocytes within the skin, they occasionally arise from melanocytes located in the uveal tract of the eye (~5%), which is composed of the iris, ciliary body, and choroid (Figure 1). In rare cases, melanoma develops within mucous membranes or meninges, or is diagnosed in a metastatic setting with an unknown primary site.[2-4]

Although uveal melanoma accounts for only 5% of all melanomas, it accounts for 13% of all deaths due to this cancer type.[5] This is closely related to the large number of uveal melanoma patients that will eventually develop metastases (up to 50%) while there is no effective systemic therapy.[6] The prognosis for metastatic cutaneous melanoma patients has improved significantly with the introduction of immunotherapy and BRAF-targeted therapy, but these therapies are not effective in patients with uveal melanoma.[7]

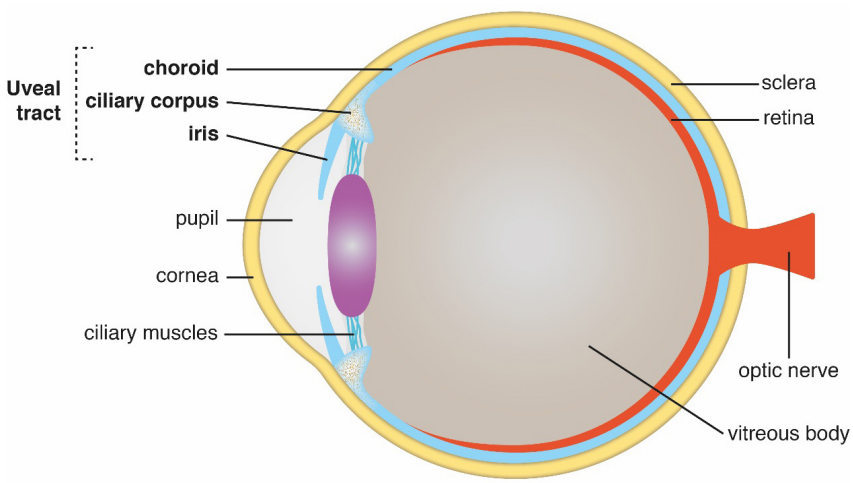

FIGURE 1. Uveal tract
The uveal tract or uvea is a vascular and pigmented layer of tissue located between the outer layer (cornea and sclera) and inner layer (retina) of the eye. The uvea is composed of three components that are continuous with one another: the iris, ciliary corpus and choroid.

Cutaneous and uveal melanoma have a different metastatic pattern and biological behaviour. While cutaneous melanoma initially spreads to regional lymph nodes after which any organ can be affected through lymphatic and/or hematogenous spreading, uveal melanoma spreads purely hematogenously as the eye has no lymphatic vessels.[7-9] When uveal melanoma patients are diagnosed with metastatic disease, the liver is affected in

more than 90% of cases and remains the only site of metastases in about 50%.[6] On the contrary, metastatic cutaneous melanoma is rarely liver-dominant and hepatic metastases occur in only 10-20% of patients.[7-9] Because the survival of most patients with metastatic uveal melanoma is determined by the status of the disease in the liver, liver-directed therapies play a key role in the management of these patients. Systemic treatment is the treatment of choice for most patients with metastatic cutaneous melanoma.

Hepatic metastases from cutaneous and uveal melanoma also differ in terms of mutation status. Activating mutations in the *BRAF* oncogene are most common in cutaneous melanoma (50-60%), making the majority of patients eligible for treatment with *BRAF* inhibitors. Combining *BRAF* inhibitors with *MEK* (mitogen-activated protein kinase) inhibitors resulted in an objective response rate (ORR) of 70%, median progression-free survival (PFS) of 14.9 months, and overall survival (OS) of 22.3 months.[1,10] Typical for all *BRAF* inhibitor-based therapies is the rapid tumor response that occurs within days to a few weeks, making them particularly beneficial in patients with symptoms and/or rapidly progressive disease. *BRAF*-targeted therapy is not an option for metastatic uveal melanoma, which does not harbour *BRAF* mutations. Mutations in genes encoding the G-protein-alpha subunits *GNAQ* or *GNA11* are characteristic for uveal melanoma metastases (80-90%), but these remain difficult targets for systemic therapy. The introduction of mutation independent immune-checkpoint inhibitors against *CTLA4* (ipilimumab) and *PD-1* (pembrolizumab, nivolumab) has further improved OS in patients with metastatic cutaneous melanoma including those without *BRAF* mutations. Unfortunately, also these immune-checkpoint inhibitors have not been able to improve OS in metastatic uveal melanoma.[11]

Liver-directed therapies may be considered when the liver is the only or dominant site of metastatic disease. In this chapter, we will highlight the liver-directed therapies that are currently used for the treatment of hepatic melanoma metastases, focusing on metastases from cutaneous and uveal melanoma. Treatment reports for liver-directed therapies in melanoma literature are, however, often dominated by or restricted to uveal primaries. We will briefly discuss the techniques and give an overview of published literature.

LIVER-DIRECTED THERAPIES: ARTERIAL THERAPIES

The liver has a unique dual blood supply. Approximately 70-80% of the blood supply to the liver parenchyma is derived from the portal vein and the hepatic arteries supply the remaining 20-30%. In contrast, most hepatic malignancies have a dominant or exclusive vascular supply from the hepatic arteries. When a drug or embolic agent is delivered through the hepatic artery, this will mainly affect the liver malignancies with relative sparing of the normal liver parenchyma.

All arterial therapies share the same common advantage of being an intensified

treatment to both radiologically visible and occult tumors (micrometastases), while systemic toxicity is limited. Established arterial therapies in the treatment of hepatic melanoma metastases include:

- Hepatic arterial infusion (HAI)
- Transarterial chemoembolization (TACE)
- Transarterial radioembolization (TARE)
- Percutaneous hepatic perfusion with melphalan (M-PHP)

Hepatic arterial infusion (HAI)

In this procedure, also referred to as intra-arterial chemotherapy (IAC) or transarterial chemotherapy (TAC), tumor cell necrosis is induced by the direct cytotoxic effect of chemotherapeutics. It is a repeatable procedure in which the number of received cycles depends on clinical response and the occurrence of toxic effects.

Table 1 gives an overview of studies on HAI as treatment of hepatic melanoma metastases.[12-19] The most frequently used chemotherapeutic agent is fotemustine (Muphoran®), generally administered at a dose of 100 mg/m^2 over 4 hours. Two different techniques have been used. In some studies, an implantable catheter connected to a subcutaneous access chamber (Port-A-Cath) was surgically placed into the hepatic artery through the gastroduodenal artery. This was accompanied by ligature or occlusion of collateral arteries and prophylactic cholecystectomy.[12,14] In other studies, femoral access was achieved by an interventional radiologist after which a microcatheter was placed in the hepatic arterial tree and chemotherapeutics were administered.[15,16,18,19]

As shown in Table 1, for uveal melanoma the ORR ranges from 0-40% and the median OS from 2.9-21 months. The unfavourable outcomes reported by Boone et al. are partly explained by the fact that their patients had very advanced disease with a median lactate dehydrogenase (LDH) level at baseline of 654 IU/L. They were already found ineligible for M-PHP due to hyperbilirubinemia (n = 8), hepatomegaly due to massive tumor infiltration (n = 5), and prior M-PHP (n = 1).[18] However, 3/14 patients (21%) had nearly 1-year survival after treatment, suggesting a potential benefit for a subset of patients.

Leyvraz et al. demonstrated in a randomized trial that intra-arterially infused fotemustine has a higher ORR and longer PFS compared to intravenous (IV) treatment.[17] However, this did not translate into a significant improved OS. As expected, severe hematologic toxicity was less frequent in the HAI than IV arm; grade 3-4 thrombocytopenia in 21.2% versus 42.1% and neutropenia in 28.7% versus 62.6%. The non-hematologic toxicity was mainly related to HAI therapy, with abdominal pain grade ≥ 3 in 12.1% of patients, and gastric ulcers in 3%. In addition, 31.8% of patients had a catheter-induced complication and 4.5% had liver toxicity grade ≥ 3. The two reported deaths, one case of septic shock and one case of mesenteric artery thrombosis followed by sepsis, both occurred in the HAI arm.

TABLE 1. Overview of studies on HAI (≥ 10 patients) as treatment for hepatic melanoma metastases

First author (year)	Study design	Melanoma type	No. pts (median no. procedures)	Chemotherapeutic agent	ORR	Median PFS (mo)	Median OS (mo)
Leyvraz (1997)[12]	Phase II	UM	31 (6)	Fotemustine	40%	NR	14
Peters (2006)[13]	Phase II	UM	101 (8)	Fotemustine	36%	NR	15
Siegel (2007)[14]	RS	UM (*n* = 18), CM (*n* = 12)	30 (8)	Fotemustine	Total 30%, UM 28%, CM 33%	NR	UM 22, CM 12 (*n.s.*)
Heusner (2010)[15]	RS	UM	61 (4[a])	Melphalan/combination of melphalan and additional agent[b]	Reported for each chemoperfusion session no.; max. 30% (4th session)	NR	10
Farolfi (2011)[16]	RS	UM (*n* = 18), CM (*n* = 5)	23 (4[a])	Fotemustine/ carboplatin	UM 16.7%, CM NR	UM 6.2, CM NR	UM 21, CM NR
Leyvraz (2014)[17]	Randomized phase III	UM	86 HAI (4), 85 IV (3)	Fotemustine (intra-arterial vs intravenous)	HAI 10.5%, IV 2.4%	HAI 4.5, IV 3.5, (*p* = 0.002)	HAI 14.6, IV 13.8 (*n.s.*)
Boone (2018)[18]	RS	UM	14 (2)	Melphalan	7%[c]	NR	2.9
Vera-Aguilera (2018)[19]	Phase I/II	UM (*n* = 16), CM (*n* = 9), mucosal (*n* = 1), unknown (*n* = 1)	30 (NR)	Nab-paclitaxel	UM 0%, CM 11%, mucosal 0%, unknown 100%	NR	6.5

[a] Mean no. of procedures per patient.

[b] Melphalan during 1st cycle, combination of melphalan and additional agent (fotemustine, dacarbazine, mitomycin, doxorubicin, or gemcitabine) during other cycles.

[c] Based on 7/14 patients.

CM cutaneous melanoma, *HAI* hepatic arterial infusion, *IV* intravenous, *mo* months, *NR* not reported, *n.s.* not significant, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *RS* retrospective, *UM* uveal melanoma.

Transarterial chemoembolization (TACE)

Classical TACE involves the injection of an emulsified mixture of a chemotherapeutic agent and oily contrast medium, which acts as a drug carrier, into the tumor-feeding arteries. Although the oily contrast medium (ethiodized oil or Lipiodol®) has some embolic effects itself, an additional embolic agent is generally administered to achieve stasis in the target vessel. By slowing the drug efflux from the hepatic circulation, embolic agents increase the drug concentration delivered to the tumor and increase the duration of drug exposure. In addition, embolic agents cause occlusion of tumor-feeding arteries, which promotes ischemia and tumor necrosiss.[11] Common used embolic agents are gelatine sponge (GS), polyvinyl alcohol particles (PVA) and microspheres. GS causes transient embolization with recanalization occurring within approximately 2 weeks, while PVA and microspheres are considered permanent embolic agents.[20]

Drug-eluting beads have been increasingly used over the past years. They are non-resorbable microspheres that can be pre-loaded with chemotherapeutic agents such as doxorubicin and irinotecan, and are available in different sizes. In contrast with classical TACE, drug-eluting beads allow for a one-step process in which the chemotherapeutic and embolic agent are delivered simultaneously. Drug-eluting beads lead to a more sustained drug release and lower concentrations of chemotherapeutics in the systemic circulation than in classical TACE.[21,22]

Absolute contraindications for TACE include insufficient portal vein inflow, hepatic encephalopathy, and jaundice. Relative include extrahepatic disease, < 50% healthy liver tissue, biliary obstruction, LDH level > 425 IU/L, aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) level > 5 × upper limit of normal (ULN), and total bilirubin > 2.0 IU/L.[20]

Table 2 gives an overview of studies on TACE as treatment of hepatic melanoma metastases.[23-38] For cutaneous melanoma, Ahrar et al. reported an ORR of 39%, median PFS of 6 months, and median OS of 7.7 months. Responders showed a significant longer OS than those who did not respond to TACE (14.08 versus 7.4 months in patients with stable disease (SD), and 8.5 months in patients with progressive disease (PD), $p = 0.031$).[34]

Studies with more than 20 patients with metastatic uveal melanoma, reported an ORR ranging from 14-46%, median PFS from 3-8 months, and median OS from 5.2-28.7 months. Again, several studies found a significant longer OS in responders than in non-responders.[23,24,26,27,30,32,33] Interestingly, Sharma et al. reported that patients with lesions with a nodular angiographic appearance had a longer PFS and OS than patients with lesions that had an infiltrative appearance (PFS 249 versus 63 days; mean OS 621 versus 114 days; $p = 0.0002$).[28]

TABLE 2. Overview of studies on TACE (≥ 10 patients) as treatment of hepatic melanoma metastases

First author (year)	Sudy design	Melanoma type	No. pts (mean no. TACEs)	Drug(s)	Embolic agent(s)	ORR	Median PFS (mo)	Median OS (mo)
Mavligit (1988)[23]	RS	UM	30 (NR)	Cisplatin	PVA	46%	6	11
Bedikian (1995)[24]	RS	UM	44 (3[a])	Cisplatin ± additional agent[b]	PVA	36%	NR	6
Agarwala (2004)[25]	Phase I/II, dose-esc.	UM	19 (NR)	Cisplatin	± PVS	16%	NR	8.5
Patel (2005)[26]	Phase II	UM	30 (3[a])	BCNU	Ethiodized oil, GS	17%	8	5.2
Vogl (2007)[27]	PS, pilot	UM	12 (4.6)	MMC	Ethiodized oil, microspheres	25%	NR	21
Sharma (2008)[28]	RS	CM (*n* = 3), UM (*n* = 17)	20 (2.4)	Cisplatin, doxorubicin, MMC	Ethiodized oil, GS/PVA	0%	6.1	8.9
Fiorentini (2009)[29]	Phase II	UM	10 (1.5)	Irinotecan loaded drug-eluting beads		100%	NR	NR
Dayani (2009)[30]	RS	UM	21 (2.3)	MMC, cisplatin, doxorubicin	Ethiodized oil, GS/PVA	NR	NR	7.6 (mean)
Schuster (2010)[31]	RS	UM	25 (2)	Fotemustine/cisplatin	Ethiodized oil, starch microspheres	16%	3	6
Gupta (2010)[32]	RS	UM	125 (2)	Mostly cisplatin[c]	GS/PVA	27%[d]	3.8	6.7
Huppert (2010)[33]	PS, pilot	UM	14 (2.4)	Cisplatin/carboplatin[e]	PVA	57%	8.5	11.5
Ahrar (2011)[34]	RS	CM	42 (2)	Cisplatin/cisplatin, paclitaxel/paclitaxel	Gelfoam/PVA	39%	6	7.7
Edelhauser (2012)[35]	RS	UM	21 (3.3)	Fotemustine	Ethiodized oil, PVA	14%	7.3	28.7
Valpione (2015)[36]	RS	UM	58 (NR)	Irinotecan loaded drug-eluting beads[f]		28%	NR	16.5
Abbott (2017)[37]	RS	CM (*n* = 9), UM (*n* = 3)	12 (1)	Doxorubicin, MMC, cisplatin	Ethiodized oil, microspheres	NR	1.7	8.8
Shibayama (2017)[38]	RS	UM	29 (4)	Cisplatin	GS	21%	6	23

[a] Median.
[b] In all TACE procedures (*n* = 64): cisplatin (*n* = 44), cisplatin + vinblastine (*n* = 12), cisplatin + dacarbazine + vincristine (*n* = 2), cisplatin + dacarbazine (*n* = 3), cisplatin + dactinomycin (*n* = 3).
[c] Cisplatin (*n* = 122), cisplatin + paclitaxel (*n* = 2), cisplatin + doxorubicin + MMC (*n* = 1).
[d] Based on 105/125 patients.
[e] 5/14 patients received systemic immuno-chemotherapy 2-4 weeks prior to TACE.
[f] 49/58 patients received systemic fotemustine, the induction phase starting within 3 weeks from TACE.
BCNU 1,3-bis(2-chloroethyl)-1-nitrosourea, *CM* cutaneous melanoma, *dose-esc.* dose-escalating study, *GS* gelatin sponges, *MMC* mitomycin *C, NR* not reported, *pt(s)* patient(s), *OS* overall survival, *PFS* progression-free survival, *PVA* polyvinyl alcohol particles, *PVS* polyvinyl sponges, *PS* prospective, *RS* retrospective, *TACE* transarterial chemoembolization, *UM* uveal melanoma.

The wide variety in outcomes is probably due to differences in the type of chemotherapeutic drugs and embolic agents that were used, the number of procedures per patient, and the selection of patients. Firstly, although in some studies TACE was only offered after first-line systemic therapy had failed[29,31], in other studies most patients were chemotherapeutic-naïve.[35-38] In the study by Huppert et al. and Valpione et al., a considerable number of patients even received some sort of systemic therapy shortly before or after TACE.[33,36] Secondly, although metastatic disease was liver-dominant in all patients, the percentage of patients with extrahepatic disease at the time of TACE varied from 0% to 75%.[27,37] Finally, there was a considerable variation regarding tumor load in the liver, where tumor load was limited in most patients that were evaluated in studies reporting the longest OS.[35,38]

Commonly reported side-effects of TACE were abdominal discomfort or pain, nausea and/or vomiting, (sub)febrility, and hepatotoxicity. Grade 3 thrombocytopenia was reported in 3-11% and may be partly attributed to the additional systemic chemotherapy.[25,26,31] Other serious adverse events are rare, but vascular thrombosis, splenic infarction, acute renal failure due to tumour lysis syndrome have been reported.[26,31]

Transarterial radioembolization (TARE)

In this procedure, also known as selective internal radiation therapy (SIRT), yttrium-90 (^{90}Y)-labelled microspheres are delivered into the hepatic arteries after which they eventually lodge in the end-arterioles of the tumor microvasculature. ^{90}Y is a high-energy β-emitting isotope with a mean soft-tissue penetration of 2.5 mm. As hepatic metastases are mainly perfused by the hepatic arteries, high radiation doses can be applied to the tumor while the non-tumorous parenchyma is relatively spared. Two types of ^{90}Y-microspheres are commercially available: SIR-Spheres and TheraSpheres. SIR-Spheres (Sirtex, Sydney, Australia) are non-biodegradable resin ^{90}Y-microspheres with a diameter of 20-40 μm and activity of 40-70 Bq per microsphere. TheraSpheres (MDS Nordion, Ottawa, Canada) are non-biodegradable glass microspheres with a diameter of 20-30 μm and maximum activity of 2500 Bq per microsphere at the time of calibration. To achieve a similar dose, a much larger number of SIR-Spheres has to be administered compared to the number of TheraSpheres (typically 20-40 million SIR-Spheres versus 1.2 million TheraSpheres).

Holmium-166 poly(L-lactic acid) (^{166}Ho-PLLA) microspheres (QuiremSpheres®) were recently developed as an alternative for ^{90}Y-microspheres. In addition to emitting β-radiation for tumor destruction, ^{166}Ho-microspheres emit y-radiation and are paramagnetic. This gives them the advantage of being visible on both single-photonemission CT (SPECT) and MRI, which enables the use of dosimetry and more personalised patient treatment. Because data on ^{166}Ho-radioembolization in the treatment of hepatic melanoma metastases have been very limited so far, this will not be discussed further in this chapter.[39]

Radioembolisation is preceded by preparatory angiography and administration of a test dose of 75-150 MBq ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA). The angiography is used to map out the vascular supply of the tumor and, upon indication, perform coil-embolization of hepatico-

enteric anastomosis, such as the gastroduodenal and right gastric artery. After injection of ^{99m}Tc-MAA, planar SPECT imaging and SPECT/CT are performed to rule out extrahepatic shunts and assess ^{99m}Tc-MAA distribution in the liver. ^{99m}Tc-MAA particles are believed to be representative for the distribution of ^{90}Y microspheres as they are fairly similar in size. Lung shunting with an estimated absorbed radiation dose of more than 30 Gray makes patients ineligible for TARE. Depending on the location of hepatic metastases, patients will receive whole-liver, lobar or segmental treatment with microspheres. After treatment, a bremsstrahlung ^{90}Y-SPECT/CT is performed to evaluate the actual distribution of microspheres (Figure 2).

TARE is mostly offered as salvage therapy in patients with PD following conventional chemotherapy, immunotherapy and/or other liver-directed therapies. Prospective studies evaluating the efficacy of ^{90}Y radioembolization as treatment of hepatic melanoma metastases are lacking. A few small retrospective studies, in which most patients suffered from hepatic metastases from uveal melanoma, have been published (Table 3).[40-48] In uveal melanoma, reported ORR ranges from 6-70%, median PFS from 3.2-5.9 months, and median OS from 5.9-13.5 months.

In a study including 32 patients, Gonsalves et al. reported a median OS of 10 months (range 1.0-29.0).[41] Patients were divided into three groups based on tumor burden within the liver at baseline: < 25% (n = 25), 25-50% (n = 5), and > 50% (n = 2). Patients with < 25% tumor burden had a significantly longer OS than those with ≥ 25% tumor burden (10.5 versus 3.9 months; p = 0.0003). As might be expected, patients with complete response (CR), partial response (PR) or SD had a significantly longer OS than patients with PD (14.7 versus 4.9 months; p = 0.006). Moreover, patients with < 25% tumor burden had a significantly longer PFS than patients with ≥ 25% tumor burden (6.4 versus 3.0 months; p = 0.03), and patients with CR, PR, or SD had a longer PFS than patients with PD following TARE (7.9 versus 3.1 months; p < 0.0001).

Common side-effects are abdominal discomfort or pain, nausea and vomiting, usually well-manageable with analgesics and anti-emetics. Additionally, patients often suffer from fatigue during the first weeks after treatment. Severe complications such as gastric ulcers, liver failure, or cholecystitis are rare. Xing et al. reported two patients (7%) who developed major complications in the form of ascites and hepatic encephalopathy and eventually died due to liver failure within 1 month of ^{90}Y radioembolization.[47] Both patients had diffuse hepatic metastases and decompensated liver function with a high MELD score and Child-Pugh class C at the time of treatment.

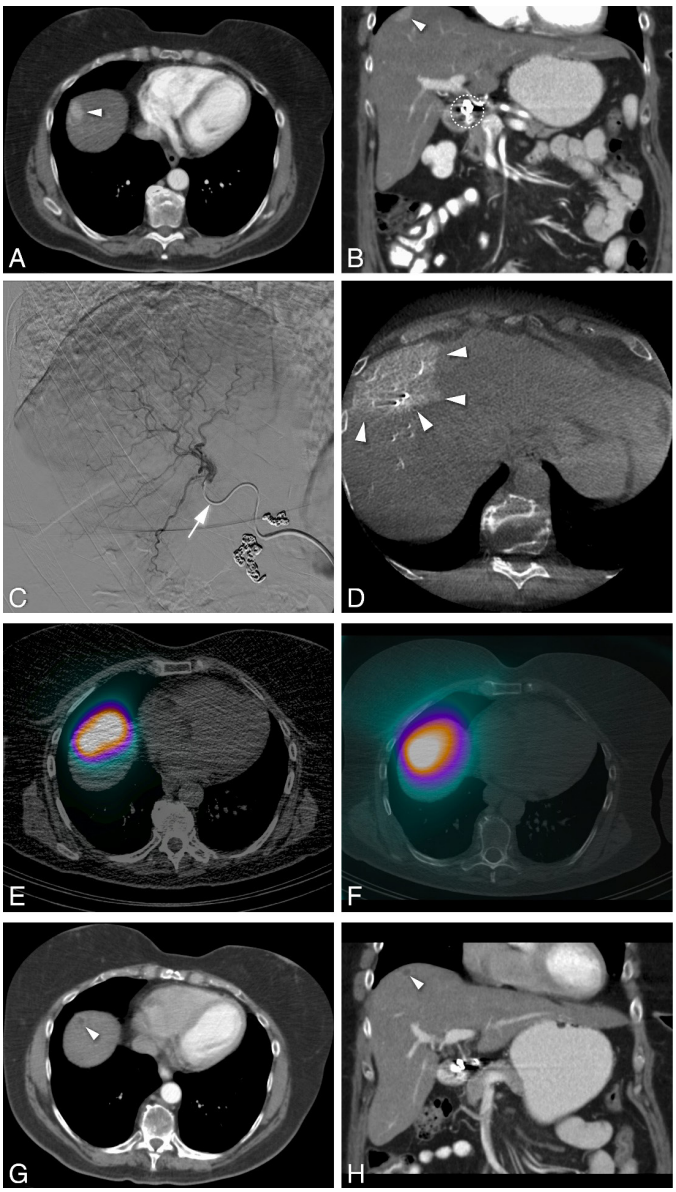

FIGURE 2. Transarterial radioembolization with yttrium-90
61-year-old female with multiple uveal melanoma metastases treated with two cycles of percutaneous hepatic perfusion with melphalan (M-PHP). Excellent response was seen with only one residual tumor in the hepatic dome. Thermal ablation was considered, but due to the limited size and location preference was given to segmental radioembolization. Axial (A) and coronal (B) CT images in arterial phase before treatment, showing a hypervascular lesion in segment 8 (white arrowheads). Note the coils (dotted circle) that were used to embolize the right gastric artery and gastroduodenal artery prior to M-PHP. (C) Angiographic image showing the microcatheter position (white arrow) during ^{99m}Tc-MAA infusion. (D) Enhanced treatment area highlighted on cone-beam CT (white arrowheads). (E) Axial ^{99m}Tc-MAA SPECT/CT image showing an adequate accumulation in the target lesion. (F) Axial bremsstrahlung ^{90}Y-SPECT/CT image demonstrating an intense ^{90}Y-accumulation in the lesion. Axial (G) and coronal (H) CT images in arterial phase 6 weeks after treatment, showing a marked devascularisation and reduction in size of the lesion (white arrowheads).

TABLE 3. Overview of studies on TARE with ^{90}Y (≥ 10 patients) as treatment for hepatic melanoma metastases

First author (year)	Study design	Melanoma type	No. pts	Type of microsphere (dosage)	ORR	Median PFS (mo)	Median OS (mo)
Kennedy (2009)[40]	RS	UM	11	SIR-Spheres® (mean 1.55 GBq)	77%	NR	NR
Gonsalves (2011)[41]	RS	UM	32	SIR-Spheres® (mean 1.08 GBq)	6%	4.7	10
Piduru (2012)[42]	RS	CM (*n* = 5), UM (*n* = 7)	12	SIR-Spheres® (NR)	NR	NR	10
Klingenstein (2013)[43]	RS	UM	13	SIR-Spheres® (mean 1.78 GBq)	62%	NR	7
Memon (2014)[44]	RS[a]	CM (*n* = 4), UM (*n* = 7), rectal (*n* = 3), unknown (*n* = 2)	16	TheraSphere® (median 1.87 GBq)	24%	4.2	Total 7.6, UM 5.9, non-UM 10.7
Klungboonkrong (2015)[a,45]	RS	UM	17	NR	NR	3.2	9.3
Eldredge-Hindy (2016)[46]	RS	UM	71	SIR-Spheres® (median right lobe 0.88, median left lobe 0.33)	9%	5.9	12.3
Xing (2017)[47]	RS	CM (*n* = 13), UM (*n* = 15)	28	SIR-Spheres® (mean 1.86 GBq)	18%	5.1	10.1
Tulokas (2018)[48]	RS	UM	16	NR (median 1.9 GBq)	17%	5.6	13.5

[a] Only abstract available.

CM cutaneous melanoma, *GBq* gigabecquerel, *mo* months, *NR* not reported, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *RS* retrospective, *TARE* transarterial radioembolization, *UM* uveal melanoma.

Percutaneous hepatic perfusion with melphalan (M-PHP)

Isolated hepatic perfusion (IHP) is a complex surgical procedure in which the liver is isolated from the systemic circulation by clamping the inferior vena cava (IVC) and portal vein, and ligation of IVC tributaries and arterial hepatico-enteric anastomoses. Subsequently, the liver is perfused with a high dose of melphalan that is injected through a catheter in the proper hepatic artery. For metastatic uveal melanoma, response rates of 37-52% have been reported.[49-52] High morbidity and mortality rates, however, prohibited a widespread application of IHP.[53-56]

Percutaneous hepatic perfusion with melphalan (M-PHP) was developed by Delcath Systems Inc. (New York, USA) as a minimally invasive, repeatable and safer alternative for IHP. M-PHP is performed under general anaesthesia by a team consisting of an interventional radiologist, anaesthesiologist, and extracorporeal perfusionist. During the procedure, a microcatheter is placed in the hepatic artery at the intended location of infusion.[57] A double-balloon catheter is placed in the IVC through the common femoral vein. The cranial balloon is inflated to occlude the atriocaval junction and the caudal balloon is inflated in the infrahepatic IVC to prevent leakage of chemotherapeutics into the systemic circulation. In between the two balloons, the catheter has multiple side holes that are used to aspirate the chemosaturated blood returning through the hepatic veins. The aspirated blood is pumped through an extracorporeal hemofilter consisting of two activated carbon filters. After filtration, the blood is returned to the patient by a vascular sheath in the right internal jugular vein (IJV) (Figure 3). Once all of the melphalan is infused, extracorporeal filtration is continued for 30 minutes to allow clearance of chemotherapeutics from the liver.[57] Because of the significant hemodynamic perturbations resulting from the combination of chemofiltration and IVC occlusion, hemodynamic monitoring and support is crucial during the procedure. Continuous arterial pressure is monitored by a cannula in the radial artery, and a triple-lumen line placed in the left IJV enables central venous pressure monitoring and infusion of sympathomimetics and fluids. The duration of the procedure is generally 3-4 hours (compared to 9 hours for IHP).

Patients undergoing M-PHP generally receive pretreatment angiographic evaluation (Figure 4). Angiography is commonly performed several days in advance, and allows the interventional radiologist to: (1) identify possible extrahepatic tumor-supplying vessels, (2) plan an appropriate strategy for (micro)catheter positioning during treatment, and (3) perform prophylactic coil embolization of branches arising from the hepatic arterial bed (e.g. accessory left gastric artery, right gastric artery and falciform artery) to prevent non-target drug delivery and minimize the risk of side-effects and complications.

In 2005, the results of a phase I dose escalation study on M-PHP in 28 patients with primary and metastatic hepatic disease were published, establishing a maximum tolerated dose of 3 mg/kg body weight. In the 10 patients with metastatic ocular melanoma, an ORR of 50% was observed (two CR and three PR).[58]

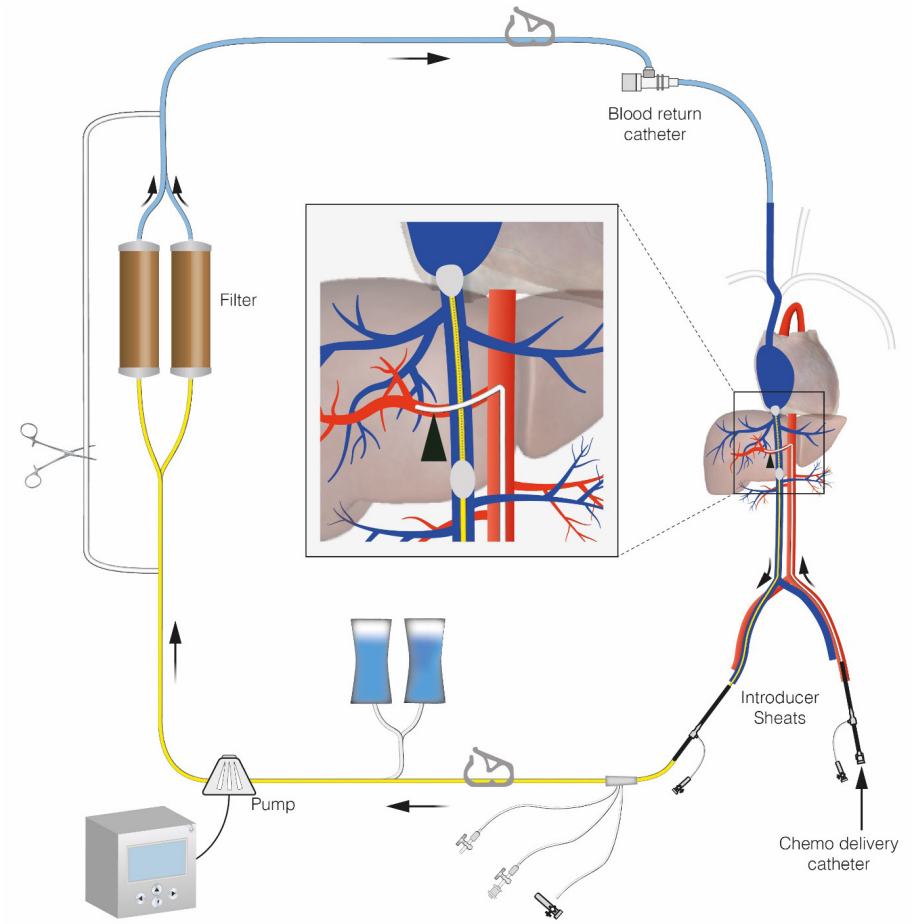

FIGURE 3. Schematic overview of the setup of percutaneous hepatic perfusion
Chemotherapeutic drugs (melphalan) are infused through a microcatheter that is placed in the hepatic artery (black arrowhead). The chemosaturated blood returning through the hepatic veins is aspirated through side holes in the double-balloon catheter. An extracorporeal hemofiltration system, consisting of a pump and two activated carbon filters, is used to filter the chemotherapeutics from the blood. The filtered blood is returned to the patient via a sheath in the right internal jugular vein.

In 2016, Hughes et al. published the results of a multi-center randomized controlled trial (RCT) comparing M-PHP with best alternative care (BAC) in patients with unresectable hepatic melanoma metastases.[59] The study included 93 patients with metastases from either ocular (*n* = 83) or cutaneous (*n* = 10) melanoma. Although in most patients (59.1%) metastases were confined to the liver, limited extrahepatic disease was not an exclusion criterion. Patients in the M-PHP arm (*n* = 44) underwent a maximum of six perfusion at 4-8 week intervals (median of three M-PHPs per patient). Patients in the BAC-arm (*n* = 49) received active treatment such as systemic chemotherapy, TACE, TARE, or surgery in 81.6%.

A significant improved hepatic objective response (hOR), hepatic progression-free survival (hPFS) and overall progression-free survival (oPFS) was observed in patients treated with M-PHP compared to BAC. The hOR was 36.4% for M-PHP and 2.0% for BAC ($p < 0.001$), hPFS was 7.0 months for M-PHP and 1.6 months for BAC ($p < 0.0001$), and oPFS was 5.4 months for M-PHP and 1.6 months for BAC ($p < 0.0001$). Median OS was not significantly different (10.6 months for M-PHP versus 10.0 months for BAC), likely due to a high crossover rate from the BAC- to M-PHP-arm (57.1%). Despite the prophylactic administration of stem cell support, the majority of grade 3-4 adverse events (according to the Common Terminology Criteria for Adverse Events) were related to bone marrow suppression with neutropenia in 85.7%, thrombocytopenia in 80.0%, and anemia in 62.9%. Hepatic toxicity, as manifested by grade 3-4 bilirubin elevation, was observed in only 14.3% of patients and self-limiting. Rare complications included venous thrombosis, acute cholecystitis, and gastroduodenal ulcer. Four deaths were attributed to M-PHP; two resulted from bone marrow suppression, one was associated with hepatic failure due to PD, and one resulted from gastric perforation.

Recently, a retrospective study evaluating only patients with hepatic metastases from uveal melanoma ($n = 51$) was published.[60] In the majority of patients (84.3%), metastases were confined to the liver. A median of two M-PHPs per patient resulted in an ORR of 54.9% with PR in 43.1% ($n = 22$) and CR in 5.9% ($n = 3$). Median hPFS and oPFS were 8.1 and 9.1 months, respectively. Median OS was 15.3 months. Grade 3-4 neutropenia was observed in 31.3%, grade 3-4 thrombocytopenia in 31.3%, and grade 3-4 anemia in 29.4%. These low percentages of grade 3-4 hematologic adverse events in comparison with the RCT by Hughes et al. is probably due to the use of a new second-generation (GEN 2) filter that has been shown to increase melphalan extraction with almost 10%, reducing bone marrow suppression.[61] Additionally, the median number of M-PHPs per patients was lower than in the RCT.

These promising results were confirmed in a prospective study in which 35 patients received a total of 72 M-PHPs (median of two procedures at a 6-8 weeks interval) using the GEN 2 filter. Best overall response was CR in 3.1%, PR in 68.8%, SD in 12.5%, and PD in 15.6%. Median OS was 20.3 months. Median PFS and median hPFS were 8.1 and 10.9 months, respectively.[62] Although hematologic grade 3-4 events were seen in the majority of patients, these were all well manageable or self-limiting. Grade 3-4 thrombocytopenia, leukopenia and neutropenia was seen in 54.5%, 75.6%, and 66.7% of patients, respectively. Grade 3 anemia was reported in 18.1%. There was only case of grade 3 hepatotoxicity with increased aminotransferases immediately after treatment, which normalized one week after treatment. Of all non-hematologic and non-hepatic grade 3 events ($n = 14$), posttreatment hemorrhage ($n = 2$; epistaxis and vaginal bleeding), febrile neutropenia ($n = 3$) and pulmonary emboli ($n = 2$) were most common. These patients were successfully treated with platelet transfusion, intravenous antibiotics, and low-molecular-weight heparin, respectively.[63] There was one non-hematologic grade 4 event. This was a case of sepsis due to bacterial pharyngitis with formation of a retropharyngeal abscess, which was treated with intravenous antibiotics, immunoglobulins, and aspiration of the abscess.

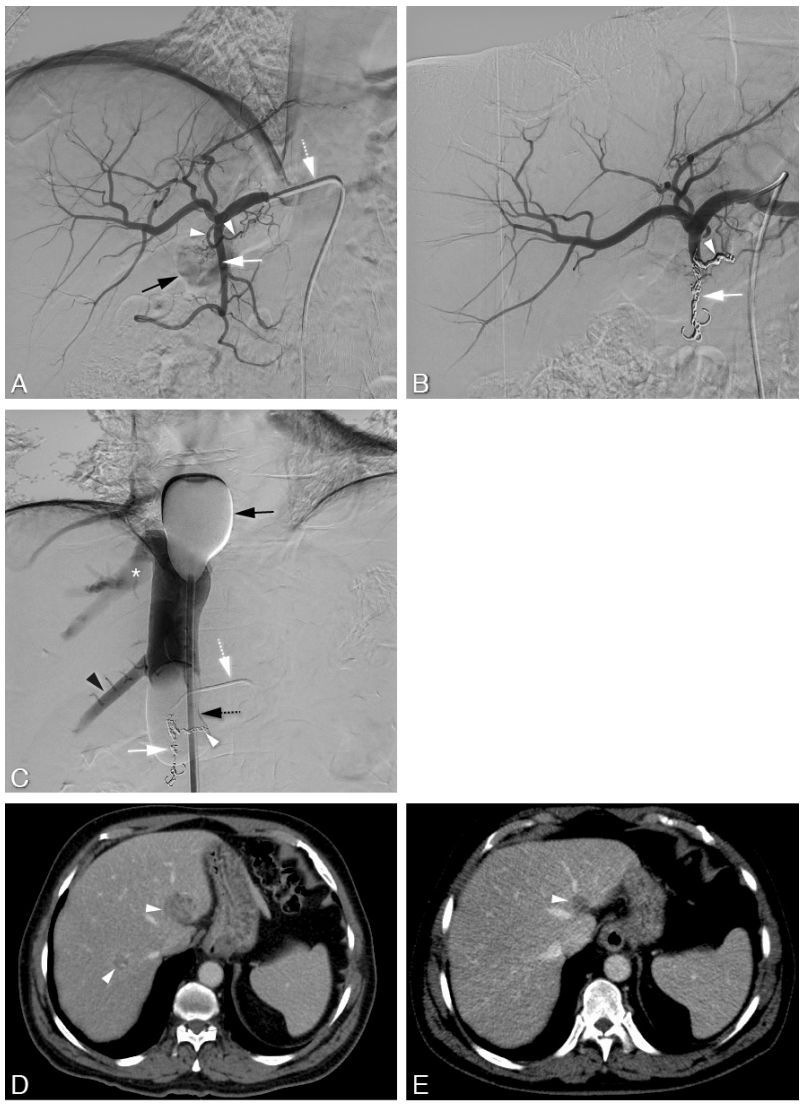

FIGURE 4. Percutaneous hepatic perfusion with melphalan
66-year-old male with bilobar hepatic metastases from uveal melanoma. (A) Pretreatment angiographic image from the common hepatic artery (CHA) showing a right gastric artery (RGA, white arrowheads) and gastroduodenal artery (GDA, white arrow). Also the macrocatheter in the CHA (dotted white arrow) and duodenal bulb (black arrow) are seen. (B) Successful coiling of the RGA (white arrowhead) and GDA (white arrow). (C) Postero-anterior image during venography performed by injection of contrast medium through side holes of the double-balloon catheter. The cranial balloon (black arrow) is inflated at the atriocaval junction to prevent flow to the right atrium, and the caudal balloon (dotted black arrow) is inflated in the infrahepatic portion of the inferior vena cava (IVC) to prevent retrograde flow to the infrarenal IVC. A microcatheter is inserted through the macrocatheter (dotted white arrow) and placed into the proper hepatic artery for the infusion of melphalan. The right hepatic vein (asterisk) and accessory right inferior hepatic vein (black arrowhead) are opacified. Note the coils in the RGA (white arrowhead) and GDA (white arrow). (D) Axial CT image in portovenous phase before treatment showing a metastasis in liver segment 2 and segment 7/8 (white arrowheads). A third lesion in segment 6 is not shown. (E) Axial CT image in portovenous phase after two cycles of M-PHP showing reduction in size of the metastasis in liver segment 2 (white arrowhead). The other two lesions showed complete radiological response.

LIVER-DIRECTED THERAPIES: MISCELLANEOUS

Surgical resection and thermal ablation (TA) are considered the only curative treatments for hepatic melanoma metastases. Unfortunately, in most patients (> 95%) resection or TA is no first-line treatment option because metastatic disease in cutaneous melanoma is often not liver-dominant, and patients with metastatic uveal melanoma most commonly present with diffuse liver disease (90-95%).[64,65] The few patients that are candidates are selected with MRI. Notably, for uveal melanoma, the sensitivity for detection of intraparenchymal hepatic metastases is 68-86% and only 41-54% for metastases in the subcapsular regions of the liver.[66] A careful inspection of the liver surface during surgery is therefore essential. In particular TA does play a role in patients with a few small residual lesions after showing a good radiological response upon arterial therapy (Figure 5).

Table 4 gives an overview of studies on surgical resection and TA as treatment of hepatic melanoma metastases.[67-74] The median OS after surgical resection ranges from 14-29 months for uveal melanoma[67-70,74], and 24-27 months for cutaneous melanoma.[67,68] The percentage of patients in whom complete microscopic resection (R0) was achieved, varies between 13% in a study by Frenkel et al. and 95.8% in a study by Pawlik et al. In a large retrospective review by Mariani et al. that was conducted to evaluate the evolving surgical management of hepatic metastases from uveal melanoma, 255/798 (32%) patients with liver metastases underwent surgical resection. The authors underlined the importance of R0 resection as this increased the median OS from 14 months, as was seen in the total cohort, to 27 months in the group with R0 resection ($p < 0.0001$).[69] Although Frenkel et al. also found a longer median posthepatectomy survival in patients with R0 resection than in patients with R1/R2 resection (65.6 versus 16.6 months, $p = 0.14$), there was no statistically significance. In addition, they found no correlation between the status of the surgical borders (R0 or R1/2) and recurrence of the metastases ($p = 0.79$).

There have been several retrospective studies on surgical resection and/or TA in patients with hepatic melanoma metastases.[71,72,74] Doussot et al. found no significant difference in median OS between resection ($n = 32$) and percutaneous TA ($n = 16$) in patients with uveal and cutaneous melanoma; 26 months for resection versus 18 months for TA ($p > 0.2$).[71] Four patients in the resection group received an additional resection of extrahepatic metastatic disease and portal lymphadenectomy was performed in eight patients. R0 resection was achieved in 30 patients (93.8%). Percutaneous TA included radiofrequency ablation (RFA, $n = 8$), microwave ablation ($n = 6$), and cryoablation ($n = 2$) along with additional transarterial hepatic embolization in three cases. Notably, patients in the TA group presented with more adverse disease characteristics with a significantly shorter interval between primary melanoma diagnosis and treatment for liver metastases (11 versus 31 months; $p = 0.011$) and more often had extrahepatic disease (56.3% versus 18.8%; $p = 0.008$). Nine out of 48 patients with extrahepatic disease received systemic therapy at the time of the procedure. Patients without extrahepatic disease tended to have a longer OS and PFS. Extrahepatic

disease was associated with a significantly worse OS in the resection group (p = 0.034).

In a paper by Bale et al., a retrospective review of 20 patients was presented, with a total of 75 hepatic melanoma metastases that were treated with RFA.[73] Primary tumors were uveal in 6 patients and cutaneous in 14 patients. A median number of two lesions (range 1-14) per patient with a median size of 1.7 cm (range 0.5-14.5) were treated. Most lesions (89.3%) were < 3 cm. A total of 34 ablation sessions were performed with a median of one session per patient (range 1-4). There were no procedure-related deaths. Three cases of pleural effusion requiring pleural drainage were reported. Computed tomography one month after initial therapy, demonstrated successful ablation in 89.3% (67/75). Residual tumor was retreated in three patients, resulting in a secondary success rate of 93.3% (70/75). Overall local recurrence rate was 13.3%. During follow-up, 10/20 patients developed liver recurrence at any location and 9/20 developed extrahepatic metastases. The median OS following initial RFA was 19.3 months with a large, but not statistically significant difference between patients with cutaneous and uveal melanoma (11.6 versus 38 months, p = 0.063). The median disease-free survival for all patients was 9.5 months. The authors conclude that RFA is a good alternative for resection due to the high potential for local cure and promising effects on survival with minimal morbidity and mortality.

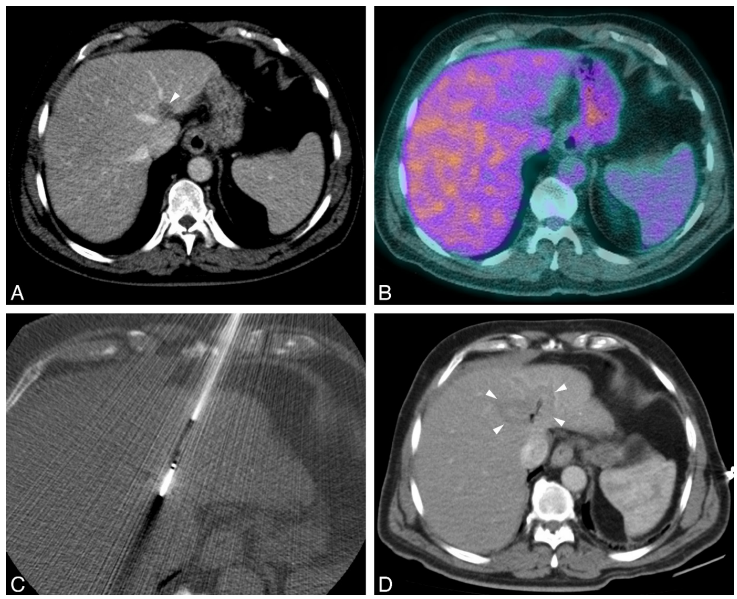

Figure 5. Microwave ablation (MWA) of a solitary liver lesion
Same patient as in figure 4. 66-year-old male who already received two cycles of M-PHP as treatment of bilobar hepatic metastases from uveal melanoma. Two metastases had shown complete radiological response, while a third metastasis in segment 2 (S2) was still visible. (A) Axial CT image in portovenous phase showing a hypodense lesion in S2 (white arrowhead). (B) Axial PET/CT image showing no increased 18F-FDG accumulation in S2. Despite this, it was decided to perform ablation to minimize the risk of recurrence. (C) Axial CT images during MWA, showing the positioning of the probe from anterior. (D) Contrast-enhanced CT immediately after MWA shows successful ablation (white arrowheads) with a peripheral ring of enhancement that usually disappears after a few weeks.

TABLE 4. Overview of studies on surgical resection and TA (≥ 10 patients) as treatment for hepatic melanoma metastases

First author (year)	Study design	Melanoma type	No. pts	Treatment	Median OS (mo)	R0/R1/R2 (%)
Adam (2006)[67]	RS	UM (*n* = 104), CM (*n* = 44)	148	Resection	UM 19, CM 27	83/8/9 (total)
Pawlik (2006)[68]	RS	UM (*n* = 16), CM (*n* = 24)	40	Resection[a]	UM 29, CM 24 (*p* = 0.2)	87.5/12.5/0 (UM) 95.8/4.2/0 (CM)
Mariani (2009)[69]	RS	UM	798	Resection (*n* = 255), no surgery (*n* = 543)	Resection 14, no surgery 8 R0 27, R1 17, R2 11 (*p* < 0.0001)	30/9/61
Frenkel (2009)[70]	RS	UM	74	Resection (*n* = 35), no surgery (*n* = 39)	Resection 23.0, no surgery 6.8 (*p* = 0.0001) R0 65.6, R1/R2 16.6 (*p* = 0.14)	13/NR/NR
Faries (2014)[64]	RS	UM (*n* = 121) CM (*n* = 957)	1078	Resection ± RFA (*n* = 58)[c], no surgery (*n* = 1020)	Resection ± RFA 24.8, no surgery 8 (*p* < 0.01)	NR
Doussot (2015)[71]	RS	UM (*n* = 22), CM (*n* = 26)	48	Resection (*n* = 32), percutaneous TA (*n* = 16)	Resection 26, TA 18 (*p* > 0.2)	94/NR/NR (total)
Akyuz (2015)[72]	RS	UM	44	Lap. resection (*n* = 2), lap. RFA (*n* = 14), systemic therapy (*n* = 28)	Lap. group 35, systemic therapy group 15 (*p* ≤ 0.0001)	NR
Bale (2016)[73]	RS	UM (*n* = 6), CM (*n* = 14)	20	RFA[c]	UM 38, CM 11.6 (*p* = 0.063)	N/A
Mariani (2016)[74]	RS	UM	72	Resection (*n* = 57), RFA ± resection (*n* = 15)	Resection 27, RFA ± resection 28 (n.s.)	NR

[a] 26/40 patients received additional perioperative systemic therapy.
[b] 9/58 of surgical patients had ocular primaries as did 112/1020 patients in the non-surgical group (*p* = 0.27).
[c] In 19% of cases, extrahepatic disease was resected at the time of hepatic resection. All patients with cutaneous melanoma received additional systemic chemotherapy.
Lap. laparoscopic, *mo* months, *NR* not reported, *OS* overall survival, *R0* microscopically complete resection, *R1* microscopically incomplete resection, *R2* macroscopically incomplete resection, *RFA* radiofrequency ablation, *RS* retrospective, *TA* thermal ablation.

SUMMARY

In this chapter, we discussed several liver-directed therapies that are currently used for the treatment of hepatic melanoma metastases. These therapies can be considered when the liver is the only or dominant site of metastatic disease. Treatment reports for liver-directed therapies in melanoma literature are dominated by studies on patients with uveal primaries as these patients often present with metastases that are confined to the liver. Although considered the only curative treatments, in most patient (> 95%) surgical resection or thermal ablation are no first-line treatments option. There is no current consensus on what liver-directed therapy would be best practice for patients with hepatic melanoma metastases, but M-PHP has been studied most extensively. M-PHP is the only treatment with proven efficacy in a randomized controlled trial on patients with hepatic metastases from melanoma.

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